

3.1 Introduction

This chapter deals with 5 clinically relevant defects of the amino acids GABA, glycine, serine and proline.

Two genetic diseases due to a defect in brain γ -aminobutyric acid (4-aminobutyric acid; GABA) metabolism have been reported: GABA transaminase deficiency and succinic semialdehyde dehydrogenase deficiency. Both are catabolic defects. Pyridoxine-responsive convulsions have traditionally been ascribed to a deficiency of the GABA synthesizing enzyme glutamic acid decarboxylase. However, recently linkage of this disease to the two genes for glutamic acid decarboxylase was excluded in six patients [1, 2]. Therefore, pyridoxine-responsive convulsions will no longer be included in this chapter, although it remains possible that some patients with this presentation have glutamic acid decarboxylase deficiency [3].

In the serine-glycine metabolism, two disorders are discussed: 3-phosphoglycerate dehydrogenase deficiency, a synthesis defect and nonketotic hyperglycinemia, a catabolic defect.

Several disorders are known in the proline pathway but only δ^1 -pyrroline 5-carboxylate synthase deficiency is clinically relevant; hyperprolinemia type 1 and type 2, hydroxyprolinemia and iminoglycinuria are most probably “non-diseases”.

■ GABA Transaminase (GT) Deficiency

This autosomal recessive disease has been reported in only one family (brother and sister) [4]. The patients showed a pronounced axial hypotonia and generalized convulsions. From birth they had severe feeding problems, which often necessitated nasogastric tube feeding. Evolution was further characterized by lethargy and an extremely pronounced psychomotor retardation. A paradoxical acceleration of the growth velocity was noted and found to be due to hypersecretion of growth hormone. A huge increase of free GABA was found in the CSF. Homocarnosine and β -alanine were also increased but to a lesser extent. This was associated with a decreased GABA transaminase activity in liver and lymphocytes. The same enzyme

defect was assumed to be present in the brain. No efficient treatment was found for this disease, which had a rapidly fatal evolution in both children.

■ Succinic Semialdehyde Dehydrogenase (SSD) Deficiency

This autosomal recessive disorder has been documented in at least 150 patients with some 60 of them reported [5]. The clinical presentation varies from mild to severe. It comprises a wide range of neurological abnormalities, mainly psychomotor retardation, hypotonia, ataxia, hyporeflexia, convulsions, aggressive behavior, hyperkinesia, choreoathetosis and nystagmus. γ -Hydroxybutyric acid (4-OH-butyric acid), a neuropharmacologically active compound, accumulates in urine, plasma and particularly in CSF. There is a tendency in some patients towards clinical and biochemical amelioration with age. Diagnosis is made by organic acid analysis of urine, plasma and/or CSF. The enzyme deficiency can be demonstrated in lymphocytes and other tissues.

Treatment has been attempted with γ -vinyl GABA (vigabatrin, Sabril®), an inhibitor of GABA transaminase, in order to reduce substrate accumulation [6]. This resulted in a decrease of CSF γ -hydroxybutyric acid levels and improvement of cerebellar signs in a majority of patients.

■ Glycine Cleavage System (GCS) Deficiency (Nonketotic Hyperglycinemia)

The disorder is clinically divided into two groups: neonatal severe and variant late-onset. Neonatal patients are seen more commonly. Patients present in the first days of life with lethargy progressing to coma, hypotonia, seizures, hypoventilation, and apnea requiring artificial ventilation. The EEG shows a burst-suppression pattern. In the second to third week spontaneous respiration resumes. These patients develop severe mental retardation, a severe myoclonic and generalized seizure disorder, pronounced axial hypotonia, and spastic quadriplegia. Some patients have hypoplasia of the corpus callosum, cortical malformations, or hydrocephalus with posterior fossa cystic malformation. Patients who do not die in the neonatal period live for several years. Variant patients tend to have late onset in infancy or childhood. They present with seizures, moderate mental retardation, ataxia, hyperactivity and/or chorea. Plasma glycine and CSF glycine are elevated, with increased CSF: plasma glycine ratio. Confirmation relies on measurement of GCS enzyme activity in liver or in lymphoblasts. Prenatal diagnosis is possible by measuring GCS activity in chorionic villi. A few common mutations have been identified. There is no effective treatment so far [7].

