

12.1 Introduction

This chapter deals with the inborn errors of the amino acids ornithine, lysine, hydroxylysine and tryptophan. Tryptophan is included in this chapter because it shares part of its catabolic pathway with that of lysine.

With the exception of glutaric aciduria type I and hyperornithinemia there is no or a very doubtful causal relationship between the biochemical abnormality and the symptoms of psychomotor/neurological impairment.

Ornithine – a non-protein amino acid – is produced from dietary or endogenous arginine by the action of arginase and in the first step of creatine synthesis by the action of glycine transaminidase. It is the substrate for several biochemical reactions. The first step of the formation of proline from ornithine is a transamination to γ -glutamylsemialdehyde, catalyzed by ornithine aminotransferase (OAT). A deficiency of this enzyme leads to autosomal recessive *hyperornithinemia* associated with gyrate atrophy of the choroid and retina (HOGA). A defective transport of ornithine across the mitochondrial membrane leads to hyperornithinemia with homocitrullinuria and hyperammonemia (see Sect. 11.8, [1]).

The main pathway of lysine degradation is via mitochondrial oxidation predominantly in liver and kidney with saccharopine as a stable intermediate. The two degradative steps of lysine:2-oxoglutarate reductase and saccharopine dehydrogenase are performed by a bifunctional protein, 2-aminoadipic semialdehyde synthase and the activities of the two components can be differently affected by mutations of the gene. Decreases in both enzymatic activities combined leads to predominant hyperlysinemia (*hyperlysinemia type I*), whereas a partial loss of lysine:2-oxoglutarate reductase activity in combination with severely reduced activity of saccharopine dehydrogenase results in saccharopinemia/-uria with less increase in lysine (*hyperlysinemia type II*). Only two patients with this pattern and enzymatic defect have been described [2–5].

Approximately thirteen cases of *2-aminoadipic aciduria* have been reported in the literature. Nine of the reported patients excreted in addition more or less significant amounts of 2-oxoadipic acid, some also 2-hydroxyadipic acid and variable amounts of glutaric acid. The latter results obviously from spontaneous decarboxylation of 2-oxoadipic acid.

2-Aminoadipic acid is formed in the degradation of lysine and hydroxylysine from 2-aminoadipic semialdehyde. It is deaminated to 2-oxoadipic acid by a mitochondrial 2-aminoadipate aminotransferase. 2-Oxoadipic acid is presumably decarboxylated to glutaryl-CoA by 2-oxoadipate dehydrogenase. 2-Oxoadipic acid is also formed in the degradation of tryptophan and transaminated by cytosolic 2-aminoadipate aminotransferase to 2-aminoadipic acid. The latter is transported into the mitochondria, back transaminated to 2-oxoadipic acid and further degraded.

If the outlined metabolic pathway is correct, *2-aminoadipic aciduria* without or with minimal 2-oxoadipic aciduria could result from a defect in mitochondrial 2-aminoadipate aminotransferase deficiency with 2-oxoadipic aciduria only originating from tryptophan. A defect in 2-oxoadipate dehydrogenase would be the cause of *2-oxoadipic aciduria* [6].

Only *tryptophanuria* due to (presumed) defects in tryptophan degradation via the kynurenine pathway is considered here. Tryptophan transport defects, renal and/or intestinal (Hartnup disorder, blue-diaper syndrome) are discussed in Sect. 13.4. The symptomatology of reported cases is caused by nicotinic acid deficiency, one of the products of the said pathway. The postulated enzymatic defects have not been confirmed by in vitro investigations [7–9].

Only four patients with presumed *kynureninase deficiency* have been described which would explain the consistent high excretion of 3-hydroxykynurenine (3OH-Kyn), xanthurenic acid (XA), kynurenic acid (KynA) and kynurenine, without anthranilic acid (AnA) and 3-hydroxyanthranilic acid (3OHAnA). This pattern is similar to that seen in vitamin B₆ deficiency but refractive to vitamin B₆ therapy [10, 11].

The first enzyme in the kynurenine pathway of tryptophan degradation, liver tryptophan pyrrolase, is inducible by tryptophan and inhibited by reduced nicotinamide adenine dinucleotide. In the case of dietary nicotinic acid deficiency the kynurenine pathway becomes important for nicotinic acid synthesis. Nicotinic acid deficiency causes pellagra. Blocks in the kynurenine pathway because of cofactor deficiencies and/or enzymatic defects result quite often in pellagra-like symptoms.

Persistent *hydroxylysinuria* has been described in only six patients, four of whom also had hydroxylysinemia. All had mental retardation and neurologic symptoms. The low turnover of the collagen amino acid hydroxylysine makes a diagnosis of hydroxylysinuria a difficult task. An enzyme defect has not been established [12, 13].

Two unrelated patients with neurological abnormalities were found to excrete hydroxylysinephosphate. A defect of vitamin B₆-dependent O-phosphohydroxylysine phosphohydrolase was suggested [14].

Glutaric aciduria due to mitochondrial glutaryl-CoA dehydrogenase deficiency is an autosomal recessively inherited disorder. The defect involves the degradation of lysine, hydroxylysine, and tryptophan and leads in most

patients to a severe neurological disease characterized predominantly by extrapyramidal movement disturbances. There are typical morphological changes of the brain. The urinary organic acid analysis typically shows glutaric and 3-hydroxyglutaric aciduria and rarely glutaconic aciduria. However, there are some observations of clinically normal persons with glutaryl-CoA dehydrogenase deficiency and glutaric/3-hydroxyglutaric aciduria and there are also some rare cases with the typical clinical course and morphological changes but without or minimal glutaric aciduria or with only a glutarate increase in cerebrospinal fluid. The severity of the clinical picture and/or of glutaric acid excretion does not correlate with the residual activity of glutaryl-CoA dehydrogenase in cultured fibroblasts or peripheral blood white cells [6, 15].

