Amino Acid Transport Defects

6

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Contents

Summary

Disorders associated with the malfunction of amino acid transporters mainly affect the function of the intestine, kidney, brain, and liver. Mutations of brain amino acid transporters, for example, alter neuronal excitability. Examples presented in this chapter are episodic ataxia due to EAAT3 defect, hyperekplexia due to GLYT2 deficiency, global cerebral hypomyelination due to AGC1 deficiency, and neonatal myoclonic epilepsy due to GC1 deficiency. Mutations of renal and intestinal amino acid transporters cause renal problems (cystinuria and dicarboxylic aminoaciduria) and malabsorption that can affect whole-body homoeostasis (Hartnup disorder, lysinuric protein intolerance, and hyperdibasic aminoaciduria type 1). Inborn errors associated with the mitochondrial SLC25 family with a liver phenotype such as the ones affecting SLC25A13 (aspartate/glutamate transporter 2), citrin deficiency and SLC25A15 (ornithine–citrulline carrier 2), homocitrullinuria, hyperornithinemia, and hyperammonemia will be dealt with in Chap. 4.

6.1 Introduction

Amino acid transporters are essential for the absorption of amino acids from nutrition, mediating the interorgan and intercellular transfer of amino acids and the transport of amino acids between cellular compartments (Broer and Palacín 2011). To date, 11 SLC families are known to comprise amino acid transporters. Defects due to mutations in amino acid transporters in 4 of these families affecting renal tubular reabsorption (Fig. 6.1) and intestinal absorption, neurotransmitter reuptake in the synapse, and mitochondrial oxidation are considered in this chapter: (1) Mutations in the members of the glutamate transporter family SLC1A1 (excitatory amino acid transporter 3, EAAT3) and SLC1A3 (excitatory amino acid transporter 1, EAAT1) cause the primary inherited aminoaciduria named dicarboxylic

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aminoaciduria and episodic ataxia type 6, respectively (Bailey et al. 2011; Jen et al. 2005). (2) Mutations in the heteromeric amino acid transporters (HAT) SLC3A1/SLC7A9 (rBAT/$b^{0,+}$AT) and SLC3A2/SLC7A7 (4F2hc/y^+LAT1) cause the primary inherited aminoacidurias cystinuria and lysinuric protein intolerance (LPI), respectively (Calonge et al. 1994; Feliubadaló et al. 1999; Torrents et al. 1999; Borsani et al. 1999). In cystinuria, mutations are found in either of the two subunits (SLC3A1 or SLC7A9), whereas in LPI mutations are only present in the light subunit SLC7A7. (3) Mutations in the members of the neurotransmitter transporter family SLC6A5 (neuronal glycine transporter GLYT2) and SLC6A19 (sodium-dependent neutral amino acid transporter B^0AT) cause hyperekplexia and the primary inherited aminoaciduria named Hartnup disorder, respectively (Seow et al. 2004; Kleta et al. 2004; Rees et al. 2006). (4) Mutations in the mitochondrial transporters SLC25A12 (neuronal- and muscle-specific mitochondrial aspartate/glutamate transporter 1, AGC1) and SLC25A22 (mitochondrial glutamate/H+ symporter 1, GC1) cause global cerebral hypomyelination and neonatal myoclonic epilepsy, respectively (Wibom et al. 2009; Molinari et al. 2005). Finally, for dibasic aminoaciduria type 1, only two families have been described and the causing gene is unknown (Kihara et al. 1973).

The principal biochemical and structural characteristics of these amino acid transporters have been reviewed recently (Broer and Palacin 2011). SLC1 family members (glutamate/aspartate transporters named EAAT for excitatory amino acid transporters 1–5) mediate high-affinity sodium- and potassium-dependent uptake of glutamate and aspartate in mammalian cells. SLC1A1 (EAAT3) is expressed in the apical membrane of epithelial cells of the kidney proximal convoluted tubule (Fig. 6.1) and the small intestine and in the brain cortex, particularly in the hippocampus, the basal ganglia, and the olfactory bulb. SLC1A3 (EAAT1) is found throughout the brain. It is the main glutamate transporter in the cerebellum, inner ear, circumventricular organs, and retina. Expression in peripheral organs is limited (Danbolt 2001). HAT are composed of a heavy subunit (SLC3 family) and a light subunit (SLC7 family), which are linked by a conserved disulfide bridge (Fig. 6.1). Both subunits are required to form functional transporters at the cell surface. Transporter SLC3A1/SLC7A9 (rBAT/$b^{0,+}$AT) is expressed in the apical membrane of epithelial cells of the kidney proximal convoluted tubule (Fig. 6.1) and the small intestine. Transporter SLC3A2/SLC7A7 (4F2hc/y^+LAT1) is mainly expressed in the basolateral plasma membrane of the epithelial cells of the kidney proximal convoluted tubule (Fig. 6.1) and the small intestine and in white blood cells. The SLC6 family comprises 20 members in humans that can be grouped into four subfamilies, namely, the monoamine transporter branch, the GABA (γ-aminobutyric acid) transporter branch, and the amino acid transporter branches I and II. SLC6A5 (GLYT2) and SLC6A19 (B^0AT) belong to the two latter subfamilies and mediate reuptake of glycine in synapses and the uptake of neutral amino acids in epithelial cells, respectively. GLYT2 is mainly found in the spinal cord where it terminates inhibitory neurotransmission. B^0AT1 is found in the apical membrane of kidney proximal tubular epithelial cells (Fig. 6.1) and enterocytes of the small intestine. Finally, the SLC25 family comprises a total of ~30 members, including three ADP/ATP carrier isoforms, five uncoupling protein isoforms, and six amino acid transporters. In the inner mitochondrial membrane, SLC25A12 (AGC1) exchanges glutamate and aspartate, and SLC25A22 (GC1) mediates proton-dependent transport of glutamate. AGC1 is highly expressed in the inner mitochondrial membrane in the brain, heart, and skeletal muscle. GC1 is more highly expressed in brain astrocytes than in neurons.

6.1 Cystinuria. Renal reabsorption and intestinal absorption of cystine, lysine, arginine, and ornithine. Metabolites important for diagnosis: cystine, lysine, arginine, and ornithine in urine.

6.2 *Dicarboxylic aminoaciduria*. Reuptake of neurotransmitter glutamate, absorption of glutamate and aspartate in the intestine, and reabsorption of glutamate in the kidney. Metabolites important for diagnosis: glutamate and aspartate in the urine.

6.3 *Hartnup disorder*. Renal reabsorption and intestinal absorption of neutral amino acids. Metabolites important for diagnosis: neutral amino acids in the urine. Glycine is usually normal.

