Disorders of Glycine, Serine, GABA, and Proline Metabolism

5

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Summary

In addition to the role as components of protein synthesis, several amino acids have other functions in the brain such as building blocks of other brain molecules or a role in neurotransmission. Disorders in catabolism of glycine and of proline are known. The disorders of the synthesis of serine and proline cause severe abnormalities. Serine is required for the synthesis of white matter compounds such as specialized lipids, and its deficiency results in severe hypomyelination. Proline is required for the synthesis of connective tissue proteins, and its deficiency results in laxity of skin and joints. Early treatment of synthetic defects such as serine has shown promise to avoid severe symptoms. Disturbance of the neurotransmitter roles of GABA, glycine, and 4-hydroxybutyric acid results in severe neurological symptoms. The pathophysiology of these disorders is complex, as has been shown in the mouse model of 4-hydroxybutyric aciduria. In most disorders, diagnostic studies rely on careful measurement of metabolites using age-appropriate reference ranges, followed by molecular analysis.

5.1 Glycine Disorder

Nonketotic hyperglycinemia (glycine encephalopathy). The primary disorder of glycine is a deficiency of the main catabolic enzyme, the glycine cleavage enzyme. Glycine is part of many biochemical pathways, but deficiency of the glycine cleavage enzyme removes the main catabolic breakdown of glycine resulting in increased levels of glycine. The disorder is known as nonketotic hyperglycinemia (NKH) or glycine encephalopathy. All forms of the disorder are characterized by cerebral dysfunction.

The glycine cleavage enzyme breaks glycine down into carbon dioxide and ammonia, and a methyl group is transferred to tetrahydrofolate creating methylene-tetrahydrofolate (Fig. 5.1). The enzyme consists of four subunits: the P-protein (pyridoxal-containing subunit), the H-protein (hydrogen carrier protein), the T-protein (tetrahydrofolate-requiring protein), and the

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N. Blau et al. (eds.), *Physician's Guide to the Diagnosis, Treatment, and Follow-Up of Inherited Metabolic Diseases*,
DOI 10.1007/978-3-642-40337-8_5, © Springer-Verlag Berlin Heidelberg 2014

L-protein (lipoamide dehydrogenase protein). The P-protein requires pyridoxal-phosphate, and disorders that affect the availability of pyridoxal-phosphate (such as *PNPO*) result in secondary deficiency of the enzyme activity. The H-protein is lipoylated and disorders in the biogenesis of the lipoylation result in variant forms of nonketotic hyperglycinemia.

Typical nonketotic hyperglycinemia (NKH) can be divided into three main clinical presentations based on the severity of the condition. The most severe form is classic, severe NKH. Patients with residual activity, but presenting in the first year of life, have attenuated NKH. Patients presenting later than 1 year of age usually have mild NKH. The primary difference is related to outcome and is based on the amount of residual activity of the particular mutation (Dinopoulos et al. 2005; Hennermann et al. 2012). Signs and symptoms of NKH are listed in Table 5.1.

Patients with NKH most often present neonatally in the first week of life (Hennermann et al. 2012). They develop lethargy, fail to feed, and progress to coma with frequent hiccupping and seizures. They have severe hypotonia. They often have a burst suppression pattern on EEG. These patients spontaneously recover from respiratory failure and regain spontaneous breathing within the first 3 weeks of life. Patients presenting during infancy have hypotonia, lethargy, and seizures (spasms or myoclonic seizures) with either multifocal epilepsy or hypsarrhythmia on EEG.

Patients with *severe NKH* develop spasticity in the first 6 months of life. They develop progressively therapy-resistant seizures, requiring multiple anticonvulsants. They lose any developmental skills with only spontaneous smiling maintained. Most require tube feeding.

Patients with *attenuated NKH* have developmental delay (IQ 20–70) but still make progress (Dinopoulos et al. 2005; Hennermann et al. 2012). They may learn to sit, walk, and communicate. They have better receptive than expressive language skills and often use signing. They remain hypotonic, with chorea, hyperactivity, and intermittent ataxia. Half the patients have seizures, which are often treated with a single anticonvulsant. They can have intermittent episodes of severe lethargy and depression, which are related to increased glycine levels.

Patients with *mild NKH* have a range of learning disabilities spanning from mild mental retardation to normal intelligence. They have attention deficit hyperactivity disorder and intermittent episodes of ataxia, chorea, lethargy, and poor school performance. They usually do not have a seizure disorder.

On brain MRI almost all patients with severe NKH have diffusion restriction of the posterior limb of the internal capsule and/or the long tracts in the brain stem, which disappears in the first months. Half the patients with severe NKH have brain malformations: agenesis or severe hypoplasia of the corpus callosum, simplification of gyration, and hydrocephalus with posterior fossa malformations (Hennermann et al. 2012).