Apart from glutaric aciduria II (ETF or ETF dehydrogenase deficiency, see Sect. 14.10) a third disorder with peroxisomal glutaryl-CoA oxidase deficiency leading to glutaric aciduria has been described (glutaric aciduria III, see Chap. 24).

12.2 Nomenclature

No.	Disorder	Tissue distribution	Chromosomal localization	MIM
12.1	Ornithine-5-aminotransferase deficiency (hyperornithinemia)	Lymphocytes, fibroblasts, liver, muscle, hair roots	10q26	258870
12.2	2-Aminoadipic semialdehyde synthetase deficiency	Fibroblasts, liver, heart, kidney		
12.2a	Hyperlysinemia I		7q31.3	238700
12.2b	Hyperlysinemia II or saccharopinuria			268700
12.3	Presumed 2-aminoadipate aminotransferase/2-oxoadipate dehydrogenase deficiency (2-amino-/2-oxoadipic aciduria)	Fibroblasts	Unknown	204750/ 245130
12.3a/b				
12.4	Presumed tryptophan-2,3-dioxygenase deficiency (tryptophanuria)	Liver	4q31	276100/ 600627
12.5	Presumed kynureninase deficiency (hydroxykynureninuria)	Liver	Unknown	236800
12.6	Presumed hydroxylysinekinase deficiency (hydroxylysinuria)	–	Unknown	236900
12.7	Glutaryl-CoA dehydrogenase deficiency (glutaric aciduria I)	Leukocytes, fibroblasts, liver, kidney	19p13.2	231670

12.3 Metabolic Pathways

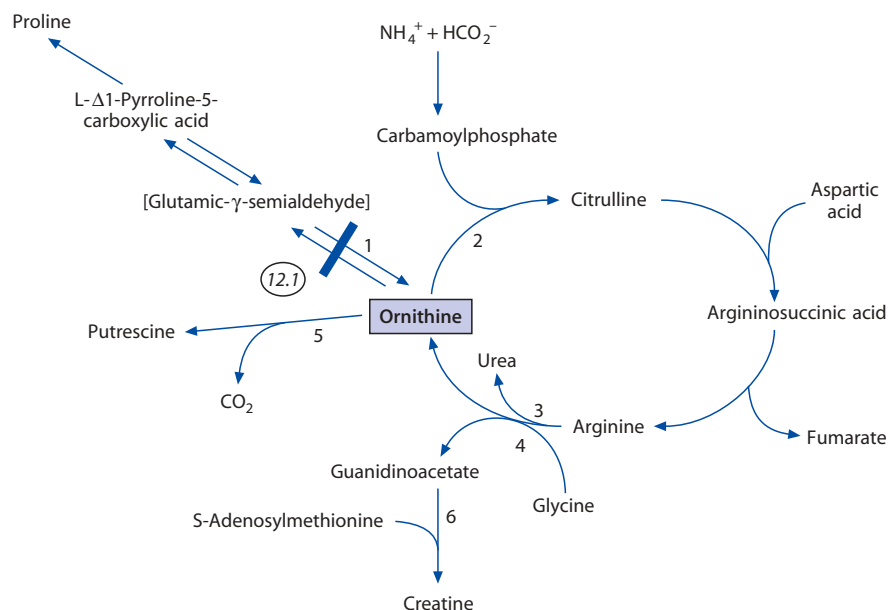


Fig. 12.1. Position of ornithine in the urea cycle and in biosynthetic pathways for proline, polyamines and creatine. 12.1, defect in hyperornithinemia; 1, ornithine-5-aminotransferase (mitochondrial); 2, ornithine transcarbamylase (mitochondrial); 3, arginase (cytosolic); 4, glycine transaminidase; 5, ornithine decarboxylase (cytosolic); 6, guanidinoacetate methyltransferase (cytosolic)