6.4 *Lysinuric protein intolerance*. Renal reabsorption and intestinal absorption of dibasic amino acids. Metabolites important for diagnosis: dibasic amino acids in the plasma (decreased) and urine (increased) and orotic acid in urine (increased).

6.5 *Dibasic aminoaciduria type 1*. Renal reabsorption and intestinal absorption of lysine, arginine, and ornithine. Metabolites important for diagnosis: lysine, arginine, and ornithine in urine.

6.6 *Episodic ataxia due to EAAT1 defect*. Reuptake of neurotransmitter glutamate.

6.7 *Hyperekplexia*. Reuptake of inhibitory neurotransmitter glycine.

6.8 *Global cerebral hypomyelination due to AGC1 defect*. Malate–aspartate shuttle for mitochondrial oxidation of cytosolic NADH and efflux of aspartate from neuronal mitochondria for myelin formation. Metabolite important for diagnosis: N-acetylaspartate in the brain (magnetic resonance ^{1}H spectrum in cerebral areas).

6.9 *Neonatal myoclonic epilepsy due to mitochondrial glutamate carrier GC1 defect*. Mitochondrial glutamate import/metabolism and neuronal excitability.

6.2 Nomenclature

No.	Disorder	Alternative name	Abbreviation	Gene symbol	Chromosomal localization	Affected protein	OMIM no.	Subtype
6.1	Cystinuria		Cystinuria	*SLC3A1*, *SLC7A9*	2p16.3, 19q12	Amino acid transport system b(0,+), composed of proteins rBAT (SLC3A1) and b(0,+)AT (SLC7A9)	220100	All forms
6.2	Dicarboxylic aminoaciduria		DA	*SLC1A1*	9p24	Neuronal/epithelial high-affinity glutamate transporter, excitatory amino acid transporter 3 (EAAT3)	222730	All forms
6.3	Hartnup disorder		HD	*SLC6A19*	5p15.33	Sodium-dependent neutral amino acid transporter (B^0AT)	234500	All forms
6.4	Lysinuric protein intolerance	Hyperdibasic aminoaciduria type 2	LPI	*SLC7A7*	14q11.2	Amino acid transport system y + L (4F2hc/ y^+LAT1)	222700	All forms
6.5	Dibasic aminoaciduria type 1		–	–	–	–	222690	All forms
6.6	Episodic ataxia due to EAAT1 glutamate transporter defect	Episodic ataxia type 6	EA6	*SLC1A3*	5p13	Glutamate/aspartate transporter (GLAST), excitatory amino acid transporter 3 (EAAT3)	612656	All forms
6.7	Hyperekplexia due to Gly transporter GLYT2 defect	Startle disease, familial	HE	*SLC6A5*	11p15.1	Neuronal glycine transporter GLYT2	149400	All forms
6.8	Global cerebral hypomyelination due to AGC1 defect	Aspartate/ glutamate transporter 1 (AGC1) deficiency	AGC1 deficiency	*SLC25A12*	2q31.1	Neuronal- and muscle-specific mitochondrial aspartate/glutamate transporter 1 (AGC1; Aralar)	612949	All forms
6.9	Neonatal myoclonic epilepsy due to mitochondrial glutamate carrier GC1 defect	Early infantile epileptic encephalopathy-3 (EIEE3)	EIEE3	*SLC25A22*	11p15.5	Mitochondrial glutamate/ H+ symporter 1 (glutamate carrier 1, GC1)	609304	All forms

