

3.1 Introduction

Only for three of the known defects in the metabolism of the amino acids GABA, glycine, serine, and proline has a more-or-less efficient treatment been reported: the GABA catabolic defect, succinic semialdehyde dehydrogenase deficiency (vigabatrin, causing substrate depletion by inhibition of GABA transaminase); the glycine catabolic defect, nonketotic hyperglycinemia (diet combined with benzoate and an *N*-methyl-*D*-aspartate, NMDA, receptor blocker); and 3-phosphoglycerate dehydrogenase deficiency (serine supplementation, in some patients to be associated with glycine supplementation).

No treatment has as yet been attempted in Δ^1 -pyrroline-5-carboxylate (P5CS) synthase deficiency; and the remaining six known defects probably have no clinical significance except for prolidase deficiency.

3.2 Nomenclature

No.	Disorder	Definitions/comment	Gene symbol	OMIM No.
3.1	GABA transaminase (GT) deficiency	Increased GABA and β -alanine in body fluids particularly in CSF	<i>ABAT</i>	137150
3.2	Succinic semialdehyde dehydrogenase (SSD) deficiency	Increased γ -hydroxybutyric acid in body fluids	<i>ALDH 5A1</i>	271980
3.3	Glycine cleavage system (GCS) deficiency (nonketotic hyperglycinemia)	Increased glycine in body fluids particularly in CSF		
	P (pyridoxal phosphate-containing) protein		<i>GCSP</i>	238300
	H (lipoid acid-containing) protein		<i>GCSH</i>	238330
	T (tetrahydrofolate-requiring) protein		<i>GCST</i>	238310
3.4	3-Phosphoglycerate dehydrogenase (PGDH) deficiency	Decreased serine (and to a variable extent glycine) in fasting plasma and in CSF	<i>PHGDH</i>	601815

No.	Disorder	Definitions/comment	Gene symbol	OMIM No.
3.5	Δ^1 -Pyrroline-5-carboxylate synthase (P5CS) deficiency	Decreased proline, ornithine, citrulline, and arginine in plasma	<i>PYCS</i>	138250
3.6	Proline oxidase deficiency (hyperprolinemia type 1)	Increased proline in body fluids	<i>PRODH</i>	239500
3.7	Δ^1 -Pyrroline-5-carboxylate dehydrogenase (P5CDH) deficiency (hyperprolinemia type 2)	Increased proline and Δ^1 -pyrroline-5-carboxylate in body fluids	<i>P5CDH</i>	239510
3.8	Prolidase deficiency	Increase of iminopeptides in urine	<i>PEPD</i>	170100
3.9	Hydroxyproline oxidase deficiency	Increase of hydroxyproline in body fluids		237000
3.10	Sarcosine dehydrogenase deficiency	Increase of sarcosine in body fluids	<i>SARDH</i>	268900
3.11	Iminoglycinuria	Increase of glycine, proline and hydroxyproline in urine		242600

3.3 Treatment

■ 3.2 Succinic semialdehyde dehydrogenase deficiency

Vigabatrin, 50–100 mg/kg per day (divided into two daily doses) (Jaeken et al. 1989). This therapy has shown inconsistent results and may have serious side-effects (see below). The associated epilepsy may be controlled by this drug; however, in this condition worsening of epilepsy has also been reported.

■ 3.3 Glycine cleavage system deficiency (nonketotic hyperglycinemia)

Two clinical presentations are observed, the severe neonatal form and a late-onset form (Hamosh and Johnston 2001). In the severe neonatal form, symptoms occur in the 1st days of life, with hypotonia, seizures, coma, and apnea requiring artificial ventilation. Some patients have structural abnormalities of the brain.

Whether treatment of the biochemical abnormalities should be initiated needs to be discussed in detail with the parents, because this condition has a very poor prognosis, with 30% of patients dying early despite intensive care treatment. Those who survive the neonatal period show no psychomotor development and usually live not longer than a few years (Hamosh and Johnston 2001). Treatment is aimed at reducing seizure frequency with moderate protein restriction (1.5–2 g/kg BW per day), in combination with sodium benzoate (250–750 mg/kg BW per day), aiming to normalize plasma glycine levels (100–250 μ M) with plasma benzoate levels below 2000 μ M. Folinic acid should be administered (15 mg/day).

If control of seizures is insufficient, an NMDA receptor antagonist should be added (such as dextromethorphan, 3.5–22.5 mg/kg BW per day). Great individual differences occur in dextromethorphan metabolism, and this should be taken into account when using dextromethorphan. Biochemical correction and reduction in seizure frequency does not prevent severe psychomotor retardation and spastic tetraplegia. Spontaneous respiration and reduction of apneas usually occurs after 2–3 weeks and should not be interpreted as success of the treatment or a good prognostic sign.