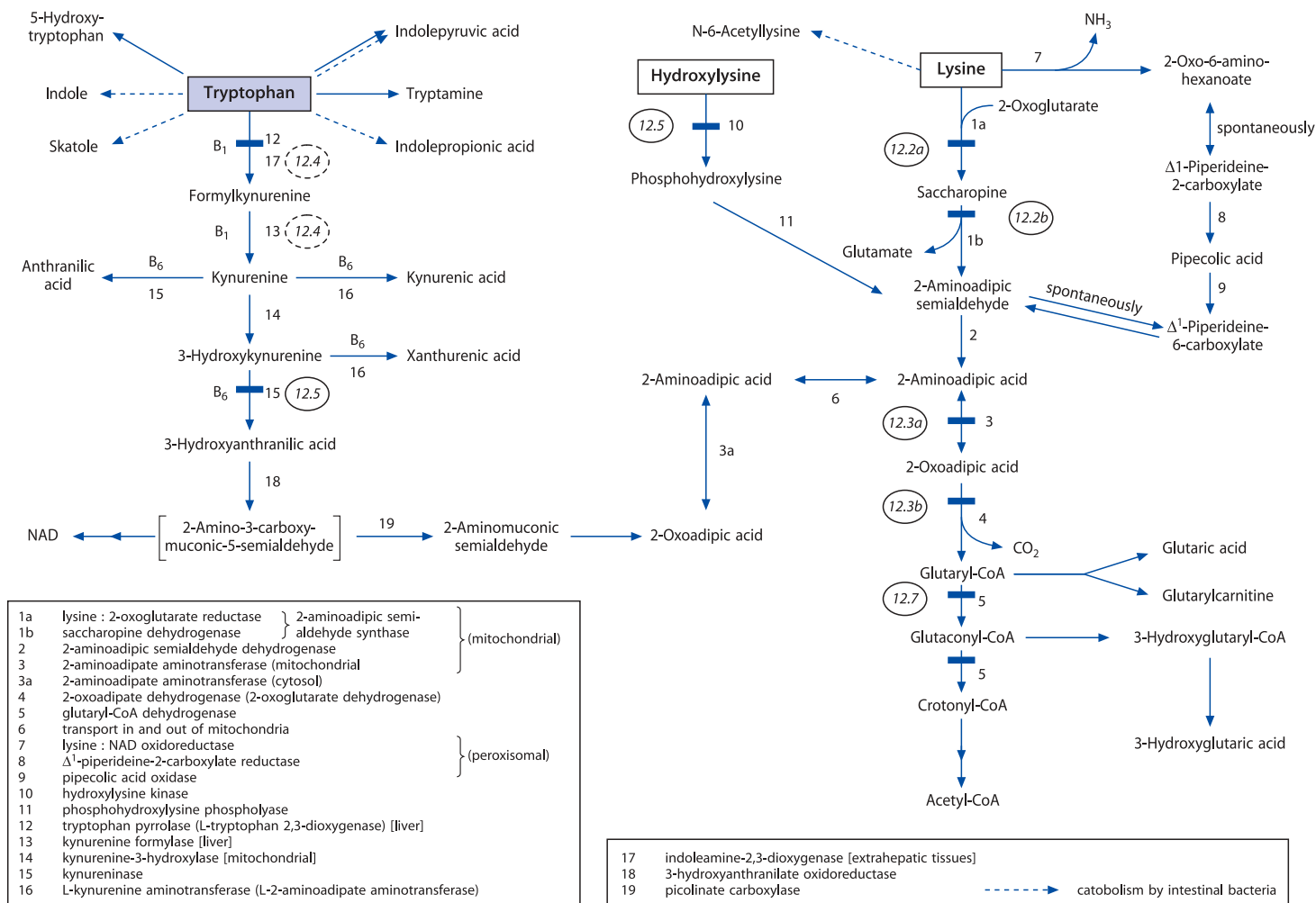


Fig. 12.2. Degradation pathways of tryptophan, lysine, and hydroxylysine and their interrelationship. *12.2a/b*, Defect in hyperlysinemia I and hyperlysinemia II (saccharopinuria); *12.3a*, presumed defect in 2-aminoadipic aciduria; *12.3b*, presumed defect in 2-oxoadipic aciduria; *12.4*, presumed defect in tryptophanuria; *12.5*, presumed defect in hydroxykynureninuria; *12.6*, presumed defect in hydroxylysinuria; *12.7*, defect in glutaric aciduria I; *NAD*, nicotinamide adenine dinucleotide

12.4 Signs and Symptoms

Table 12.1. Ornithine-6-aminotransferase deficiency (hyperornithinemia) (more than 150 patients known)

System	Symptoms/markers	Childhood	Adolescence	Adulthood
Characteristic clinical findings	Gyrate atrophy of choroid and retina	+	++	+++
Routine laboratory	Blindness			+
	Creatinine (P)			N-↓
	Creatine (P)			N-↓
	Creatinine (U)			N-↓
Special laboratory	Ornithine (P)	↑	↑	↑
	Ornithine (U)	↑	↑	↑
	Ornithine (CSF)	↑	↑	↑
	Arginine + lysine (U)	↑	↑	↑
	3-Amino-2-piperidone (U)	↑	↑	↑
	Extinct electroretinogram		+	+
	EEG ^a	±	±	±
	EMG	±	±	±
	MRS (muscle)	↓	↓	↓
	Phosphocreatine/phosphate			
	Phosphocreatine/ATP			
	Muscle electronmicroscopy ^b	±	±	±
	Liver electronmicroscopy ^c		±	±
CNS	Cortical atrophy ^d	±	±	±
	Posterior subcapsular cataract		±	±
	Hemeralopia	+	+	+
	Myopia	+	+	+
	Proximal muscle weakness	±	±	±

^a Abnormal in 50% of patients.

^b Tubular aggregates in type 2 fibers, abnormal mitochondria.

^c Abnormal mitochondria.

^d In 60% of patients.

Table 12.2a. 2-Aminoadipic semialdehyde synthase deficiency (hyperlysinemia I) (less than 20 patients known)

System	Signs/symptoms	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Characteristic clinical findings ^a						
Special laboratory	Lysine (P)	↑	↑	↑	↑	↑
	Lysine (U)	↑	↑	↑	↑	↑
	“Cystinuria” pattern (U)	+	±	±	±	±
	Saccharopine (U)	N-↑	N-↑	N-↑	N-↑	N-↑
CNS	Motor a/o mental retardation		±	±	±	±
	Seizures		±	±	±	
	Muscular hypotonia		±	±	±	
	Spasticity/hyperreflexia		±	±	±	±
	Ataxia			±	±	
	Subluxation of lens ^b			±		
	Spherophakia ^c			±		
	Laxity of ligaments			±	±	
Other	Small stature			±	±	±

^a Possibly none; ~50% of probands are asymptomatic.^b One patient.^c One patient.**Table 12.2b.** 2-Aminoadipic semialdehyde synthase deficiency (hyperlysinemia II or saccharopinuria) (3 patients known)

System	Signs/symptoms	Adulthood
Characteristic clinical findings ^a		
Special laboratory	Saccharopine (U)	↑
	Saccharopine (P)	↑
	Saccharopine (CSF)	↑
	Lysine (P)	↑
	Lysine (U)	↑
	Lysine (CSF)	↑
	Citrulline (U)	↑
	Citrulline (P)	↑
	EEG abnormal	+
	Mental retardation	+
CNS		
Other	Small stature	+

^a One patient investigated because of mental retardation.