6.3 Metabolic Pathways

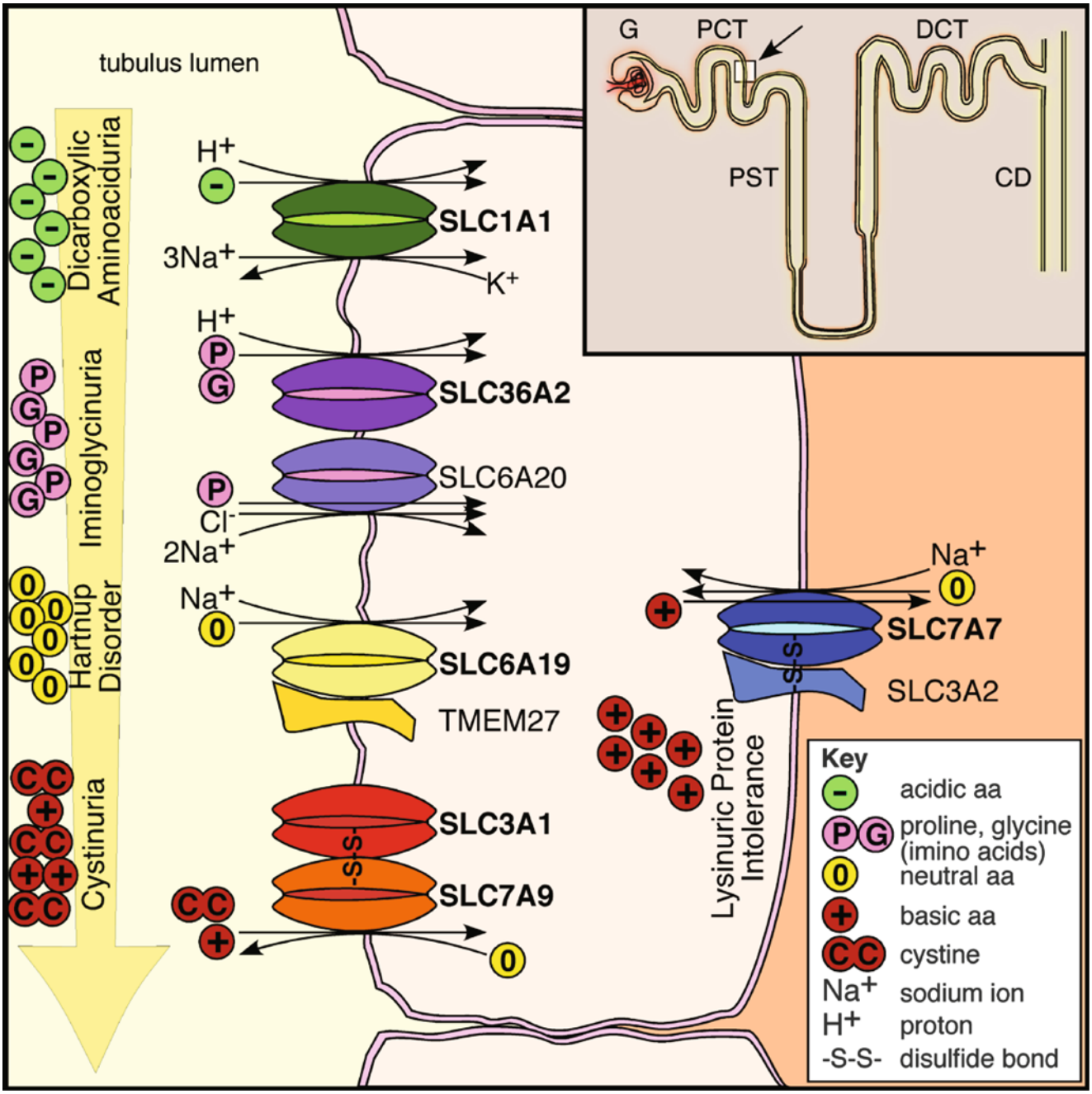


Fig. 6.1 Principal epithelial transporters involved in amino acid reabsorption, which are mutated in human aminoacidurias. A nephron is depicted (*inset*), showing the glomerulus, proximal convoluted tubule (*PCT*), proximal straight tubule (*PST*), distal convoluted tubule (*DCT*), and collecting duct (*CD*). A cross section of the proximal convoluted tubule (*white square* indicated with an *arrow*) is represented in the main diagram. Four of the aminoacidurias, including DA, iminoglycinuria, Hartnup disorder, and cystinuria, manifest at the apical surface of the renal tubule, while lysinuric protein intolerance manifests at the basolateral surface (see text for details). Iminoglycinuria results from complete inactivation of SLC36A2, a proline and glycine transporter, or from additional modifying mutations in the high-affinity proline transporter SLC6A20 when SLC36A2 is not completely inactivated (Broer et al. 2008). Iminoglycinuria is not further discussed in this chapter because it is a benign condition with no associated pathology. Mutations in the neutral amino acid transporter, SLC6A19, are responsible for Hartnup disorder (Kleta et al. 2004; Seow et al. 2004). The neutral amino acid transport defect can also be caused by a kidney-specific loss of heterodimerization of mutant SLC6A19 with TMEM27 (Kowalczuk et al. 2008). Finally, no mutations have been identified in SLC3A2, coding for the ancillary protein of y^+LAT1 (SLC7A7) in patients with LPI (Broer and Palacín 2011) (Figure extracted from Bailey et al. (2011))

6.4 Signs and Symptoms

Table 6.1 Cystinuria

System	Symptom	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Renal	Obstructive uropathy	–	±	±	±	±
	Renal failure, chronic	–	–	±	±	±
	Urinary infections	–	±	±	±	±
	Urolithiasis[a]	–	±	±	±	++
	Urolithiasis, cystine stones	–	±	±	±	++
Routine laboratory	Hematuria	–	±	±	±	±
	Leukocytes (U)	–	±	±	±	±
Special laboratory	Cys, Lys, Arg, Orn (P)		↓-n	↓-n	↓-n	↓-n
	Cystine (U)		↑↑	↑↑	↑↑	↑↑
	Cystine crystals (U)	+	+	+	+	+
	Lysine, arginine, ornithine (U)[b]		↑↑	↑↑	↑↑	↑↑

[a]Cystine stones usually appear in the third decade of life. A small proportion of patients, with the 2 mutated alleles in any of the two cystinuria genes, do not produce them
[b]In isolated cystinuria there is no hyperexcretion of dibasic amino acids in urine (Eggermann et al. 2007)

Table 6.2 Dicarboxylic aminoaciduria

System	Symptom	Neonatal	Infancy	Childhood	Adolescence	Adulthood
CNS	Behavior, psychotic	–	–	±	±	±
	Mental retardation[b]	–	±	±	±	±
Renal[a]	Urolithiasis, glutamate stones	–	±	±	±	±
Special laboratory	**Aspartic acid (U)**	↑	↑	↑	↑	↑
	Glutamic acid (U)	↑↑	↑↑	↑↑	↑↑	↑↑

No characteristic clinical findings in DA
[a]Two out of the three patients presented in Bailey et al. (2011) presented stones of unknown nature
[b]Reported in several cases, but most likely ascertainment bias

Table 6.3 Hartnup disorder

System	Symptom	Neonatal	Infancy	Childhood	Adolescence	Adulthood
CNS	Ataxia	–	±	±	±	–
	Psychosis	–	±	±	±	–
Dermatological	**Photosensitivity**	–	±	±	±	–
Special laboratory	Glutamic acid (U)	n-↑	n-↑	n-↑	n-↑	n-↑
	Neutral amino acids (U)	↑↑	↑↑	↑↑	↑↑	↑↑

Table 6.4 Lysinuric protein intolerance

System	Symptom	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Cardiovascular	Valvulitis, mitral	–	–	±	±	±
CNS	**Coma, hyperammonemic**	–	±	±	±	±
	Mental retardation	–	–	±	±	±
Dermatological	Sparse hair	–	–	±	±	±
Digestive	Diarrhea	–	±	±	±	±
	Hepatosplenomegaly	±	±	±	±	±
	Protein intolerance	–	–	±	±	±
	Vomiting	–	±	±	±	±
Hematological	Hemophagocytic lymphohistiocytosis, macrophage activation syndrome	–	–	±	±	±
Musculoskeletal	Bone growth	n	n	↓-n	↓-n	↓-n
	Osteoporosis	–	–	±	±	±

(continued)

Table 6.4 (continued)

System	Symptom	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Renal	Glomerulonephritis	–	–	±	±	±
	Hypertension	–	–	–	±	±
	Renal failure, end stage	–	–	–	±	±
Respiratory	Interstitial changes (chest radiographs)	–	–	±	±	±
	Pulmonary alveolar proteinosis	–	–	±	±	±
	Respiratory insufficiency	–	–	±	±	±
Other	Combined hyperlipidemia			±	±	±
Special laboratory	Arginine, ornithine (U)	–	–	↑	↑	↑
	Gln, Ala, Gly, Pro, Cit (P)	–	–	↑	↑	↑
	Lys, Arg, Ornithine (P)	n	n	↓-n	↓-n	↓-n
	Lysine (U)	–	–	↑↑	↑↑	↑↑
	Orotic acid (U)	–	↑	↑	↑	↑

Table 6.5 Dibasic aminoaciduria type 1

System	Symptom	Neonatal	Infancy	Childhood	Adolescence	Adulthood
CNS	Athetosis	–	±	+		
	Dysarthria	–	±	+		
	Hyperactivity	–	+	++		
	Mental retardation	–	+	++		
Other	**Adverse reaction to phenothiazines**	–	++	++		
Special laboratory	Cys, Lys, Arg, Orn (P)		n	n	n	
	Lysine, arginine, ornithine (U)[a]			↑	↑	
	Lysine, intestinal absorption				↓	

Signs and symptoms correspond to the only suspected homozygous patient described (Kihara et al. 1973). The parents of the patient, as well members of another family, showed moderated hyperdibasic aminoaciduria (lysine, arginine, and ornithine) and presented no pathological signs and therefore had been considered heterozygotes. The patients described by Whelan and Scriver (1968) were free of characteristic symptoms
[a]The patient showed a moderated urine hyperexcretion of cystine