■ 3-Phosphoglycerate Dehydrogenase (PGDH) Deficiency

Nine patients have been identified and seven of them reported [8, 9]. All suffered from congenital microcephaly, severe psychomotor retardation, usually present in the first months of life, and intractable seizures. Other neurological abnormalities included hyperexcitability, spastic tetraparesis and nystagmus. In some patients adducted thumbs, cataract, hypogonadism, megaloblastic anemia and thrombocytopenia were present [10–12]. Cranial MRI may show a profound white matter attenuation and hypomyelination [13]. The biochemical diagnosis is based on the detection of low concentrations of serine (and to a lesser degree of glycine) in fasting plasma and CSF, and low 5-methyltetrahydrofolate in CSF. The diagnosis can be confirmed by enzyme analysis in cultured skin fibroblasts and by mutation analysis [14]. In contrast to most amino acid disorders which are catabolic, this is a defect in amino acid synthesis and hence treatable by serine (and glycine) supplementation.

■ Δ^1 -Pyrroline-5-Carboxylate Synthase (PCS) Deficiency

This disease has been described in two siblings with progressive neurodegeneration, joint laxity, skin hyperelasticity and bilateral subcapsular cataracts. Besides hyperprolinemia, the metabolic phenotype consisted of hyperammonemia, hypoornithinemia, hypocitrullinemia, and hypoargininemia because proline as well as ornithine synthesis are impaired [15]. The disease is expected to be treatable with dietary proline and ornithine supplements.

3.2 Nomenclature

No.	Disorder	Tissue distribution	Chromosomal localization	MIM
3.1	GABA transaminase (GT) deficiency	Brain, liver, lymphocytes, lymphoblasts, not in fibroblasts	6p13.3	137150
3.2	Succinic semialdehyde dehydrogenase (SSD) deficiency	Brain, liver, kidney, lymphocytes, lymphoblasts, fibroblasts	6p22	271980
3.3	Glycine cleavage system (GCS) deficiency (non-ketotic hyperglycinemia)	Liver, lymphoblasts		
	a. P (pyridoxal phosphate containing) protein		9p22	238300
	b. H (lipoid acid containing) protein		–	238330
	c. T (tetrahydrofolate requiring) protein		3p21.1–21.2	238310
3.4	3-Phosphoglycerate dehydrogenase (PGDH) deficiency	Fibroblasts, liver	1q12	601815
3.5	Δ^1 -Pyrroline-5-carboxylate (P5CS) synthase deficiency	Fibroblasts (mRNA)	10q24.3	138250
3.6	Proline oxidase deficiency (Hyperprolinemia type 1)	Liver, kidney, brain	10p	239500
3.7	Δ^1 -Pyrroline-5-carboxylate (P5CDH) dehydrogenase deficiency (Hyperprolinemia type 2)	Liver, kidney, brain, leukocytes, fibroblasts		239510
3.8	Prolidase deficiency	Erythrocytes, leukocytes, fibroblasts	19p13.2	170100
3.9	Hydroxyproline oxidase deficiency	Liver		237000
3.10	Sarcosine dehydrogenase deficiency	Liver		268900
3.11	Iminoglycinuria	Renal tubule and intestine		242600