Table 12.3 a+b. 2-Aminoadipate aminotransferase/2-oxoadipate dehydrogenase deficiency (2-amino/2-oxoadipic aciduria) (13 patients known)

System	Signs/symptoms	Neonatal	Infancy	Childhood	Adolescence
Characteristic clinical findings ^a ?					
Routine laboratory	Metabolic acidosis	±			
Special laboratory	2-Aminoadipate (P)	↑	↑	↑	↑
	2-Aminoadipate (U)	↑	↑	↑	↑
	2-Oxoadipate (S)		↑		
	2-Oxoadipate (U)		↑	↑	↑
	2-Hydroxyadipate		↑	↑	
CNS	Psychomotor retardation		±	±	±
	Seizures		±	±	
	Muscular hypotonia	±	±		
	Ataxia			±	
	Clumsiness			±	
	Dysphagia			±	
	Speech disturbance			±	
	Dysmorphism		±		
	Failure to thrive		±		
	Oedema hand/feet	±	±		
Hematological	Cardiac anomaly		±		
	B cell defect		±		

^a Possibly none.**Table 12.4.** Tryptophan-2,3-dioxygenase deficiency (tryptophanuria) (4 patients known)

System	Signs/symptoms	Infancy	Childhood	Adulthood
Characteristic clinical findings	Photosensitivity ^a	+	+	
	Ataxia ^a	+	+	
Special laboratory	Tryptophan (U) ^b		↑	↑
	Tryptophan (P) ^b		↑	↑
	Indoluria		±	+
	Kynurenine (U)		N↓	N↓
	Mental retardation	+	+	+
CNS	Motor retardation	+	+	
	Spasticity		±	
	Speech disturbance		+	+
	Impaired vision			+
	Impaired hearing			±
	Small stature		+	

^a Two of four patients; seasonal rashes.^b One patient only after tryptophan load.

Table 12.5. Kynureninase deficiency (hydroxykynureninuria) (4 patients known)

System	Signs/symptoms	Neonatal	Infancy	Childhood	Adolescence
Characteristic clinical findings	Stomatitis/gingivitis	+	+	+	
	Mental retardation			+	+
Routine laboratory	Ferric chloride positive (U)		+	+	+
Special laboratory	3-Hydroxykynurenine (U)		↑	↑	
	Kynurenic acid (U)		↑	↑	
	Xanthurenic acid (U)		↑	↑	
GI	Hepatosplenomegaly ^a	+			
	Diarrhea ^a	+			
	Colitis ^a	+			
CNS	Conductive deafness			±	
	Headache			±	
Dermatological	Photosensitivity ^b			±	
Hematological	Hemolytic anemia ^a	+			

^a One patient in neonatal period.^b Same patient without added nicotinic acid.**Table 12.6.** Hydroxylysinekinase deficiency (hydroxylysinuria) (6 patients known)

System	Signs/symptoms	Infancy	Childhood	Adolescence
Characteristic clinical findings	Mental retardation	+	+	+
Special laboratory	Free hydroxylysine (U)	↑	↑	↑
	Free hydroxylysine (P)		N-↑	N-↑
	Total hydroxylysine (U)	N	N	N
CNS	Seizures	±	±	±
	Myoclonus	±	±	±
	Speech disturbance		±	±
	Hyperactivity	±	±	

Table 12.7. Glutaryl-CoA dehydrogenase deficiency (glutaric aciduria I) (more than 200 patients known)

System	Signs/symptoms	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Characteristic clinical findings	Dystonia		±	±	±	±
	Macrocephaly	±	+	±		
	Episodic encephalopathy		+	+	±	±
Routine laboratory	Metabolic acidosis ^a					
	Hypoglycemia ^a					
	Ketosis ^a					
Special laboratory	Hepatopathy ^a					
	Glutarate (U) ^b	↑	↑	↑	↑	↑
	Glutarate (S)	N-↑	N-↑	N-↑	N-↑	N-↑
	Glutarate (CSF)	↑	↑	↑	↑	↑
	Glutaryl carnitine (U)	↑	↑	↑	↑	↑
	3-Hydroxyglutarate (U)	N-↑	N-↑	N-↑	N-↑	N-↑
	Glutaconate (U)	N-↑	N-↑	N-↑	N-↑	N-↑
	CCT/NMR abnormal ^c		+	+	+	+
CNS ^d	Muscular hypotonia	±	±			
	Spasticity		±	±	±	
	Mental retardation		±	±	±	±
	Ataxia			±	±	±
	Dysarthria			±	±	±
	Abasia			±	±	±
	Astasia			±	±	±
	Choreoathetosis			±	±	±

^a Concurrent with encephalopathic episodes.^b Can be normal in exceptional cases (!).^c Frontotemporal atrophy; atrophy of the N. caudatus and putamen; hypodensities of white matter; ventriculomegaly.^d Asymptomatic cases have been described.