Table 6.6 Episodic ataxia due to EAAT1 glutamate transporter defect

System	Symptom	Neonatal	Infancy	Childhood	Adolescence	Adulthood
CNS	**Ataxia**[a]	–	–	+	+	+
	Epilepsy	–	–	+	+	+
	Hemiplegic migraine	–	–	+	+	+
	Interictal nystagmus	–	–	+	+	+
Digestive	Nausea/vomiting	–	–	+	+	+
Eye	Photophobia	–	–	+	+	+

Signs and symptoms according to a very small number of cases described by Jen et al. (2005) and de Vries et al. (2009)
[a]Ataxia episodes lasting hours to days. Normal routine laboratory

Table 6.7 Hyperekplexia due to Gly transporter GLYT2 defect

System	Symptom	Neonatal	Infancy	Childhood	Adolescence	Adulthood
CNS	Head-retraction reflex[a]	↑	↑	↑	↑	↑
	Mental retardation, mild	–	±	±	±	±
	Startle reflex	+	+	+	+	+
	Stiffness	+	+	±	±	±
	Sudden infant death	±	±	–	–	–
Musculoskeletal	Hernias	–	±	±	±	±
	Hip dislocation	±	±	±	±	±
	Periodic limb movement during slip	±	±	±	±	±

Signs and symptoms according to de-Koning-Tijssen and Rees (2007) and Bakker et al. (2006)
[a]Short period of stiffness following startle response. Normal routine laboratory

Table 6.8 Global cerebral hypomyelination due to AGC1 defect

System	Symptom	Neonatal	Infancy	Childhood	Adolescence	Adulthood
CNS	Apnea[a]	–	–	+		
	Muscular hypotonia	–	–	++		
	Retardation, psychomotor[b]	–	+	+		
	Spasticity[c]	–	–	++		
	Sporadic tonic seizures	–	+	+		
Routine laboratory	Lactate (P)			↑		
Special laboratory	ATP production (muscle biopsy)[d]			↓↓		
	Cerebrum volume[e]			↓		
	Hypomyelination, global[f]			++		
	Mitochondrial respiratory complexes[g]			n		
	N-Acetylaspartate (CNS)			↓↓		

Signs and symptoms correspond to the only patient identified so far, a 3-year-old girl (homozygous for the missense mutation Q590R) (Wibom et al. 2009)
[a]Episodic
[b]Affecting mainly motor skills
[c]With generalized hyperreflexia
[d]Using glutamate + succinate or glutamate + malate as substrates
[e]Detected by magnetic resonance imaging in the cerebral hemispheres with reduced cerebral volume (cerebellum, brainstem, and thalami normal)
[f]Detected by magnetic resonance single-volume spectroscopy (^{1}H spectrum) in the left basal ganglia, occipital midline, and frontal lobe
[g]Activities of complexes I, I + III, II, II + III, and IV in muscle biopsy

Table 6.9 Neonatal myoclonic epilepsy due to mitochondrial glutamate carrier GC1 defect

System	Symptom	Neonatal	Infancy	Childhood	Adolescence	Adulthood
CNS	Encephalopathy, progressive[a]	–	±	++		
	Hypotonia	++	++	++		
	Myoclonic epilepsy[b]	++	++	++		
	Spasticity	–	–	±		
	Vegetative state[c]	–	–	±		
Musculoskeletal	Microcephaly	–	–	+		
Routine laboratory	EEG: abnormal[d]	++	++	++		
	ERG: abnormal[e]			±		
	MRI (CNS): abnormal[f]			++		
Special laboratory	Glutamate oxidation (FB)[g]			↓↓		

Signs and symptoms correspond to the few patients identified, four affected children in one family (homozygous for the missense mutation P206L) and one affected child in another family (homozygous for the missense mutation G236W) (Molinari et al. 2005, 2009)
[a]One of the patients showed no psychomotor development at the age of 10 years
[b]Refractory to vigabatrin, carbamazepine, stiripentol, and phenobarbital
[c]One of the identified patients died at the age of 8 years
[d]Abnormal EEG with burst suppression pattern and hypsarrhythmia suggesting West syndrome
[e]Electroretinogram with progressive alteration and abolition of macular and peripheral responses
[f]Abnormal magnetic resonance imaging with cerebellar hypoplasia and other alterations
[g]Strongly defective mitochondrial oxidation of glutamate, but not succinate, in cultured skin fibroblasts

6.5 Reference Values

Fasting plasma amino acid levels (mM) (range limits) measured by amino acid analyzer

	Neonatal	Infancy	Childhood to adulthood
Amino acid	Fasting	Fasting	Fasting
Alanine	0.19–.34	0.17–0.44	0.23–0.42
Arginine	0.05–0.08	0.05–0.12	0.05–0.10
Asparagine	0.05–0.12	0.05–0.12	0.03–0.11
Aspartate	<0.02	<0.02	<0.02
Citrulline	<0.04	0.01–0.05	0.01–0.05
Cystine	0.02–0.06	0.02–0.06	0.02–0.06
Glutamate	<0.08	<0.08	<0.08
Glutamine	0.42–0.75	0.33–0.67	0.33–0.63
Glycine	0.11–0.29	0.11–0.29	0.11–0.29
Histidine	0.05–0.10	0.05–0.10	0.05–0.10
Isoleucine	0.04–0.09	0.04–0.09	0.04–0.09
Leucine	0.08–0.15	0.08–0.15	0.06–0.16
Lysine	0.07–0.20	0.12–0.24	0.11–0.23
Methionine	0.01–0.04	0.01–0.04	0.01–0.04
Ornithine	0.04–0.11	0.04–0.11	0.04–0.11
Phenylalanine	0.04–0.07	0.04–0.07	0.04–0.07
Proline	0.09–0.27	0.09–0.27	0.12–0.23
Serine	0.10–0.20	0.10–0.20	0.10–0.20
Threonine	0.06–0.29	0.06–0.29	0.10–0.20
Tyrosine	0.04–0.11	0.04–0.08	0.04–0.09
Valine	0.13–0.29	0.13–0.29	0.13–0.29

Reference values from the Hospital San Joan de Deu, Barcelona, Spain (Rafael Artuch)

Urine amino acid levels (mmol/mol creatinine) (5–95 percentile limits) measured by amino acid analyzer