3.3 Metabolic Pathways

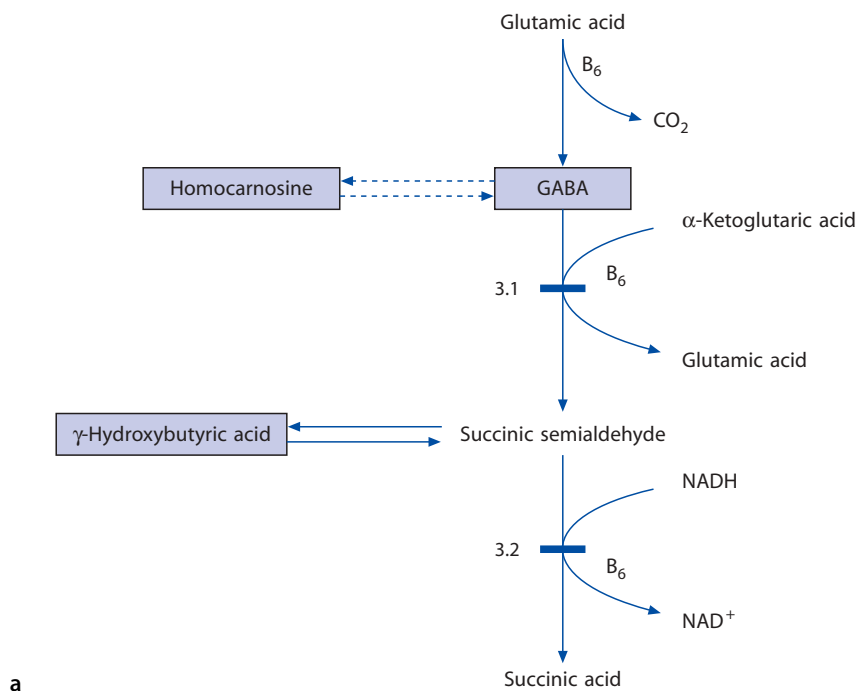


Fig. 3.1. Pathways of (a) GABA, (b) glycine and serine, (c) proline metabolism, and (d) hydroxyproline. 3.1, GABA transaminase (GT); 3.2, succinic semialdehyde dehydrogenase (SSD); 3.3, glycine cleavage system (GCS); 3.4, 3-phosphoglycerate dehydrogenase (PGDH); 3.5, Δ^1 -pyrroline-5-carboxylate synthase (P5CS); 3.6, Proline oxidase; 3.7, Δ^1 -Pyrroline-5-carboxylate (P5CDH) dehydrogenase; 3.8, prolidase; 3.9, Hydroxyproline oxidase; 3.10, Sarcosine dehydrogenase; B₆, pyridoxine coenzyme; THF, tetrahydrofolate; P5-C, Δ^1 -pyrroline 5-carboxylate