12.5 Reference Values

	Orni- thine	3-Ami- no-2- piperi- done	Gluta- myl-or- nithine	Lysine	Saccha- ropine	Homo- argi- nine	Pipecolic acid		2-Ami- noadi- pate	2-Oxo- adipate	2-Hy- droxy- adipate	Gluta- rate	3-Hy- droxy- gluta- rate	Gluta- conate	Glutar- ylcarni- tine
							New- born	Adult							
(P) $\mu\text{mol/l}$	75 \pm 5			71–151	n.d.	n.d.	12 \pm 5.6	2.1 \pm 1.6	<5			0.4–0.9			
(U) mmol/mol creat		trace	trace	12–65	n.d.	n.d.		0.004 \pm 0.002	<17	n.d.	n.d.	0.6–4	<10	n.d.	n.d.
(CSF) $\mu\text{mol/l}$	6–11			18 \pm 6	n.d.	n.d.		<1.5				0.38–0.87			
	Trypto- phan	Indole- acetate	Indole- lactate	Indole- pyruvate	5-Hy- droxyin- doleace- tate	3-Hy- droxyky- nurenine	Xanthu- renic acid	Kynurenic acid	3-Hy- droxyky- nurenine- sulfate	Acetyl-3- hydroxy- kynure- nine	Acetylky- nurenine	Con- jugated xanthu- renic acid			
(P) $\mu\text{mol/l}$	51–81														
(U) $\mu\text{mol/24 h}$	59–184	8–23	7–22	<3	10–30	4.5–26.6	20–59	8–470	n.d.	n.d.	n.d.	n.d.			
	Free hydroxylysine				Total hydroxylysine										
(P) $\mu\text{mol/l}$															
(U) mmol/mol creat															

12.6 Pathological Values

Disorder	Ornithine (P) μmol/l		Ornithine (CSF) μmol/l		Ornithine (U) μmol/l/24 h		3-Amino-2-piperidone (U) mmol/mol creat		Glutamylornithine (U) mmol/mol creat	
12.1 Ornithine amino-transferase def.	400–1340		210–314		940–6000		85–145		1.5–2.7	

Disorder	Lysine (P) μmol/l	Lysine (CSF) μmol/l	Lysine (U) mmol/mol creat	Saccharo-pine (P) μmol/l	Saccharo-pine (CSF) μmol/l	Saccharo-pine (U) mmol/mol creat	Homoargi-nine (CSF) μmol/l	Homoargi-nine (U) mmol/mol creat	Pipecolic acid (U) mmol/mol creat	2-Amino-adipate (U) mmol/mol creat
12.2a Hyper- lysinemia I	Up to 1700	Up to 270	1240–14400	0–85	13–85	0–79	3	Up to 86	3–6	0–162
12.2b Hyper- lysinemia II	608	222	Up to 1000	24.5	250	>2000		↑	↑	↑

Disorder	Lysine (P) μmol/l	2-Amino- noadi- pate (P) μmol/l	2-Amino- adipate (U) mmol/mol creat	2-Oxoadi- pate (U) mmol/mol creat	2-Hy- droxyadi- pate (U) mmol/mol creat	Glutarate (S) μmol/l	Glutarate (U) mmol/mol creat	Glutarate (CSF) μmol/l	3-Hy- droxy- glutarate (U) mmol/mol creat	Glutaco- nate (U) mmol/mol creat	Glutaryl carnitine (U) mmol/mol creat	Saccharo- pine (U) mmol/mol creat
12.3 2-Amino/2-oxo-ad- ipic aciduria	N-310	0–118	45–1910	0–360	0–180		0–53					
12.7 Glutaric aciduria I			Up to 625			N-225	N-5000	1.6–38	N-530	0–592	92	Up to 265

Disorder	Trypto- phan (P) μmol/l	Trypto- phan (U) μmol/ 24 h	Indoleace- tate ^a (U) μmol/24 h	Indolelac- tate ^a (U) μmol/24 h	Indolepy- ruvate ^a (U) μmol/24 h	5-Hydroxy- indoleace- tate (U) μmol/24 h	3-Hydroxy- kynurenine (U) μmol/24 h	Xanthu- renic acid (U) μmol/24 h	Kynurenic acid (U) μmol/24 h	3-Hydroxykynurenine sulfate, acetyl-3-hy- droxykynurenine, acetylkynurenine, con- jugated xanthurenic acid
12.4 Trypto- phanuria	Up to 530	Up to 70× normal	Up to 850	Up to 830	Up to 250	Up to 340				
12.5 Hy- droxy- kynu- reninuria							Up to 980	Up to 1100	Up to 1200	present

^a In the 2 patients described in ref. [8].

Disorder	Hydroxylysine (P) μmol/l	Free hydroxylysine (U) mmol/mol creat	Total hydroxylysine (U) mmol/mol creat
12.6 Hydroxy- lysinuria	Up to 37	Up to 62	13–68

12.7 Loading Tests

Loading tests are unnecessary in the diagnosis of hyperornithinemia, the hyperlysinemias, 2-amino-/2-oxoadipic aciduria and hydroxylysinuria provided careful analysis of metabolites is performed.

■ Disorder 12.4: Tryptophanuria

L-Tryptophan (40 or 100 mg/kg bw orally) given to patients with insignificant hypertryptophanemia in the basic state resulted in

- a delayed return of plasma tryptophan to baseline
- a higher increase of tryptophan excretion over baseline (two to eight times vs < 2 times in controls)
- no increase in formylkynurenine excretion (present in controls)
- a small increase in kynurenine excretion (< 2 times vs 15 to 30 times in controls).

■ Disorder 12.5: Hydroxykynureninuria

L-Tryptophan (100 mg/kg bw orally) given to one patient and 5 control children resulted in the following metabolite excretions in μmol/24 h:

	Patient		Controls	
	Before	After	Before	After
Xanthurenic acid	644	3059	4–15	18–71
3-Hydroxykynurenine	982	2361	11–16	7–76
Kynurenine	73	746	6–21	9–83
Kynurenic acid	31	483	2–19	30–90
Acetylkynurenine	23	459	6–22	8–32
Indican	190	147	175–669	167–760
N ¹ -Methylnicotinamide	15.2	15.7		

■ Disorder 12.7: Glutaric Aciduria I

L-Carnitine (500 mg TID or 100 mg/kg bw) resulted in a normalization of pre-dose low total serum carnitine, a further increase of the fractional

clearance rates for free and esterified carnitines and the appearance of glutarylcarnitine in suspect cases with normal baseline glutarate excretion.