	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Amino acid	Fasting	Fasting	Fasting	Fasting	Fasting
Alanine	75–244	36–206	33–130	17–92	16–68
Arginine	<14	<11	<9	<6	<5
Asparagine	<84	<58	<32	<24	<23
Aspartate	2–12	2–16	2–10	1–10	2–7
Citrulline	<10	<10	<10	<10	<10
Cystine	24–78	12–48	8–30	7–23	6–34
Glutamate	<30	<29	<11	<9	<12
Glutamine	52–205	63–229	45–236	20–112	20–76
Glycine	283–1,097	210–743	110–356	64–236	43–173
Histidine	80–295	72–342	61–287	43–184	26–153
Isoleucine	<6	<6	<6	<6	<4
Leucine	3–25	4–16	3–18	3–16	2–11
Lysine	22–171	13–199	10–69	10–56	7–58
Methionine	7–27	6–29	5–29	3–17	2–16
Ornithine	<31	<31	<14	<14	<8
Phenylalanine	4–32	7–28	6–31	5–20	2–19
Proline	21–213	<130	<13	<9	<9
Serine	80–262	42–194	32–124	23–69	21–50
Threonine	20–138	14–92	9–62	8–28	7–29
Tyrosine	6–55	11–54	9–48	6–26	2–23
Valine	3–26	4–19	3–21	3–17	3–13

6.6 Pathological Values

6.1 *Cystinuria*. Altered urine amino acid levels (5–95 percentile limits in mmol/mol creatinine) in cystinuria (Font-Llitjos et al. 2005).

Amino acid	Controls[a]	Cystinuria patients[b]
Cystine	3–12	73–385
Lysine	4–56	300–1,315
Arginine	<5	26–946
Ornithine	1–8	66–389

Urine samples randomly collected (morning or 24 h) from 83 controls and 34 patients of any age
[a]Controls were relatives of cystinuria patients without mutations in SLC3A1 and SLC7A9
[b]Patients with two mutated SLC3A1 alleles (cystinuria type A); similar range of values were obtained from the urine of patients with cystinuria type B (two mutated SLC7A9 alleles)

6.2 *Dicarboxylic aminoaciduria*. Altered urine amino acid levels (lower and upper values in mmol/mol creatinine) in DA (Bailey et al. 2011).

	Reference values		DA patients	
Amino acid	Infancy	Adulthood	Infancy	Adulthood
Aspartate	<26	<15	50	46–51
Glutamate	<63	<36	1,225	1,052–1,377

Urine samples obtained by random collection

6.3 *Hartnup disorder*. Altered urine amino acid levels (lower and upper values in mmol/mol creatinine) in adults with HD (Potter et al. 2002).

Amino acid	HD patients
Alanine	384–1,436
Glutamate	15–29
Glutamine	515–2,010
Glycine	159–708
Histidine	325–653
Isoleucine	14–194
Leucine	16–200
Lysine	2–88
Methionine	5–51
Phenylalanine	12–122
Serine	546–842
Threonine	233–665
Tyrosine	2–281
Valine	43–566

Urine samples obtained by random collection. Glutamate and lysine are usually slightly elevated, but not in all HD patients

6.4 *Lysinuric protein intolerance*. Altered amino acid plasma concentration (mM) in 20 patients (the range of lower–upper values is shown) (Simell 2001). Altered urine excretion values (mmol/mol creatinine) of amino acids and orotic acid after overnight fasting in one LPI patient (provided by R. Artuch from ref. Gómez et al. 2006). Reference values for urine orotic acid excretion (1.2–6.9 mmol/mol creatinine).

Amino acid	Plasma	Urine
Alanine	0.42–1.02	116
Arginine	0.01–0.06	661
Citrulline	0.14–0.53	53
Glutamine	3.64–7.16	149
Glycine	0.39–0.53	240
Lysine	0.03–0.18	1,040
Ornithine	<0.08	112
Carbamoyl phosphate metabolite		
Orotic acid	–	30

6.5 *Hyperdibasic aminoaciduria type 1*. Altered urine amino acid levels (range of values in 6 determinations within 2 years) of the only identified patient with hyperdibasic aminoaciduria type 1 (mmol/mol creatinine) (Kihara et al. 1973).

Amino acid	Controls[a]	Patient
Cystine	3	22–45
Lysine	12	400–803
Arginine	2	11–56
Ornithine	9	21–83

[a]Control reference values in the Pacific State Hospital (California, USA) at the time of the study

6.6 *Episodic ataxia due to EAAT1 defect and* **6.7** *hyperekplexia*. Not applicable.

6.8 *Global cerebral hypomyelination due to AGC1 defect*. In the only identified patient, plasma lactate was elevated (6 mM), and magnetic resonance single-volume spectroscopy (^{1}H spectrum) in the left basal ganglia, occipital midline, and frontal lobe in the only patient described with AGC1 deficiency showed severely reduced peak of N-acetylaspartate (ratio N-acetylaspartate/creatine = 0.7) (Wibom et al. 2009).

6.9 *Neonatal myoclonic epilepsy due to mitochondrial glutamate carrier GC1 defect*. Not applicable.

6.7 Diagnostic Flow Charts

6.1 *Cystinuria*

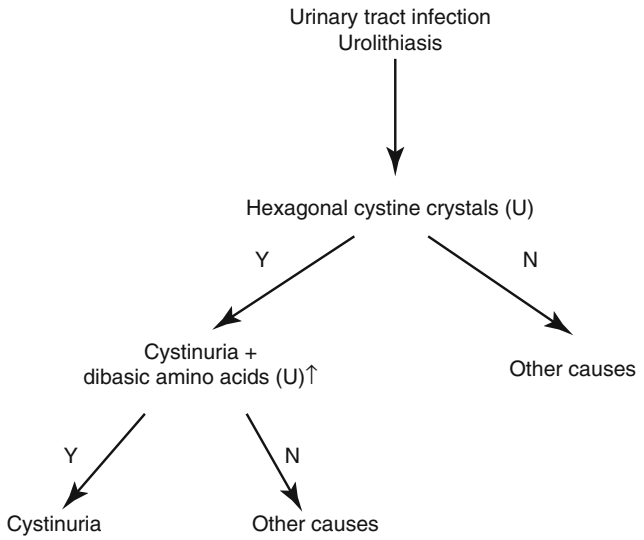


Fig. 6.2 Diagnostic flow chart for cystinuria

If patients are presented with neonatal seizures, hypotonia, developmental delay, and/or facial dysmorphism, the very rare hypotonia–cystinuria syndrome (OMIM 606407) due to homozygous deletion on chromosome 2p21 should be discarded.

6.2 *Dicarboxylic aminoaciduria*. Usually detected retrospectively, consider in cases of obsessive–compulsive disorder. Mental retardation most likely diagnosed due to ascertainment bias.

6.3 *Hartnup disorder*. Usually detected in children by urine amino acid analysis when presenting with photodermatitis of unknown origin (Fig. 6.3).