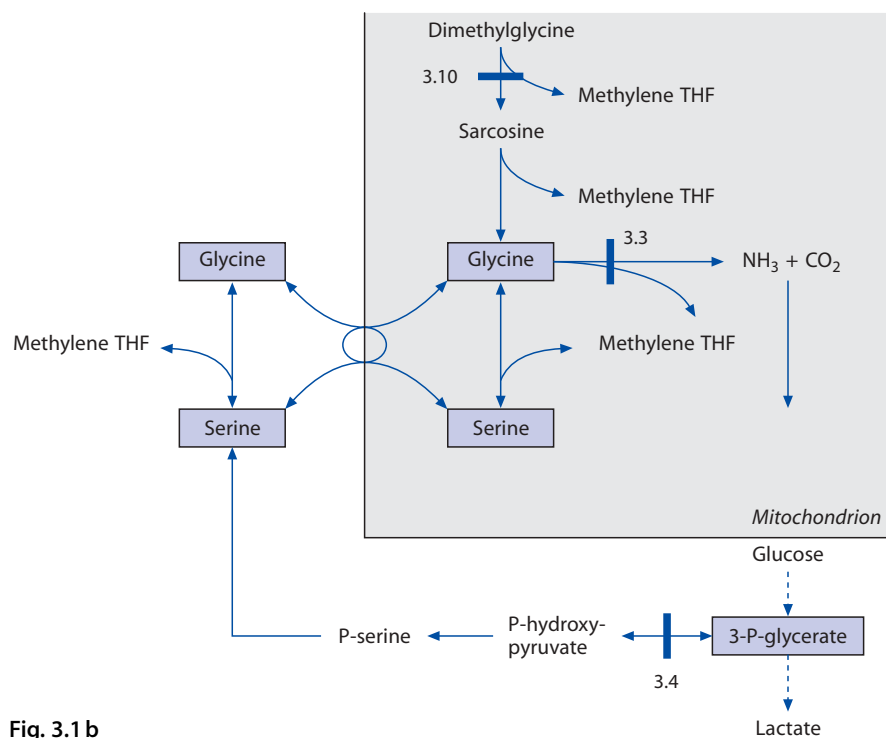


Fig. 3.1 b

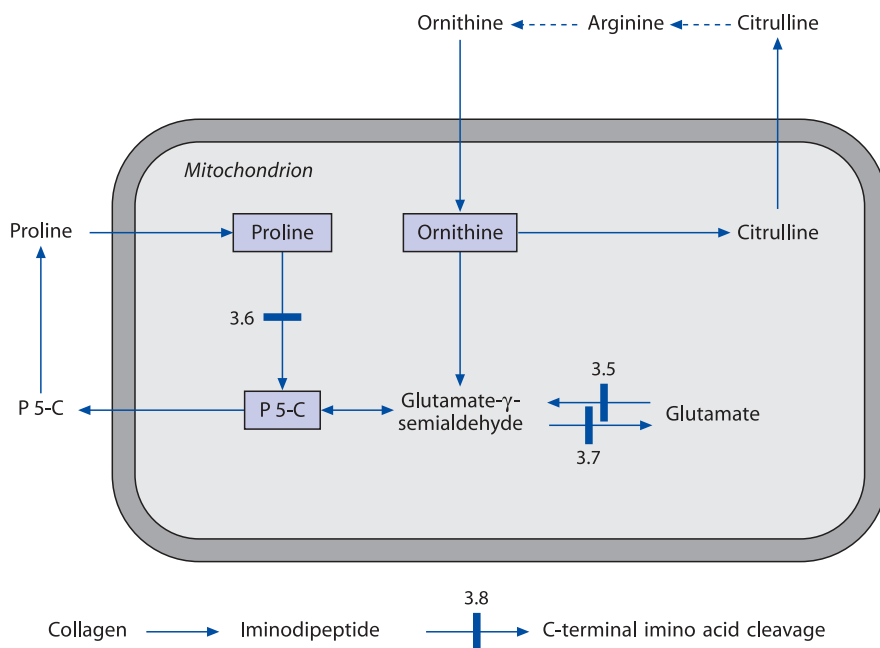


Fig. 3.1 c

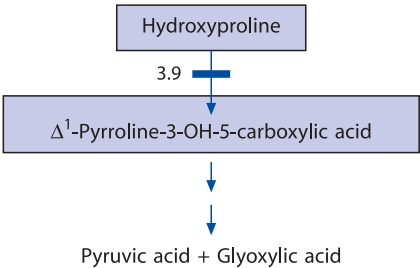


Fig. 3.1 d

3.4 Signs and Symptoms

Table 3.1. GABA transaminase (GT) deficiency [n = 2]

System	Symptoms/markers	Neonatal	Infancy	Childhood
Characteristic clinical findings	Growth acceleration	+	+	+
Special laboratory	GABA (P)	↑	↑	↑
	GABA (CSF)	↑	↑	↑
	Homocarnosine (CSF)	↑	↑	↑
CNS	Convulsions	+	+	+
	Mental retardation	++	++	++
	Lethargy	++	++	++
	Axial hypotonia	++	++	++
	Hyperreflexia	+	±	
GI	Anorexia	+	+	+
	Vomiting	+	+	+

Table 3.2. Succinic semialdehyde dehydrogenase (SSD) deficiency [n = 150]

System	Symptoms/markers	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Characteristic clinical findings	Mental retardation	+	+	+	+	+
	Ataxia	+	+	±	±	±
Special laboratory	γ-Hydroxybutyric acid (U, P, CSF)	↑	↑	↑	↑	↑
CNS	Delayed speech development			±	±	±
	Hypotonia	±	±	±	±	±
	Hyporeflexia	±	±	±	±	±
	Convulsions	±	±	±	±	±
	Aggressive behaviour	±	±	±	±	±
	Hyperkinesia	±	±	±		
	Choreoathetosis	±	±	±	±	±
	Nystagmus				±	±

Table 3.3. Glycine cleavage system (GCS) deficiency (nonketotic hyperglycinemia) [n > 100]

System	Symptoms/markers	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Characteristic clinical findings	Convulsions	+	+	+	+	+
	Muscular hypotonia	+	+			
	Spasticity	+	+	+	+	+
	Apnea	+				
	Lethargy or coma	+				
Special laboratory	Mental retardation		+	+	+	+
	EEG	+	+	+	+	+
	Glycine (P)	↑	↑	↑	↑	↑
	Glycine (U)	↑	↑	↑	↑	↑
	Glycine (CSF)	↑↑	↑	↑	↑	↑
	Glycine ratio (CSF: P)	↑↑	↑	↑	↑	↑