For patients with late-onset forms and psychomotor retardation, abnormal behavior, seizures, or a movement disorder, the same treatment regimen as in the neonatal form can be applied. In these forms, other NMDA receptor antagonists than dextromethorphan have been used with success (Wiltshire et al. 2000)

■ 3.4 *Phosphoglycerate dehydrogenase deficiency*

3-Phosphoglycerate dehydrogenase deficiency is a severe disorder affecting the central nervous system. Patients present with congenital microcephaly, severe psychomotor retardation, and seizures. The seizures show a poor response to antiepileptic drugs. Treatment with amino acids is primarily aimed at control of seizures and improvement of general well-being and growth. Even for patients diagnosed after the 1st year of life, seizure control can be very satisfactory with amino acid therapy, but has not resulted in significant improvement of psychomotor development (de Koning et al. 2002). For patients diagnosed in the 1st year of life, some amelioration of psychomotor development has been reported, and this underlines the need for early diagnosis and treatment. Fetal amino acid therapy for 3-phosphoglycerate dehydrogenase deficiency is discussed in the section Alternative Therapies/Experimental Trials.

Treatment consists of oral L-serine supplementation (400–650 mg/kg BW per day in 3 doses/day) aiming at normalization of CSF L-serine levels. If seizures persist glycine should be added (up to 200 mg/kg BW per day in 3 doses). Alterations of CSF amino acid composition have been reported at L-serine dosages above 650 mg/kg BW per day combined with glycine. For this reason 650 mg/kg BW per day seems a safe upper limit until additional data becomes available.

Dangers/Pitfalls

1. The most frequent side-effect of vigabatrin is visual field defects, which occur in about 30% of patients after several months to years and seem to be irreversible.
2. Accidental overdosing of sodium benzoate has been reported and causes vomiting, acidosis, and decreased consciousness (up to coma). Thus whenever doses of sodium benzoate > 350 mg/kg BW per day are employed or there is an unexpected decrease in consciousness, serum benzoate levels should be checked (should be below 2000 μ M).
3. CSF amino acid analysis is the preferred diagnostic method and plasma can only be used for diagnosis after an overnight fast. The diagnosis of 3-phosphoglycerate dehydrogenase deficiency can be missed on non-fasting plasma samples. Amino acids are well tolerated and in only one patient, aged 2 months, was serine therapy (500 mg/kg BW per day) associated with acoustic startles and myoclonias. Lowering the dose (400 mg/kg BW per day) resulted in cessation of myoclonias, but did not prevent the patient from developing seizures on this lower dose of L-serine. Lowering L-serine has been associated with the onset of seizures in one patient (Hausler et al. 2001), and cessation of L-serine during an episode of gastroenteritis also resulted in the reappearance of seizures (Pineda et al. 2000). In two patients, including the patient who received fetal treatment, severe dental caries occurred, which, according to the parents, was related to the use of amino acids.

3.4 Alternative Therapies/Experimental Trials

■ 3.2 Succinic semialdehyde dehydrogenase deficiency

Gamma-hydroxybutyric acid receptor antagonists have been shown to lead to significant lifespan extension in SSD-deficient mice (Gupta et al. 2002).

● 3.4 3-Phosphoglycerate dehydrogenase deficiency

Fetal treatment of this disorder has been attempted in one case. The mother of an affected fetus was treated with L-serine during pregnancy from 27 weeks onwards. The child, aged 3 years, shows a normal psychomotor development and head growth. Giving L-serine before 20 weeks of pregnancy is not recommended, because of lack of data on possible adverse affects of L-serine on the fetus (de Koning et al. 2004).

3.5 Follow-up/Monitoring

■ 3.2 Succinic semialdehyde dehydrogenase deficiency

- Clinical monitoring: 3–6 monthly

■ 3.3 Glycine cleavage system deficiency

- Clinical monitoring: 1–3 monthly
- Biochemical monitoring: plasma glycine (aim at control range) and benzoate (aim at levels below 2,000 μM): 1–3 monthly

■ 3.4 3-Phosphoglycerate dehydrogenase deficiency

- Clinical monitoring: 3–6 monthly
- Biochemical monitoring: CSF amino acids, according to clinical condition, but should be more frequent in infants than in older children. Monitoring L-serine therapy on fasted plasma samples is difficult in newborns and infants given the frequency of meals and the possible interference with dietary serine. One needs to realise that in the 1st year of life serine concentrations in CSF are higher than in later years (Gerrits et al. 1989) and treatment should aim at these higher concentrations. No adverse effects of amino acid therapy on internal organs were documented up to now, but some caution is warranted regarding kidney function because of the large amounts of amino acid ingested (de Koning et al. 2000).

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