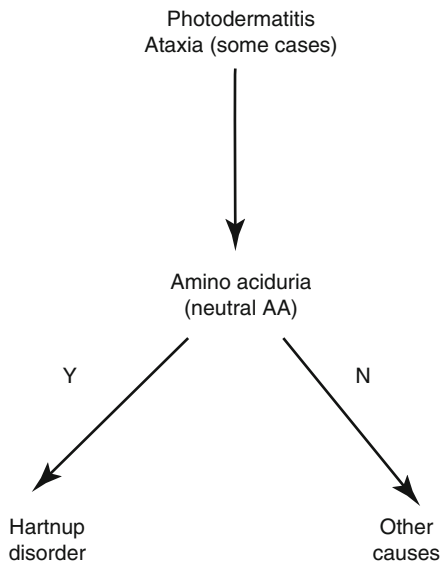


Fig. 6.3 Diagnostic flow chart for Hartnup disorder

6.4 *Lysinuric protein intolerance*

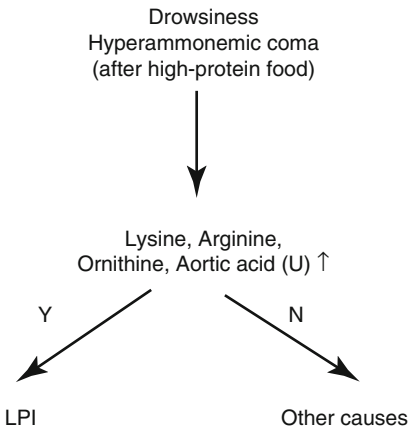


Fig. 6.4 Diagnostic flow chart for lysinuric protein intolerance

6.5 *Hyperdibasic aminoaciduria type 1*. The principal differences between the described patient with hyperdibasic aminoaciduria type 1 and LPI patients are (i) absence of hyperammonemia or protein intolerance and (ii) moderate hyperdibasic aminoaciduria in the obligated heterozygotes (e.g., parents) in the former.

6.6 *Episodic ataxia due to EAAT1 defect*. Typically, episodes of ataxia can be triggered by startle, stress, or exertion (Fig. 6.5).

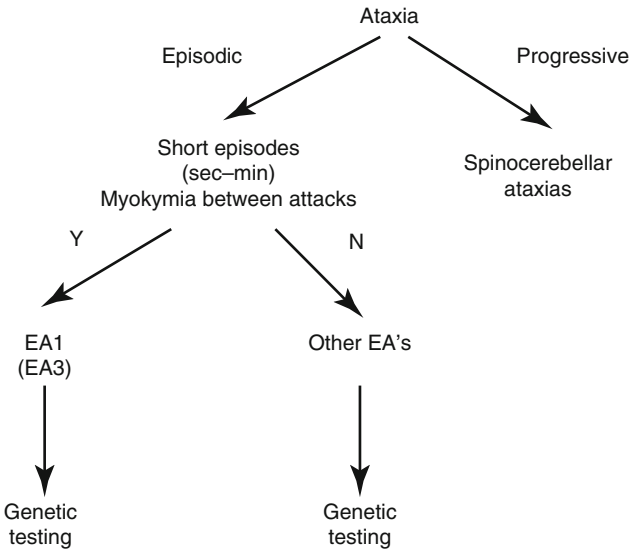
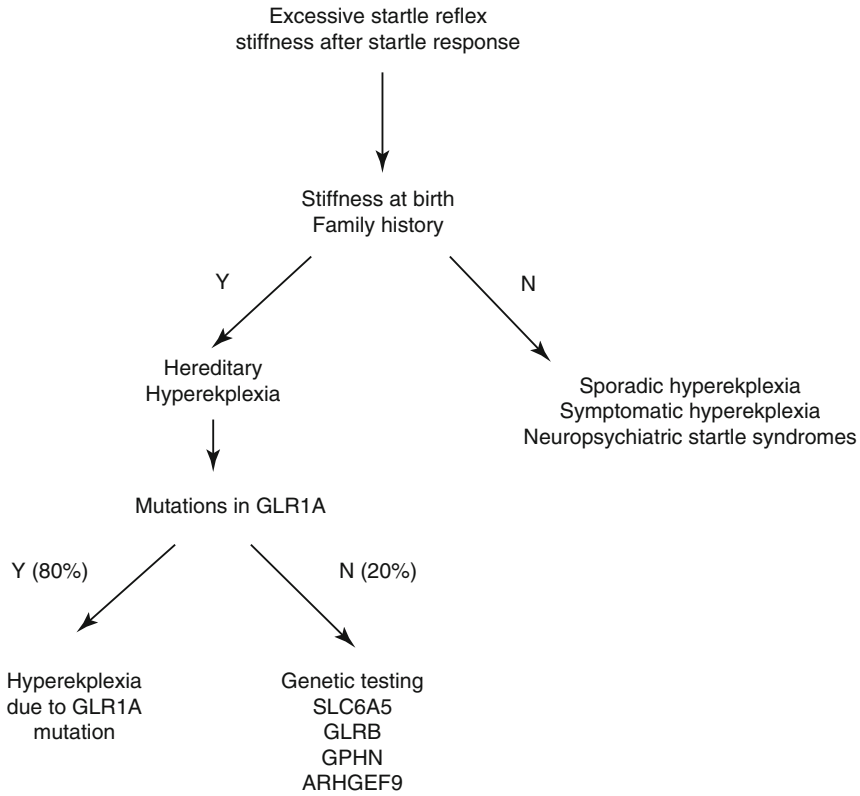


Fig. 6.5 Diagnostic flow chart for ataxia

6.7 *Hyperekplexia*. Diagnosis of HE requires three key symptoms: generalized stiffness after birth, excessive startle reflex particularly after auditory stimuli and short periods of stiffness after the startle response (Fig. 6.6).

Fig. 6.6 Diagnostic flow chart for hyperekplexia



6.8 *Global cerebral hypomyelination due to AGC1 defect*. Diagnostic flow chart followed by the authors in the only published reference of AGC1 deficiency (Wibom et al. 2009).