Table 3.4. 3-Phosphoglycerate dehydrogenase (3-PGDH) deficiency [n=9]

System	Symptoms/markers	Neonatal	Infancy	Childhood
Characteristic clinical findings	Congenital microcephaly	+	+	+
Routine laboratory	Megaloblastic anemia		+/-	+/-
	Thrombocytopenia		+/-	+/-
Special laboratory	Serine (fasting plasma)	↓	↓	↓
	Serine (CSF)	↓↓	↓↓	↓↓
	Glycine (fasting plasma)	n-↓	n-↓	n-↓
	Glycine (CSF)	n-↓	n-↓	n-↓
	5-MTHF (CSF)	↓	↓	↓
CNS	White matter attenuation (MRI)	-	+	+
	Intractable seizures	+	+	+
	Severe mental retardation	-	+	+
	Spastic tetraplegia	-	+	+
	Nystagmus	-	+	+
	Adducted thumbs	+/-	+/-	+/-
Eyes	Cataract	+/-	+/-	+/-
Genitourinary system	Hypogonadism	+/-	+/-	+/-

Table 3.5. Δ^1 -Pyrroline-5-carboxylate synthase (P5CS) deficiency [n=2]

System	Symptoms/markers	Neonatal	Infancy	Childhood
Characteristic clinical findings	Bilateral cataract	+	+	+
	Joint hyperlaxity	+	+	+
	Skin hyperelasticity	+	+	+
Routine laboratory	Ammonia (BL)	↑	↑	↑
Special laboratory	Proline (P)	↓	↓	↓
	Ornithine (P)	↓	↓	↓
	Citrulline (P)	↓	↓	↓
	Arginine (P)	↓	↓	↓
CNS	Psychomotor retardation	+	+	+

Table 3.6. Proline oxidase deficiency (hyperprolinemia type 1)

System	Symptoms/markers	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Special laboratory	Proline (U, P)	↑	↑	↑	↑	↑
	Hydroxyproline (U)	↑	↑	↑	↑	↑
	Glycine (U)	↑	↑	↑	↑	↑

Table 3.7. Δ^1 -Pyrroline-5-carboxylate dehydrogenase deficiency (P5CDH) (hyperprolinemia type 2)

System	Symptoms/markers	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Special laboratory	Proline (U, P)	↑	↑	↑	↑	↑
	Hydroxyproline (U)	↑	↑	↑	↑	↑
	Glycine (U)	↑	↑	↑	↑	↑
	P5CS	↑	↑	↑	↑	↑

Table 3.8. Prolidase deficiency (hyperiminodipeptiduria)

System	Symptoms/markers	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Characteristic clinical findings	Leg ulceration ^a		±	+	+	+
	Mild mental retardation			+	+	+
	Frequent infections	+	+	+	+	+
	Unique face	±	±	±	±	±
Special laboratory	Iminopeptides (U)	↑	↑	↑	↑	↑
	Prolidase (RBC, WBC)	↓	↓	↓	↓	↓

^a Skin lesions appear in milder form on the face, palms, and soles (diffuse telangiectatic purpuric rash, ecchymosis, crusting erythematous dermatitis) or as severe progressive ulceration, particularly on the lower legs

Table 3.9. Hydroxyproline oxidase deficiency

System	Symptoms/markers	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Special laboratory	Hydroxyproline (U, P)	↑	↑	↑	↑	↑

Table 3.10. Sarcosine dehydrogenase deficiency

System	Symptoms/markers	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Special laboratory	Sarcosine (U, P)	↑	↑	↑	↑	↑

Table 3.11. Iminoglycinuria

System	Symptoms/markers	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Special laboratory	Glycine (U)	↑	↑	↑	↑	↑
	Proline (U)	↑	↑	↑	↑	↑
	Hydroxyproline (U)	↑	↑	↑	↑	↑

■ Reference Values

Age	Free GABA ^a (nmol/l, range)		Homocarnosine ^a (μmol/l, range)	γ-Hydroxybutyrate ^b (U, S, CSF)
<1 yr	S	120–500	n.d.	
	CSF	20–40	5.5–11.8	
>1 yr	S	120–500	n.d.	P <7.6 μmol/l
	CSF	40–150	2.5–10.6	CSF <2.6 μmol/l U <9.5 mmol/mol creatinine

^a Ion-exchange chromatography with fluorimetric detection

^b GCMS

Age	Glycine (CSF) ^a (μmol/l, range)	Serine (CSF) ^a (μmol/l, range)
<1 yr	3–10	25–70
>1 yr	3–8	20–45

^a Ion-exchange chromatography with colorimetric detection.