12.8 Diagnostic Flow Charts

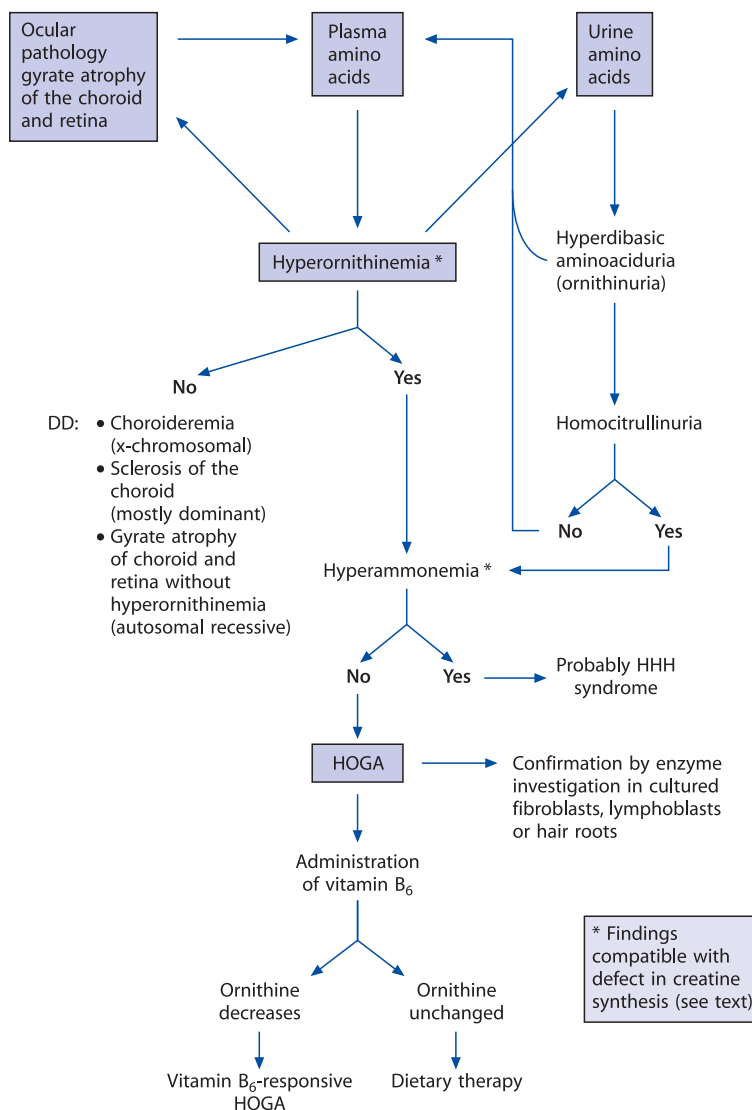


Fig. 12.3. Diagnostic policy for hyperornithinemia (HOGA): starting points are clinical symptoms and/or the finding of hyperornithinemia/-ornithinuria. *Findings compatible with defect in creatine synthesis; DD, differential diagnosis

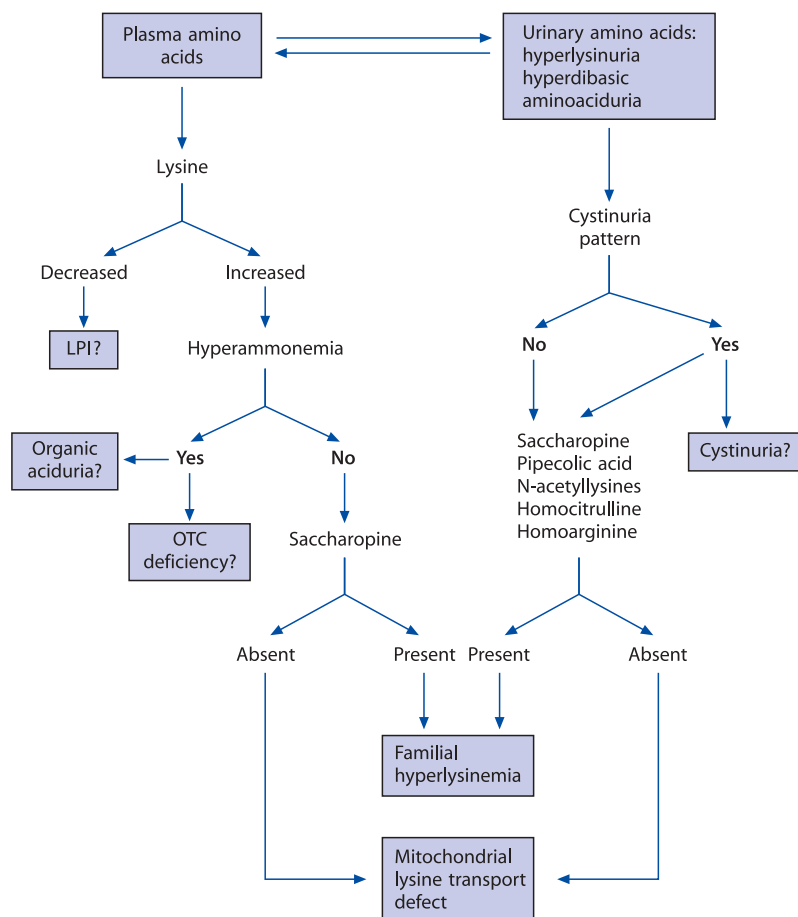


Fig. 12.4. Diagnostic policy for the hyperlysinemias: starting points are plasma and/or urine amino acid analysis