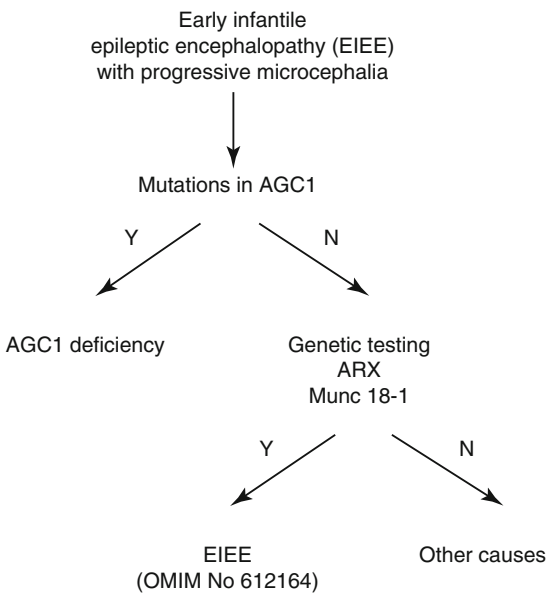


Fig. 6.7 Diagnostic flow chart for AG1 deficiency

6.9 *Neonatal myoclonic epilepsy due to mitochondrial glutamate carrier GC1 defect*

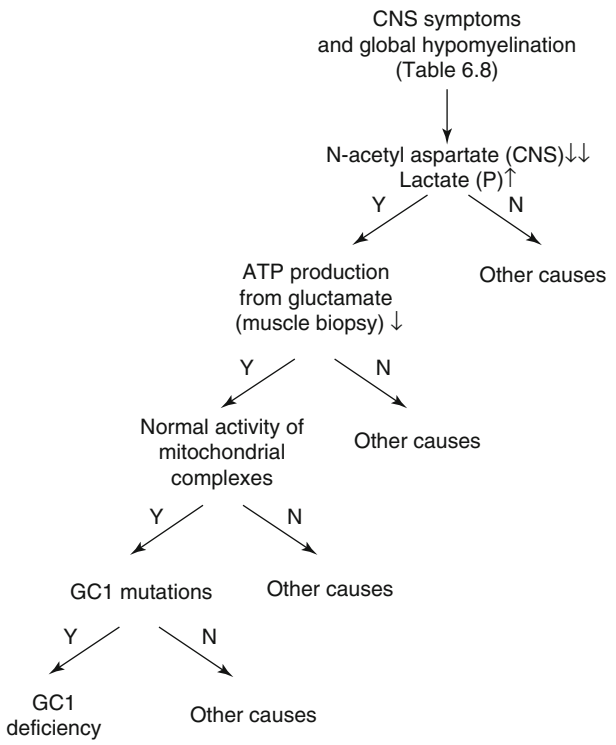


Fig. 6.8 Flow chart for GC1 deficiency

6.8 Specimen Collection

6.1 *Cystinuria*, **6.2** *dicarboxylic aminoaciduria*, **6.3** *Hartnup disorder*, **6.4** *lysinuric protein intolerance*, *and* **6.5** *hyperdibasic aminoaciduria type 1*. Standard urine sample collected for 24 h or as single sample where amino acid concentration is referred to creatinine amount. **6.6** *Episodic ataxia*. Not applicable. **6.7** *Startle disease*. Not applicable. **6.8** *AGC1 deficiency*. Muscle biopsy could be use to demonstrate reduced ATP production from glutamate. **6.9** *GC1 deficiency*. Skin specimen to prepare cultured fibroblast could be used to demonstrate deficient glutamate oxidation.

6.9 Prenatal Diagnosis

Prenatal diagnosis is not recommended in cystinuria, dicarboxylic aminoaciduria, Hartnup disorder, and lysinuric protein intolerance. For at risk pregnancies of EA and AGC1 and GC1 deficiencies, if mutations have been identified in the family, DNA sequence analysis can be performed by a research laboratory.

6.10 DNA Testing

DNA testing can be performed but is not necessary for diagnosis of cystinuria, dicarboxylic aminoaciduria, and Hartnup disorder. In cystinuria, if one mutated allele is already identified in one of the two cystinuria genes (SLC3A1 or SLC7A9), the second mutated allele most probably will be identified in the same gene because digenic inheritance in cystinuria has not been demonstrated. A small proportion (~4 %) of carriers of one mutated allele (mainly SLC7A9 heterozygotes) present with cystine lithiasis. LPI: Neonatal DNA screenings for the unique mutation present in Finland (Finnish mutation 1181-2A→T) and a northern part of Iwate (Japan) (mutation R410X) with an incidence in the population of 1:60,000 have been established due to the benefits of an early therapy. For early infantile epileptic encephalopathy, DNA sequencing of GC1, ARX, and Munc18 will explain part of the cases, but this information has no impact on therapy. DNA testing for common forms of hyperekplexia and episodic ataxia is available. For the cases associated with SLC6A5 and SLC1A3, respectively, sequencing is only available through research laboratories.

6.11 Treatment Summary

Methods to reverse the defect in transport that causes the disorders discussed in this chapter have not been developed. Treatment and management of cystinuria in children and adults relate to the prevention of stone formation by reducing the absolute amount and increasing the solubility of the poorly soluble cystine that is excreted in the urine by dietary measures and alkalization of urine. If these conservative approaches fail, thiol-chelating drugs that reduce cystine to more soluble cysteine adducts may be administered. The goal is to maintain cystine urine concentration below 1 mmol/l (~250 mg/l) and excretion below <100 µmol/mmol of creatinine (Knoll et al. 2005; Chillarón et al. 2010). Treatment is not required for dicarboxylic aminoaciduria. Photodermatitis in Hartnup disorder is treated with oral nicotinamide. For LPI they are two main directions of therapy (Sebastio et al. 2011). The first is aimed to reduce the risk of hyperammonemia [low-protein diet and L-citrulline supplementation (to refill urea cycle intermediates) or administration of ammonium scavengers (e.g., sodium benzoate)]. The second is aimed at the specific treatment of the severe complications. Acetazolamide should be tried in any patient with EA, but not all are responsive. Clonazepam is used to treat hyperekplexia. Epilepsy in the unique case reported on AGC1 deficiency is treated with carbamazepine and levetiracetam. There is no treatment for GC1 deficiency.

Emergency Treatment

6.1 *Cystinuria*. Urological interventions are often indicated for the management of cystine stones >5 mm in diameter (Chillarón et al. 2010). The almost noninvasive extracorporeal shock wave lithotripsy should be the treatment of choice at least in children (Knoll et al. 2005).

Pitfalls

Some cystine stones have crystalline structures (e.g., smooth appearance or low degree of radiopacity), which make them resistant to extracorporeal shock wave lithotripsy. Ureteroscopy and percutaneous nephrostolithotomy may be preferable in these patients to remove the stones.

6.6 *Episodic ataxia due to EAAT1 defect*. Antiepileptic drugs: carbamazepine (up to 1,600 mg/day), sulthiame (50–200 mg/day), and diphenylhydantoin (150–300 mg/day).

Dangers/Pitfalls

Drugs should be used with caution due to significant side effects.

6.7 *Hyperekplexia due to GLYT2 defect*. Sudden infant death due to apnea (stiffness of the respiratory muscles) can occur in cases of hyperekplexia. This can be prevented by the Vigevano maneuver (flexing of the head and limbs toward the trunk; Vigevano et al. 1989).