Age	Glycine (P) ^a (μmol/l, range)	Serine (P) ^a (μmol/l, range)	Proline (P) ^a (μmol/l, range)	Sarcosine (P)
<1 m	230–450	100–400	110–420	Traces
>1 m	100–350	70–200	50–350	

^a Ion-exchange chromatography with colorimetric detection

Peptide-bound Pro (U) (μmol/day)	Peptide-bound Hyp (U) (μmol/day)	Pro/Hyp (peptide-bound)
430–1250	250–725	1.21–2.35

3.5 Pathological Values/Differential Diagnosis

Disorder	Free GABA (S) (nmol/l)	Free GABA (CSF) (nmol/l)	Homocarnosine (CSF) (μmol/l)	γ-Hydroxybutyrate (U, P, CSF)	
3.1 GT def.	1600–2900 1 patient	1800–4800 1 patient	23.4–36.8 1 patient		
3.2 SSD def.		n↑	n↑	P CSF U	96–1500 μmol/l 245–3100 μmol/l 94–7600 mmol/ mol creatinine

3.3 GCS def.	Glycine (P) (μmol/l) (range; median)	Glycine (CSF) (μmol/l) (range, median)	CSF:P glycine ratio (range; median)
Neonatal severe age <2 w (n = 34)	261–2127, 1016	47–566, 154	0.08–0.38, 0.16
age >2 w (n = 15)	347–2000, 697	50–240, 87	0.06–0.23, 0.18
Variant late-onset (n = 18)	324–1000, 631	24–163, 41	0.04–0.26, 0.06

Disorder	Serine (μmol/l)	Glycine (μmol/l)	Proline (μmol/l)	Hydroxyproline (μmol/l)	Pro/Hyp	Sarcosine (μmol/l)
3.4 PGDH def.						
Plasma	28–64	128–190				
CSF	6–8	1–4				
3.5 P5CS def.			107 ± 49 (pt 1) (P) 91 ± 18 (pt 2) (P) 500–2000 (P) >2000 (P)			
3.6 Proline oxidase def.						
3.7 P5CDH def.						
3.8 Prolidase def.			5700–27000 (U)	1400–2100 (U) ^a 140–500 (P)	8.93–25.2 (U) ^a	
3.9 Hyp oxidase def.						
3.10 Sarcosine DH def.						53–760 (P)