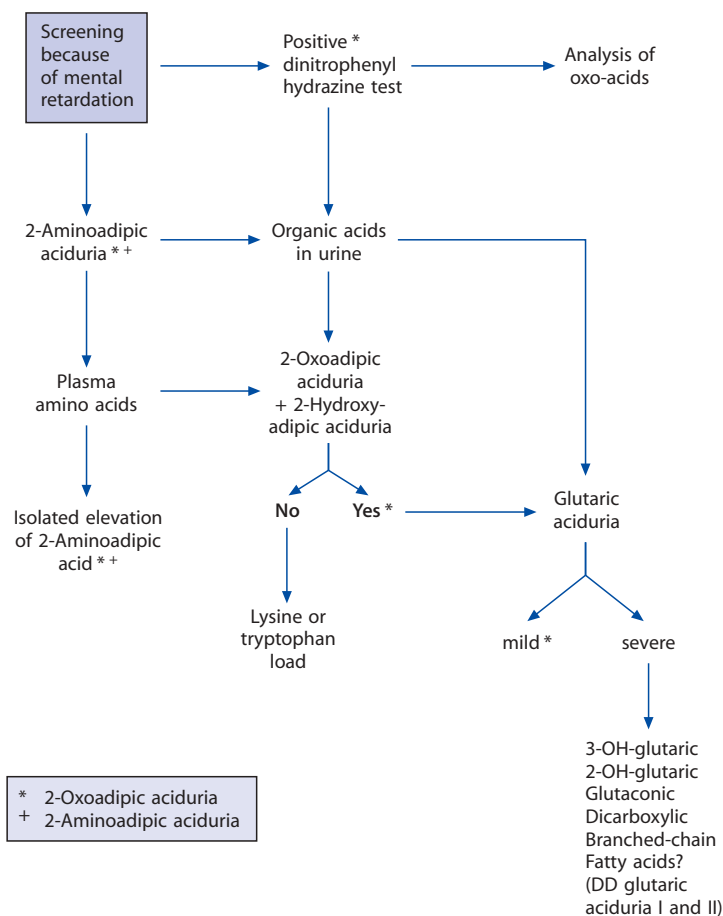


Fig. 12.5. Diagnostic policy for 2-amino-/2-oxoadipic aciduria: starting points are unspecific clinical symptoms, (e.g. mental retardation) and/or a positive 2,4-dinitrophenylhydrazine test. *, 2-oxoadipic aciduria; +, 2-aminoadipic aciduria; DD, differential diagnosis

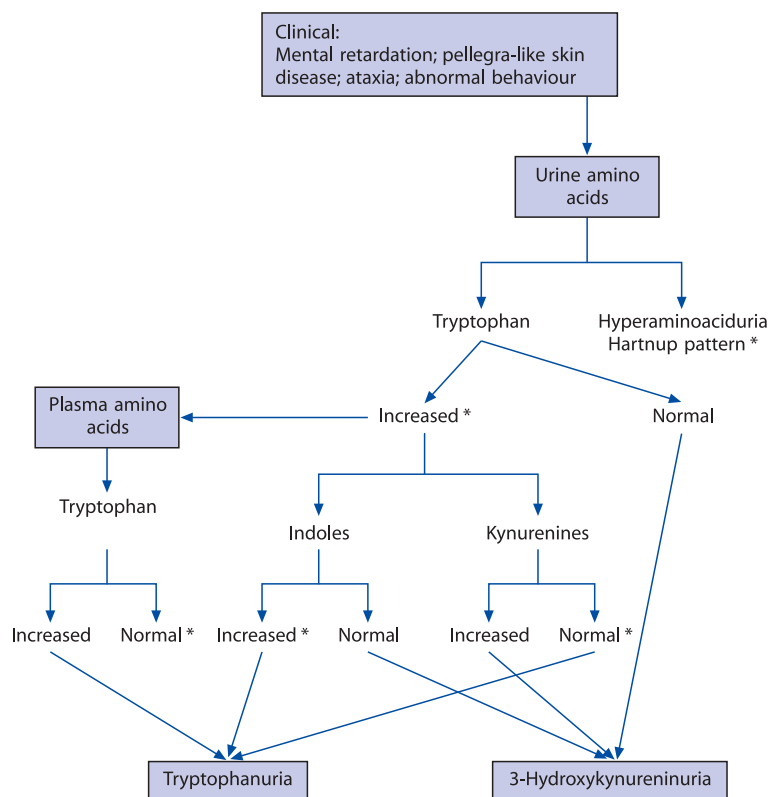


Fig. 12.6. Diagnostic policy for disorders of tryptophan metabolism: starting points are clinical symptoms, e.g. mental retardation, ataxia, photosensitive skin rashes. *These findings support the diagnosis of Hartnup disorder