The diagnosis is made by finding elevated glycine in serum and in CSF. The CSF should be without contamination of blood or serum as demonstrated by absence of red blood cells and normal protein content (Korman and Gutman 2002). Once CSF glycine is elevated, an increased ratio of CSF/plasma glycine aids in discrimination of nonketotic from ketotic hyperglycinemia (Perry et al. 1975). Organic acidurias must be excluded. Valproate use can iatrogenically raise glycine levels including the ratio.

Diagnosis is confirmed by mutation analysis of the *GLDC* gene encoding the P-protein and the *AMT* gene encoding the T-protein (Kure et al. 2006) (Fig. 5.5). No mutations have been identified in the *GCSH* gene encoding the H-protein or in the L-protein. Up to 20 % of mutations in the *GLDC* gene are exonic deletions which must be identified by either MLPA or array CGH. Patients with mutations that confer substantial residual activity such as A802V and A389V have attenuated or mild NKH, whereas patients with two mutations without any activity (deletions, nonsense mutations, or frameshift mutations) have severe NKH. About 4 % of patients do not have mutations in these two genes. Enzyme assay is possible in liver biopsy and prenatally in uncultured chorionic villi although a small rate of false-negative diagnosis is possible.

Some patients presenting with neonatal seizures have transient elevation of glycine in the neonatal period. Other patients have been identified by newborn screening without any symptoms with very elevated glycine levels. No mutations have been found in the *GLDC* or *AMT* genes in any of these patients. This likely represents a phenocopy.

Variant forms of NKH have atypical presentations with either less or more severe neurological involvement and sometimes with leukodystrophy or pulmonary hypertension. These patients can have additional symptoms such as lactic acidosis, cardiomyopathy, or leukodystrophy. The pyruvate dehydrogenase and the 2-ketoglutarate dehydrogenase enzyme are also deficient. The genes responsible are involved in the lipoate synthesis, either in the lipoate synthase gene *LIAS* or in the synthesis of its iron-sulfur cluster such as *BOLA3, GLRX5,* and *NFU1* (Cameron et al. 2011; Navarro-Sastre et al. 2011; Mayr et al. 2011; Baker et al. 2012).

5.2 Serine Disorders

Serine is obtained from diet and is synthesized endogenously starting from the glycolytic intermediate 3-phosphoglycerate in three steps using the enzymes phosphoglycerate dehydrogenase (gene *PHGDH*), phosphoserine aminotransferase (*PSAT1*), and phosphoserine phosphatase (*PSPH*) (Fig. 5.2). Three disorders of serine biosynthesis are known affecting each of the steps in this serine biosynthetic pathway (Tabatabaie et al. 2010). Characteristic for all three disorders is the decreased biosynthesis of serine resulting in serine deficiency. Serine is an essential component of phosphatidylserine, sphingolipids, and ceramides and is necessary for myelin

development (de Koning et al. 2003). L-Serine is converted through the racemase to D-serine, which is an NMDA receptor activator. Through the serine hydroxymethyltransferase enzyme, serine is converted into glycine and provides methylene-tetrahydrofolate which is important for thymidine synthesis.

3-Phosphoglycerate dehydrogenase deficiency (PHGDH) is an autosomal recessive condition and the most frequently reported cause of serine deficiency syndrome (Table 5.2).

In the severe infantile form, it presents in the neonatal period with congenital microcephaly, intractable seizures starting shortly after birth, and severe psychomotor retardation. A wide variation of seizure types are reported including West syndrome. The EEG patterns include hypsarrhythmia, multifocal epilepsy, and Lennox-Gastaut syndrome. They develop spastic tetraparesis, with adducted thumbs, and hyperexcitability. Variable symptoms observed in some patients include cataracts, hypogonadism, megaloblastic anemia, and nystagmus. The MRI of the brain shows a striking reduction in the volume of the white matter and very delayed to absent myelination. The cerebral white matter on T2 has a higher signal intensity than the cortex, indicative of a lack of myelin. There is also cortical and subcortical atrophy. MRS shows a decreased level of *N*-acetylaspartate/creatine and increased choline/creatine in the white matter.

Rare late-onset patients with milder mutations have been reported. Two teenagers had absence seizures, moderate developmental delay, and normal head circumference. An adult patient presented with a chronic axonal sensorimotor polyneuropathy compatible with Charcot-Marie-Tooth type 2, which had started at age 8 years. He also had congenital cataracts, mild psychomotor retardation, and slight cerebellar ataxia.