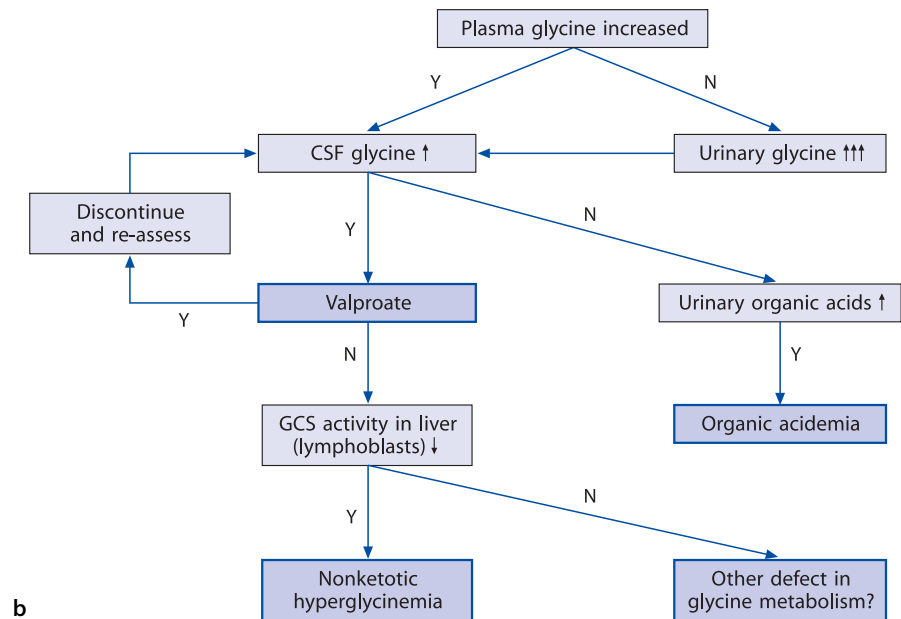
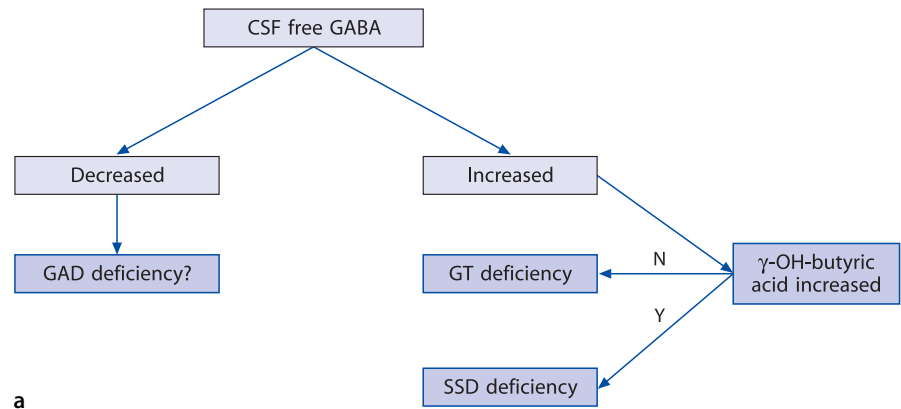
^a Peptide-bound (μmol/day)

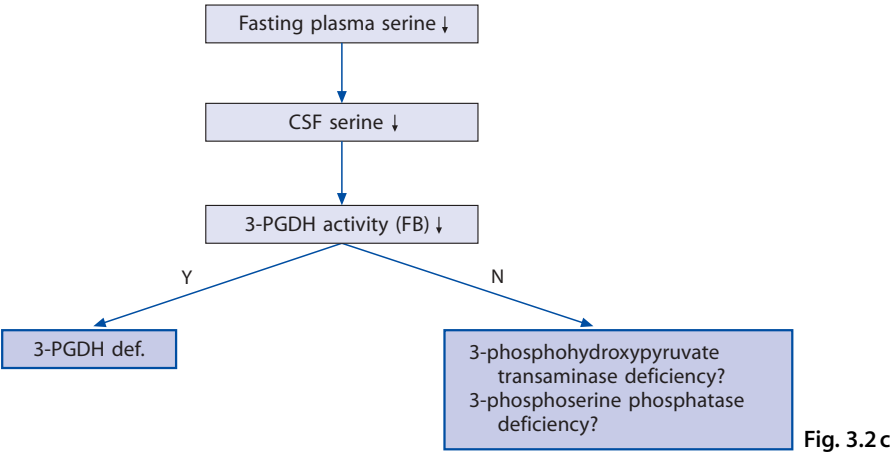
3.6 Loading Tests

No loading tests need to be performed.

3.7 Diagnostic Flow Chart

Fig. 3.2. Diagnostic flow charts (a) GABA metabolism defects; (b) hyperglycinemia; and (c) fasting hyposerinemia. GT, GABA transaminase; SSD, succinic semialdehyde dehydrogenase; GAD, glutamic acid decarboxylase





3.8 Specimen Collection

Test	Preconditions	Material	Handling	Pitfalls
Free GABA Homocarnosine	No extra B6	CSF	Freeze immediately (preferably -70 °C)	Vigabatrin (Sabril®) medication: free GABA and homocarnosine ↑
γ-Hydroxybutyric acid GT	No vigabatrin (Sabril®)	U, S, CSF LYM, lymphoblasts	Frozen (-20 °C) Frozen (-80 °C)	Vigabatrin (Sabril®) medication: GT activity ↓
SSD		FB, LYM, lymphoblasts	Frozen (-80 °C)	
Glycine	Free diet	P, CSF	Frozen (-20 °C)	
GCS	Before medication	Liver (lymphoblasts)	Frozen (-80 °C)	
Serine	Fasting	P CSF	Frozen (-20 °C) Frozen (-20 °C)	
5-MTHF		CSF	Frozen (-80 °C)	
PGDH		FB	Frozen (-80 °C)	
Proline, hydroxyproline, sarcosine		P	Frozen (-20 °C)	
Peptide-bound Pro/Hyp		U (24 h)	Frozen (-20 °C)	
Prolidase	no medic.	RBC	Frozen (-80 °C)	