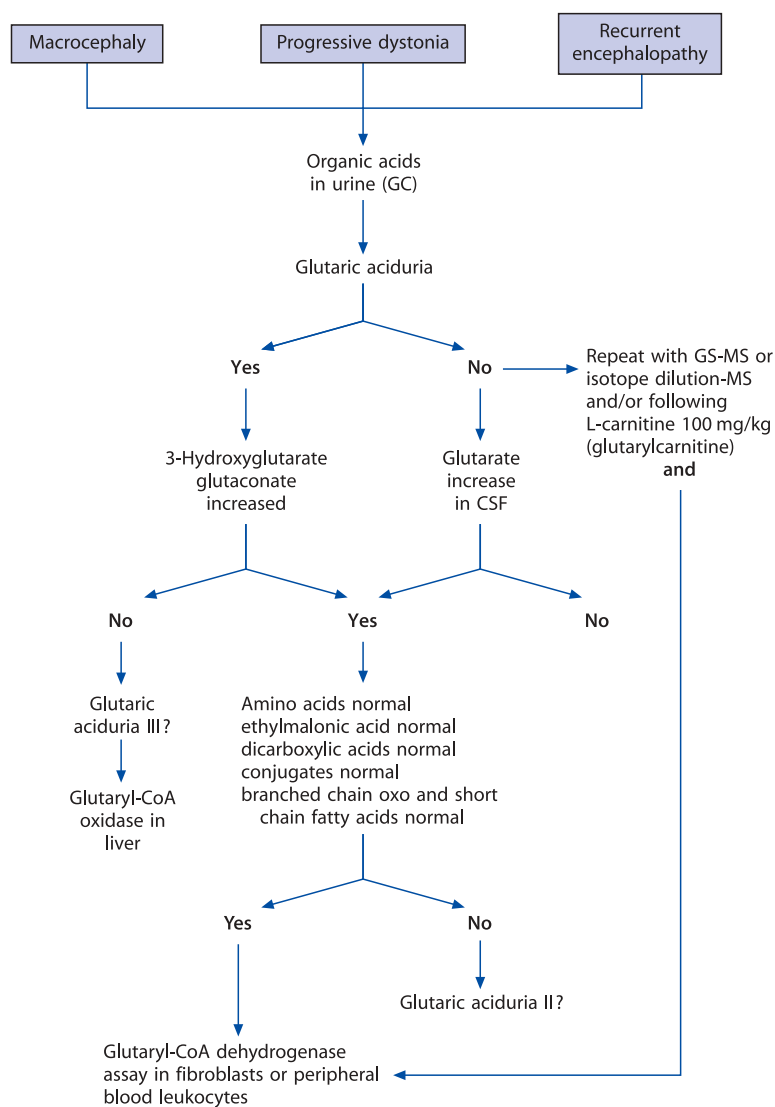


Fig. 12.7. Diagnostic policy for glutaric aciduria I: starting points are the clinical symptoms macrocephaly, progressive dystonia and/or recurrent encephalopathy. GC, gas chromatography; GCMS, gas chromatography/mass spectrometry

12.9 Specimen Collection

Dis-order	Test	Preconditions	Material	Handling	Pitfalls
12.1 12.2 12.3 12.4 12.6 12.7	Quantitative amino acids	Fasting (if possible) Normal diet	Plasma Serum CSF Urine	Keep frozen (-20°)	Insufficient sensitivity or resolution for 2-amino-adipic acid, hydroxylysine, saccharopine
12.3 12.4 12.7	Organic acids (GC/MS/NMR)	None	Plasma Serum CSF Urine	Keep frozen (-20°)	
12.4	Tryptophan	None	Plasma	Keep frozen (-20°) and dark	Losses due to inappropriate deproteinization
12.5	Tryptophan metabolites (fluorescent) (TLC/HPLC)		Urine		
12.7	Carnitine and carnitine esters (GC/MS)	None/after carnitine administration	Serum Urine	Keep frozen (-20°)	
12.1 12.2 12.3 12.7	Enzyme activity/degradation studies	None	Fibroblasts	RT	
12.1 12.7	Enzyme activity	None	Leukocytes/lymphoblasts from heparinized blood	Frozen (-20°)	
12.1 (12.2) 12.4 12.5 (12.7)	Enzyme activity	None	Liver	Frozen (-20°)	
12.1	Enzyme activity	None	Hair roots	RT	
12.1	Histology, histochemistry Electronmicroscopy	None	Muscle biopsy	Frozen (-20°) Fixed in glutaraldehyde	

RT, room temperature.

12.10 Prenatal Diagnosis

Disorder	Material	Timing, trimester
12.1	Amniocytes	II
	Chorionic villi	I
12.7	Chorionic villi	I
	Amniocytes	II
	Amniotic fluid	

12.11 DNA Analysis

Disorder	Tissue	Methodology
12.1 Ornithine-5-aminotransferase deficiency	Cultured fibroblasts	RFLP PCR SSCP Southern blot Sequencing
12.2a 2-Aminoadipic semialdehyde synthase deficiency	Cultured fibroblasts	PCR Sequencing Northern blot
12.7 Glutaryl-CoA dehydrogenase deficiency	Cultured fibroblasts	RFLP PCR SSCP Sequencing

RFLP, restriction fragment length polymorphism; PCR, polymerase chain reaction; SSCP, single-strand conformation polymorphism.

12.12 Initial Treatment

■ Disorder 12.1: Hyperornithinemia

Some patients react favorably to vitamin B₆ (40 to 200 mg/day). In cases which are not vitamin B₆ responsive dietary protein restriction is indicated. Creatine supplementation does improve muscle histology.

■ Disorders 12.2: Hyperlysinemias

A benefit from protein restriction has not been proven.

■ Disorders 12.4/12.5: Tryptophanuria/3-Hydroxykynureninuria

Because of potentially deficient formation of nicotinamide symptomatic patients should be supplemented with nicotinamide.

■ Disorder 12.7: Glutaric Aciduria I

Dietetic treatment with protein (and eventually lysine and tryptophan) restriction usually decreases glutarate excretion. However, in symptomatic patients there is poor correlation to clinical amelioration. Diet plus carnitine and riboflavin (cofactor precursor for glutaryl-CoA dehydrogenase) seems to be most effective in (pre)symptomatic and mildly affected patients.

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