Biochemically, low values of serine and of glycine are recorded in plasma after an overnight fast and in CSF, with the CSF values more reliable (Fig. 5.6). Also, 5-methyltetrahydrofolate can be low in CSF. Mutations throughout the protein have been reported, but a common mutation, p.V490M, has been reported in several families from variable ethnicities.

Phosphoserine aminotransferase deficiency (PSAT1) was reported in a single family (Hart et al. 2007) (Table 5.3). They had acquired microcephaly, intractable seizures since early infancy, and hypertonia. Brain MRI showed generalized atrophy, a hypoplastic cerebellar vermis, and poor white matter development. Serine and glycine were deficient in plasma and CSF. Diagnosis was confirmed by sequencing, as the enzyme assay was not deficient.

Phosphoserine phosphatase deficiency (PSPH) has been reported in a single patient who also had Williams syndrome (Jaeken et al. 1997) (Table 5.4). The child had growth and psychomotor retardation, but no seizures. His fasting plasma serine levels were low–normal, and his CSF serine levels were low. He was homozygous for a missense mutation that decreased the enzyme activity.

5.3 Gamma-Aminobutyric Acid (GABA) Disorders

Two disorders affect the catabolism of GABA: GABA transaminase deficiency and succinic semialdehyde dehydrogenase deficiency (Fig. 5.3).

GABA transaminase deficiency. Two families have been reported with GABA transaminase deficiency (Jaeken et al. 1984; Tsuji et al. 2010) (Table 5.5). The patients had axial hypotonia, spasticity, severe convulsions, and feeding problems necessitating tube feeding. Patients in the first family had accelerated growth and increased growth hormone secretion. In the second family, MRI showed diffusion restriction in the internal and external capsule and subcortical white matter areas (Tsuji et al. 2010). Biochemically, patients have elevation of free GABA in cerebrospinal fluid but also elevation of homocarnosine and β-alanine. Elevated GABA can be recognized on magnetic resonance spectroscopy (Tsuji et al. 2010). The enzyme activity was deficient in liver and lymphocytes, and mutations were identified in the *ABAT* gene.

Succinic semialdehyde dehydrogenase deficiency (SSADH) or 4-hydroxybutyric aciduria (Table 5.6). Patients with succinic semialdehyde dehydrogenase deficiency accumulate succinic semialdehyde derived from GABA transamination, which is converted by succinic semialdehyde reductase into 4-hydrobybutyric acid and excreted in urine. Most patients present in the first 2 years of life, and whereas 26 % of patients have problems in the neonatal period, an equal number have normal early development (Gibson et al. 1997).

These patients present with a static neurological picture of developmental delay and intellectual disability with prominent deficits in expressive language, motor delay, hypotonia, and nonprogressive ataxia, each present in more than 70 % of patients (Gibson et al 1997; Pearl et al. 2003). Neuropsychiatric symptoms are frequent and include hyperactivity, inattention, and anxiety. Sleep disorders are very common and include excessive daytime sleepiness, prolonged REM latency, and reduced REM sleep (Pearl et al. 2009). Seizures are present in 48 % of patients consisting mostly of generalized tonic-clonic and atypical absence seizures and myoclonic seizures in a minority. EEG abnormalities were noted in 26 % of patients. About 10 % of patients have a degenerative course with myoclonus and extrapyramidal movements of chorea and dystonia (Pearl et al. 2009). Neuroimaging shows increased T2 signal intensity in the globus pallidus, cerebellar dentate nucleus and brain stem, and subcortical white matter (Gibson et al. 1997; Pearl et al. 2003). There may also be cerebellar and cerebral atrophy. NMR spectroscopy is usually normal, unless special edited sequences for GABA and GABA metabolites are done, which show increases in these compounds (Pearl et al. 2003).

The diagnosis is suspected on finding 4-hydoxybutyric acid on urine organic acids analysis and quantified by stable isotope dilution assay. Other accumulating metabolites include the β-oxidation product 3,4-dihydroxybutyric acid and the condensation product 4,5-dihydroxyhexanoic acid. Secondary elevations in glycine, dicarboxylic acids, and 3-hydroxypropionic acid are sometimes seen. The CSF total and free GABA is mildly elevated, and CSF glutamine can be decreased. Some patients also excrete an increased amount of D-2-hydroxyglutaric acid formed through the hydroxyacid-oxoacid dehydrogenase enzyme. False-positive results are seen with 4-hydroxybutyric acid use as a sedative drug. Confirmation can be done by enzyme assay or molecular analysis of the *ALDH5A1* gene (Akaboshi et al. 2003).