Standard Treatment

6.1 *Cystinuria*

Objective	Strategy	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Decrease in cystine excretion	Dietary sodium intake (upper limit; g/24 h)	–	–	2	2	2
	Animal protein intake (g/kg BW • 24 h)	–	–	–	<1	<1
Decrease in urine cystine concentration	Fluid intake (L/24 h)	0.5–1	2	3–4	4	4–5
Increase in cystine solubility in urine	Urine alkalization (pH 7.5) Potassium citrate (mmol/24 h) (divided in 2–3 doses/day)	–	10–20	10–60	10–60	40–90
	Tiopronin[a] (mg/kg BW • 24 h)[2]	–	–	20–40	20–40	45–60

[a]Alternative treatment with tiopronin (α-mercaptopropionylglycine) produces adducts with cysteine that increase the solubility of cysteine 50-fold

Dangers/Pitfalls

A high nocturnal fluid intake will delay the achievement of urinary control in childhood. At least two nocturnal fluid intakes are recommended, but good compliance is difficult to achieve in adolescents and adults.

Potassium citrate administration is recommended in 3 doses (one-quarter of the daily dose in the morning, one-quarter at lunchtime, and half in the evening), which is recommended to monitor urine pH (>7.5) with indicator paper three times per day to adjust treatment.

The incidence of adverse effects is similar for both agents (tiopronin (fever, proteinuria, and hyperlipidemia), D-PENICILLAMINE (rash, fever, immune-complex-mediated glomerulonephritis, leucopenia, thrombocytopenia, and taste loss)) but is slightly lower with tiopronin. Monitoring of liver enzymes, complete blood cell count, and urinary protein excretion should be performed regularly while patients are on tiopronin or D-penicillamine therapy.

6.3 *Hartnup disorder*. Oral nicotinamide treatment (50–100 mg/day) may prevent or resolve photodermatitis in Hartnup disorder.

6.4 *Lysinuric protein intolerance*

Objective	Strategy	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Prevention of hyperammonemia	Low-protein diet (upper limit; g/kg BW •24 h)	–	–	0.8–1.5	0.8–1.5	0.5–0.8
	Citrulline supplementation (mg/kg BW • 24 h) (in 4 divided doses)	–	–	100	100	100
	Sodium benzoate (mg/kg BW • 24 h) (in 4 divided doses)	–	–	100–250	100–250	100–250
	L-Carnitine (mg/kg BW • 24 h) (in 2 or more divided doses)[a]	–	–	25–50	25–50	25–50
Additional treatments	hGH (for patients with GH deficiency)	–	–	Careful evaluation for patients with severe growth retardation and delayed bone age		–
	L-Lysine (mg/kg BW • 24 h) (in presence of marked hypolysinemia)	–	–	10–40	10–40	10–40
	Statins (to treat combined hyperlipidemia)	–	–	Standard protocols		
Severe complications	Pulmonary alveolar proteinosis (PAP)	–	Bronchoalveolar lavage in specialized center. Immunosuppressors			
	Chronic renal disease	–	–	–	Standard guidelines under the direction of specialist	
	Hemophagocytic lymphohistiocytosis	–	–	Standard guidelines under the direction of specialist		

[a]Hypocarnitinemia, which strongly correlates with renal insufficiency, low-protein diet, and the use of ammonia scavenger drugs, might present in LPI. Therefore, L-carnitine is supplemented after measurement of plasma carnitine levels (Sebastio et al. 2011)

Dangers/Pitfalls

Urinary orotic acid can be used to monitor the protein tolerance and the urea cycle functioning but is not totally reliable.

Nutritional deficiency due to the low-protein diet might require supplementation of calcium, vitamin D, iron, and zinc.

Recurrent fatal pulmonary alveolar proteinosis after heart–lung transplantation in a child highlighted that this complication of LPI is caused by factors external to the lung, most likely macrophages (Santamaria et al. 2004).

Pulmonary alveolar proteinosis (PAP) of different origins is usually treated by whole lung lavage or granulocyte–macrophage colony-stimulating factor (GM-CSF) administration. GM-CSF is a hematopoietic growth factor known to stimulate stem cells to proliferate into granulocytes or monocytes, promote differentiation of monocytes into alveolar macrophages, increase the catabolism within alveolar macrophages, and increase the innate immune potential of neutrophils. Although GM-CSF may have therapeutic advantage in certain types of PAP, it may not be suitable for treating LPI-associated PAP because of the tendency of LPI alveolar macrophages to form granulomas (Douda et al. 2009).

6.6 *Episodic ataxia due to EAAT3 defect*. Typical treatment is acetazolamide (125–1,000 mg/day) (Pessia and Hanna 2010). Acetazolamide is a carboanhydrase inhibitor and particularly effective in episodic ataxia type 2 caused by mutations in the calcium channel gene CACNA1A (Jen et al. 2007). Whether bicarbonate homeostasis is deranged in episodic ataxias is unclear.

4-Aminopyridine has been shown to be effective and patients with EA (Jen et al. 2007).

Dangers/Pitfalls

Not all cases of EA are responsive to acetazolamide.

6.7 *Hyperekplexia*. Clonazepam is used to treat HE (Zhou et al. 2002; de-Koning Tjissen and Rees 2007). Initial dose is 0.5 mg twice/day, which can be increased to 2 mg twice a day. Clonazepam modulates the $GABA_A$ receptor, making it more sensitive to GABA. $GABA_A$ receptors and glycine receptors have an overlapping distribution in the brain. Clonazepam is a muscle relaxant counteracting the muscle stiffness observed in HE.

Dangers/Pitfalls

Hyperekplexia can be misdiagnosed as seizures, but commonly used anticonvulsants are ineffective. The effectiveness of valproic acid, clobazam, and fluoxetine has been reported in a few sporadic cases of unknown genetic etiology (Zhou et al. 2002), but has not been tested in controlled studies.

6.8 *AGC1 deficiency*. Epilepsy in the unique case reported on AGC1 deficiency is treated with carbamazepine and levetiracetam.

6.9 *GC1 deficiency*. There is no treatment, even for the epilepsy associated.

Experimental Treatment

6.1 *Cystinuria*. Real-time in situ atomic force microscopy bas been used to identify cystine derivatives (L-cystine dimethylester and L-cystine methylester) that binds to the surface and reduce the growth of cystine microcrystals in vitro (Rimer et al. 2010). Proof of principle of their antilithiasic activity in vivo is yet lacking.

6.4 *Lysinuric protein intolerance*. Therapy with bisphosphonates (alendronate 10 mg/kg body weight • 24 h) has been proposed for severe osteoporosis in LPI (Gómez et al. 2006), but a standardized protocol is lacking.

6.6 *Episodic ataxia due to EAAT1 defect*. See emergency treatment.

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