3.9 Prenatal Diagnosis

Disorder	Tissue	Timing (trimester)	Pitfalls
3.1	CV	I	1% risk of false negative result [16]
	Liver	II	
3.2	AF, amniocytes, liver	II	
3.3	CV	I	
3.4	CV	I	
	Amniocytes	II	
3.8	CV	I	
	Amniocytes	II	

3.10 DNA Analysis

Disorder		Material	Methodology
3.6	Proline oxidase deficiency	F, WBC	RT-PCR; genomic amplification and sequencing
3.8	Prolidase deficiency	F, WBC	RT-PCR; genomic amplification and sequencing
3.9	Hydroxyproline oxidase deficiency	F, WBC	RT-PCR; genomic amplification and sequencing
3.10	Sarcosine dehydrogenase deficiency	F, WBC	RT-PCR; genomic amplification and sequencing
3.11	Iminoglycinuria	F, WBC	RT-PCR; genomic amplification and sequencing

3.11 Initial Treatment

- 3.1 No treatment is available.
- 3.2 When there is a suspicion of SSD deficiency, a trial with vigabatrin (Sabril) 50–100 mg/kg/day (divided in two daily doses) is indicated. In most patients this treatment improves cerebellar signs.
- 3.3 a) Neonatal severe NKH
Reduction of glycine through treatment with high-dose sodium benzoate (250–750 mg/kg/d) and moderate protein restriction, aiming at therapeutic plasma glycine levels (100–250 μ M) and benzoate (<2000 μ M), improves respiration, alertness, and decreases seizures [19]. However development of severe mental retardation and spasticity is not prevented. Reduction in seizures is reported which N-methyl-D-aspartate receptor antagonists, in keeping with the excitotoxicity hypothesis of excess glycine in the brain [7]. Apnea usually resolves in

the second to third week of life, so there is limited opportunity for withdrawal of support, should that be the parents wish [7].

b) Variant late-onset NKH

Glycine reduction through individually tailored benzoate and moderate protein restriction (1.5–2 g/kg/d) usually stops seizures, and improves neurologic and mental function. Severe hyperactivity has been reported to respond to amitryptiline in addition to benzoate treatment [20, 21].

- 3.4 In 3-PGDH, L-serine should be administered orally in high doses to obtain persistent clinical and biochemical improvement. The recommended dose of L-serine is 400–600 mg/kg/day in 4–6 doses a day. If no satisfactory clinical response is obtained glycine should be added to the treatment (200–300 mg/kg/day). Treatment should start as soon as possible, because neurological outcome is much better in patients diagnosed and treated early. Patients treated after the first year of life show a decrease in seizure frequency or sometimes become free of seizures. However, no progress in psychomotor development was observed. In contrast, a girl with West syndrome, treated at the age of 10 months, not only became free of seizures, but also showed a considerable psychomotor “catch-up”. We recently attempted antenatal treatment of an affected foetus by administering L-serine to the mother during pregnancy. Although long-term follow-up is not available yet, the first results of antenatal treatment were promising; the child was born normocephalic and her psychomotor development up to 4 months was normal (de Koning et al., submitted).
- 3.5 This disease should be treatable with dietary proline and ornithine supplementation.
- 3.8 Treatment with oral ascorbate, manganese (cofactor of prolidase) and local applications of L-proline and glycine-containing ointments can improve the skin ulcers.

3.12 Summary/Comments

From two of the five clinically relevant disorders, GT deficiency and P5CS deficiency, only one family is known. Hence our knowledge about the clinical and biochemical spectrum of these diseases is very limited. SSD deficiency has a variable neurological picture. NKH is mostly a severe neurological disease with prenatal onset but the number of patients with a milder phenotype is growing. PGDH deficiency is an amino acid synthesis disorder that is overlooked when plasma amino acid analysis is performed after feeding. The results of treatment with serine (and glycine) are promising.

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