5.4 Proline Disorders

There are three types of disorders that affect proline metabolism (Fig. 5.4). The first group of disorders affects the catabolism of proline and is characterized by excessive proline. This includes the disorders hyperprolinemia type I caused by deficiency of proline oxidase and hyperprolinemia type II caused by Δ1-pyrroline-5-carboxylate dehydrogenase deficiency. The second group of disorders is characterized by a deficiency of proline due to defects in proline synthesis. These disorders include deficiency of the first step Δ-1-pyrroline-5-carboxylate synthase (P5CS) and of the second step Δ-1-pyrroline-5-carboxylate reductase. The last group of disorders includes accumulation of proline-containing peptides. This group is exemplified by prolidase deficiency. Finally, renal transporters of proline and glycine are involved in the benign condition of iminoglycinuria.

Disorders of Proline Catabolism

Hyperprolinemia type I (Proline oxidase deficiency). Proline is catabolized by proline oxidase into Δ-1-pyrroline-5-carboxylate (P5C). This enzyme is primarily present in the liver, kidney, and brain. It has a conserved α8β8 barrel structure in which FAD and proline bind. The *PRODH* gene is located in the 22q11 region and is often involved in larger deletions of the velocardiofacial syndrome (22q11 microdeletion syndrome). A pseudogene *ψPRODH* is located 1.4 Mb telomeric on chromosome 22 and has a 13.1 kb internal deletion (exon 2–7) and contains several missense mutations, which have been transferred to the *PRODH* gene by apparent gene conversion (Bender et al. 2005).

Hyperprolinemia type I is associated with an increase in plasma proline. A continuum of plasma levels of proline ranging from the upper limit of normal to >1,500 μM have been reported. In hyperprolinemia type I, proline levels are less elevated than in hyperprolinemia type II, and in addition, there is no increase in P5C in hyperprolinemia type I in contrast to hyperprolinemia type II. There is a large variation of the serum levels of proline in the same patient. There is little transport of proline across the blood-brain barrier and brain proline levels reflect primarily endogenous synthesis and catabolism. Spinal fluid proline levels were elevated 5-fold in a hyperprolinemic patient with a known severe genotype.

A recurrent 350 kb deletion, encompassing the *PRODH* and *DGCR6* genes, mediated by flanking low copy repeats is present at a frequency of 1/250 in the general population. Many polymorphic mutations exist in the population that usually do not affect the proline oxidase activity for more than 30 % reduction in activity. Most patients with velocardiofacial syndrome are hemizygous deleted for the *PRODH* gene (Guilmate et al. 2010). A subset of these patients has increased proline levels, and in half of these patients, a second mutation in the *PRODH* gene was identified, mostly in those patients with the highest proline levels. Mutations in the *PRODH* gene have been classified into three categories based upon the effect on proline oxidase activity in vitro: type I <30 % residual activity, type II >30 and <70 % residual activity, and type III >70 % residual activity (Bender et al. 2005). There is a weak, but clear correlation between residual activity and levels of proline and phenotype.

Some patients with hyperprolinemia have been asymptomatic giving the impression that this may be a non-disease and that the observed phenotype may be due to selection bias. This is likely the case for the originally reported renal symptoms. Multiple series of patients, however, with a neurological phenotype consisting of mild to moderate mental retardation, psychosis, and therapy-resistant epilepsy have been reported (Di Rosa et al. 2008). The phenotype seems to be most commonly seen in patients with very high serum levels of proline and the presence of severe mutations, such as a type I mutation L441P or deletions. In addition, in patients with velocardiofacial syndrome, increased proline is an independent risk factor for lower IQ, psychotic phenotype, and seizures (Raux et al. 2007) (Table 5.7).

A role of proline in the brain and particularly in the glutaminergic synapse has been documented, and a mouse model exists.

Hyperprolinemia type II is described in the chapter on pyridoxine metabolism.

Disorders of Proline Synthesis

Δ-1-Pyrroline-5-carboxylate synthase (P5CS) deficiency. The first step in proline synthesis is the synthesis of Δ1-pyrroline-5-carboxylate. Δ-1-Pyrroline-5-carboxylate synthase (P5CS) is an enzyme with a dual action. The N-terminal γ-glutamyl kinase domain catalyzes the phosphorylation of glutamate with ATP to γ-glutamylphosphate, an unstable intermediate, and the C-terminal γ-glutamylphosphate reductase domain catalyzes the subsequent reduction with NAD(P)H to

γ-glutamic semialdehyde, which is in tautomeric nonenzymatic equilibrium with Δ-1-pyrroline-5-carboxylate (P5C). P5C is then acted upon by the subsequent enzymes, ornithine aminotransferase, to produce ornithine or by Δ-1-pyrroline-5-carboxylate reductase to produce proline. P5CS has two isoforms caused by alternative splicing and differing in two amino acids on the N-terminal side. Both isoforms have P5CS enzymatic activity. A short isoform is highly active in the gut and participates in synthesis of ornithine and arginine, with feedback noncompetitive inhibition by ornithine and stimulation by *N*-acetylglutamate (Hu at al. 1999; Pérez-Arellano et al. 2010). A long isoform is present in most tissues for the synthesis of proline and is not inhibited by ornithine.

There have been four reports of patients with a deficiency in the enzyme Δ-1-pyrroline-5-carboxylate synthase. Two siblings presented with chronic vomiting and failure to thrive (Baumgartner et al. 2005). They had developmental delay with a DQ of 40. They had hypotonia, severe joint laxity, including pes planus and dislocated hips, skin hyperelasticity, and osteoporosis. They developed bilateral zonular cataracts. In childhood, their mental and motor skills deteriorated, and they had abnormal behavior, severe hypotonia, dystonia, a pyramidal syndrome, and an axonal motor neuropathy. Another patient at age 6 months had joint laxity with pes planus and coxa valga, bilateral inguinal hernia, lax but not hyperelastic skin showing superficial veins, sparse hair, subcapsular cataracts, and clonic seizures at day 10 of age (Martinelli et al. 2012). Imaging studies showed wormian bones, osteopenia, and limb shortness. Four affected siblings presented with very wrinkled and lax, but not hyperelastic, skin, which disappeared with age by adolescence (Bicknell et al. 2008). There was short stature and joint laxity, and two had hip dislocation. They had congenital microcephaly and static neurodevelopmental delay since early infancy, with seizures in two individuals. Brain MRI showed paucity of the white matter. One child had cataracts. Finally, a last patient was reported with prenatal contractures, short stature, and microcephaly. He had progeroid features, a thin and wrinkled skin with visible veins and sparse hair (Skidmore et al. 2011). He had cloudy cornea with absent Bowman's membrane. The brain MRI showed tortuous blood vessels. He developed seizures at 2 weeks of age, poor feeding, bilateral inguinal hernias, and severe failure to thrive. He made little developmental progress and died at age 6 months.

Patients in two families had metabolic abnormalities: they developed low fasting plasma levels of proline, citrulline, arginine, and ornithine (Baumgartner et al. 2005; Martinelli et al. 2012). Postprandial plasma levels and urine levels were normal, emphasizing the subtlety of the abnormalities. There was fasting hyperammonemia, which paradoxically decreased postprandially. In contrast, the third family showed only mild postprandial low ornithine levels, but no other biochemical abnormalities (Bicknell et al. 2008). Skin biopsy showed thin dermis with collagen bundles of variable diameters and rarefaction and size decrease of elastic fibers, but normal biochemical analysis of collagen fibers (Martinelli et al. 2012; Skidmore et al. 2011). Brain imaging showed atrophy and thin corpus callosum and a decreased creatine on MRS (Martinelli et al. 2012).

A similar phenotype was seen in patients with missense mutations in the γ-glutamyl kinase domain affecting catalysis (e.g., R84Q or G39R) (Baumgartner et al. 2005; Martinelli et al. 2012), those affecting the multimerization such as H784Y (Bicknell et al. 2008), as in those where the mutation affected splicing and protein abundance (e.g., c.1923+1G>A) (Skidmore et al. 2011). Incorporation of ^{3}H-glutamate into protein proline by fibroblasts was decreased in some, but not all (Baumgartner 2005; Bicknell et al. 2008).

Δ-1-Pyrroline-5-carboxylate reductase (P5CR) deficiency. The mitochondrial Δ-1-pyrroline-5-carboxylate reductase (P5CR) enzyme catalyzes the reduction with NADPH of pyrroline-5-carboxylate to proline. Two paralogs exist, *PYCR2* and *PYCRL*.

Reported patients presented with intrauterine growth retardation, lax and wrinkly skin, connective tissue weakness, and mild to moderate mental retardation. Several patients had osteopenia without bone fractures, hip dislocation, inguinal hernias, camptodactyly, and corpus callosum agenesis (Reversade et al. 2009; Guernsey et al. 2009; Yildirim et al. 2011; Kouwenberg et al. 2011; Lin et al. 2011). Rare symptoms are wormian bones, cataracts, and dystonia. Visible subcutaneous veins and wrinkly skin can resemble a progeroid appearance. Skin wrinkling is most pronounced on the dorsum of hands and feet. Mild dysmorphic features include triangular face, broad forehead, microcephaly, sagging cheeks, large fontanel, and large ears.

Electron microscopy of skin biopsy shows rarefaction and fragmentation of elastic fibers (Reversade et al. 2009). Serum proline levels and urine proline excretion were within the normal range (Reversade et al. 2009; Guernsey et al. 2009). Fibroblasts show abnormal mitochondrial morphology, mitochondrial fragmentation, and cell death with oxidative stress (Reversade et al. 2009). The diagnosis is made by gene sequencing with multiple mutations reported (Reversade et al. 2009; Guernsey et al. 2009; Yildirim et al. 2011; Kouwenberg et al. 2011).

Differential diagnostic syndromes for the P5CR synthase and P5CR reductase genes include the clinical cutis laxa syndromes of geroderma dysplasticum, de Barsy syndrome, and autosomal recessive cutis laxa. Mutations in the following genes have been described in these closely related syndromes: *ATP6V0A2* (ATPase H+ transporting V0 subunit 2), COG7CDG, *GORAB* (SCYL1 binding protein), *EFEMP2* (fibulin 4), *FBLN5* (fibulin 5), *ELN* (elastin), and *ATP7A* for Menkes and occipital horn syndrome. Testing for copper,

ceruloplasmin, and glycosylation of glycoprotein analysis (e.g., transferrin and apo-CIII), and a fasting proline level are good tests to consider prior to molecular testing in cutis laxa syndromes particularly when combined with developmental delay (Reversade et al. 2009) (Fig. 5.7).

Disorders of Proline Peptide Metabolism

Prolidase deficiency. Prolidase, also called peptidase D, is a peptidase that cleaves carboxy-terminal proline residues, whereas the enzyme prolinase cleaves peptides with amino-terminal proline residues. The proline-containing peptides are particularly frequent in connective tissue proteins such as collagen. The gene for prolidase, *PEPD*, has 15 exons.

There is substantial phenotypic variability between and within families, even with the same genotype (Lupi et al. 2006; Falik-Zaccai et al. 2010) (Table 5.8). Typical features are dermatologic and immune. Skin lesions are pruritic eczematous lesions, erythematous papular eruptions, telangiectasis, lymphedema, impetigo-like eruptions, and necrotic papules. Characteristic chronic, slowly healing ulcerations, particularly on the legs and feet, develop. They are tender, covered with granulomatous tissue, and can be a source of infection. Splenomegaly, recurrent pulmonary infections, and chronic ear and sinus infections, sometimes mimicking cystic fibrosis, are often reported. A malar rash and the presence of anti-DNA antibodies can lead to a diagnosis of systemic lupus erythematosus (Klar et al. 2010). Mild to severe mental retardation is common. Facial dysmorphisms include low hairline and hirsutism, ocular hypertelorism, micrognathia, mandibular protrusion, and high palate. Rare symptoms include anemia and thrombocytopenia, likely due to hypersplenism. Most patients present early, but late-onset cases are known. Clusters of patients have been reported in Ohio Amish families and in Druze and Palestinian families (Falik-Zaccai et al. 2010).

Patients excrete multiple dipeptides and tripeptides containing proline and to a lesser extent hydroxyproline in the urine. The most common are glycylproline and alanylproline. Iminodipeptides can also be found in hypophosphatemic rickets or in hyperparathyroidism but at much lower levels than in prolidase deficiency (Kelly et al. 2010). Proline levels in serum are normal. In red blood cells, prolidase activity measured after activation with manganese, is reduced. It is also reduced in serum, leucocytes, and fibroblasts. Mutations in the gene *PEPD* encoding peptidase D are found and have been summarized (Lupi et al. 2006).

5.5 Disorders of the Renal Handling of Proline, Hydroxyproline, and Glycine

Iminoglycinuria. Iminoglycinuria is characterized by the excretion of large quantities of the imino acids, proline, and hydroxyproline and of glycine in the urine. The intestinal absorbance of these amino acids is unaffected. The condition is generally asymptomatic. Patients identified through newborn screening have been asymptomatic. It is generally assumed that the symptoms initially reported with the condition of iminoglycinuria or glycinuria likely reflect ascertainment bias (Coşkun et al. 1993; Bröer et al. 2008). The condition is inherited as a codominant trait. The primary gene involved is the high-affinity transporter for proline, hydroxyproline, and glycine in the proximal renal tubulus *SLC36A2* (Bröer et al. 2008). Patients who are homozygous for a null allele in *SLC36A2,* such as IVS1+1G>A, have iminoglycinuria, whereas the heterozygous carriers have isolated glycinuria with variable expression. Patients who have a mild mutation in *SLC36A2* such as G87V have iminoglycinuria if they also are heterozygous for a polymorphism in *SLC6A19* which impairs the distal renal tubular transport of the imino acids or in *SLC6A18* which affects glycine transport (Bröer et al. 2008). There is no need for treatment and no specific treatment for this condition exists. See also Chap. 44.

5.6 Nomenclature

No.	Disorder	Alternative name	Abbreviation	Gene symbol	Chromosomal localization	Affected protein	OMIM no.	Subtype
5.1	Nonketotic hyperglycinemia	Glycine cleavage deficiency	NKH	*GLDC*; *AMT*; *GCSH*	9p24.1, 3p21.31, 16q23.2	P-protein; T-protein; H-protein	238300, 238310, 238330, 605899	All forms
5.2	Phosphoglycerate dehydrogenase deficiency	PHGDH deficiency	PHGDH	*PHGDH*	1p12	Phosphoglycerate dehydrogenase	606879, 601851	All forms
5.3	Phosphoserine phosphatase deficiency		PSPHD	*PSPH*	7p11.2	Phosphoserine phosphatase	172480, 614023	All forms
5.4	Phosphoserine aminotransferase deficiency	PSAT deficiency	PSAT	*PSAT1*	9q21.2	Phosphoserine aminotransferase	610992, 610936	All forms

No.	Disorder	Alternative name	Abbreviation	Gene symbol	Chromosomal localization	Affected protein	OMIM no.	Subtype
5.5	GABA transaminase deficiency		GT	*ABAT*	6p13.2	GABA transaminase	137150, 613163	All forms
5.6	Succinic semialdehyde dehydrogenase deficiency	4-Hydroxybutyric aciduria	SSADH	*ALDH5A1*	6p22.3	Succinic semialdehyde dehydrogenase	271980, 610045	All forms
5.7	Hyperprolinemia I	Proline oxidase deficiency	PRODH	*PRODH*	22q11.2	Proline oxidase	239500, 606810	All forms
5.8	Pyrroline-5-carboxylate synthase deficiency	Hypoprolinemia type I	P5CS	*PYCS*	10q24.1	Pyrroline-5-carboxylate synthase	138250, 219150	All forms
5.9	Δ1-pyrroline-5-carboxylate reductase deficiency	Hypoprolinemia type II	P5CR	*PYCR1*	17q25.3	Δ1-pyrroline-5-carboxylate reductase	179035, 612940, 614438	All forms
5.10	Prolidase deficiency	Iminopeptiduria		*PEPD*	19q13.11	Peptidase D	170100, 613230	All forms

5.7 Metabolic Pathways

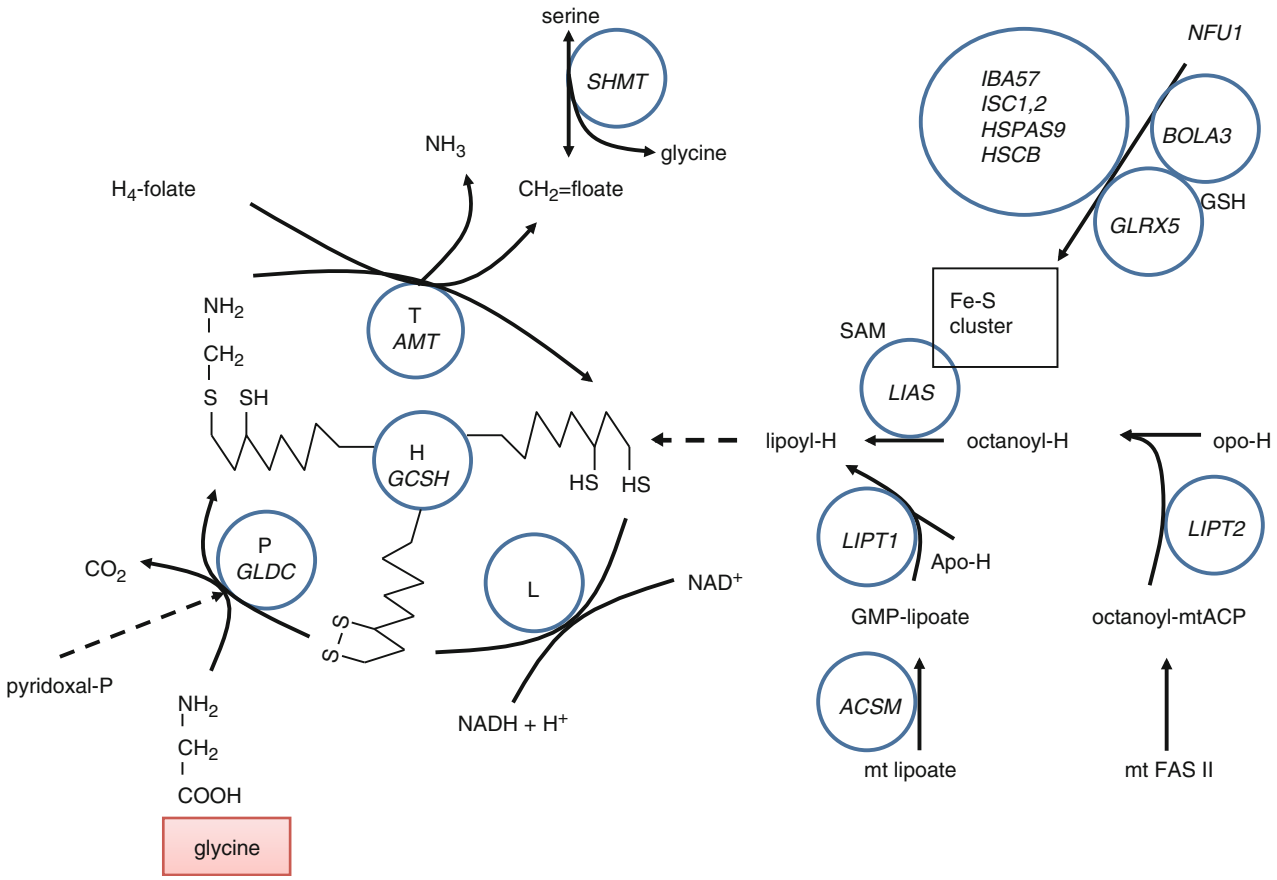

Fig. 5.1 Biochemistry of glycine metabolism. CH_2=folate is methylene-tetrahydrofolate. Reproduced from "Variant non-ketotic hyperglycinaemia is caused by mutations in *LIAS*, *BOLA3*, and the novel gene *GLRX5*" (Baker et al. 2013) Brain 2013:10.1093/brain/awt328 with permission from Oxford University Press

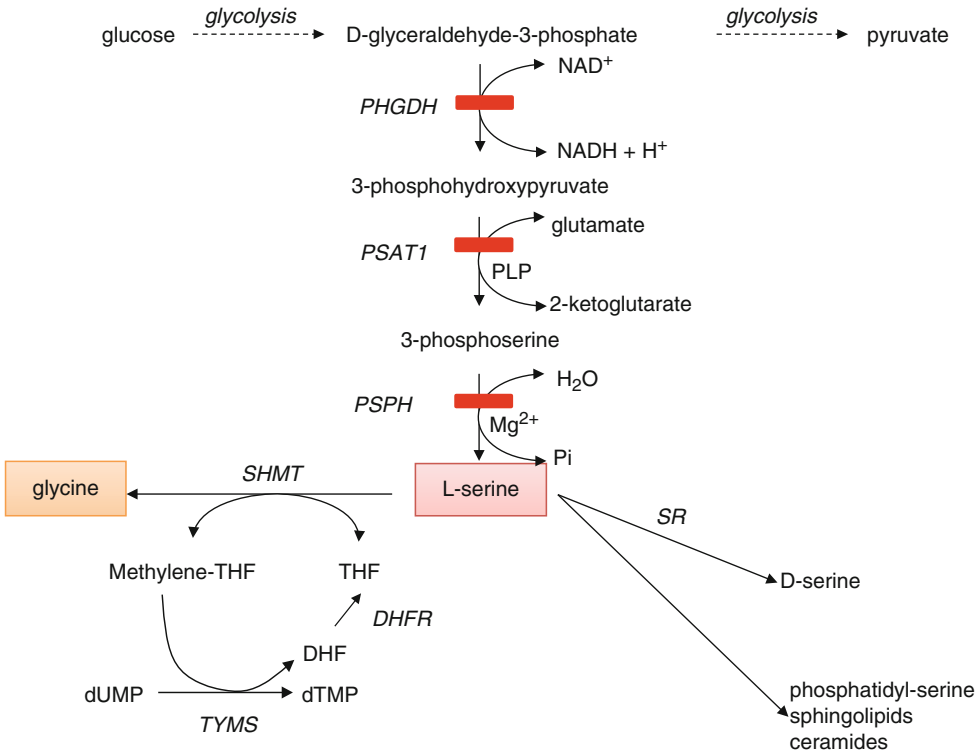

Fig. 5.2 Biochemistry of serine metabolism. *PHGDH* is 3-phosphoglycerate dehydrogenase, *PSAT1* is phosphoserine aminotransferase, *PSPH* is phosphoserine phosphatase, *SHMT* is serine hydroxymethyltransferase, *THF* is tetrahydrofolate, *DHF* is dihydrofolate, *DHFR* is dihydrofolate reductase, *TYMS* is thymidylate synthase

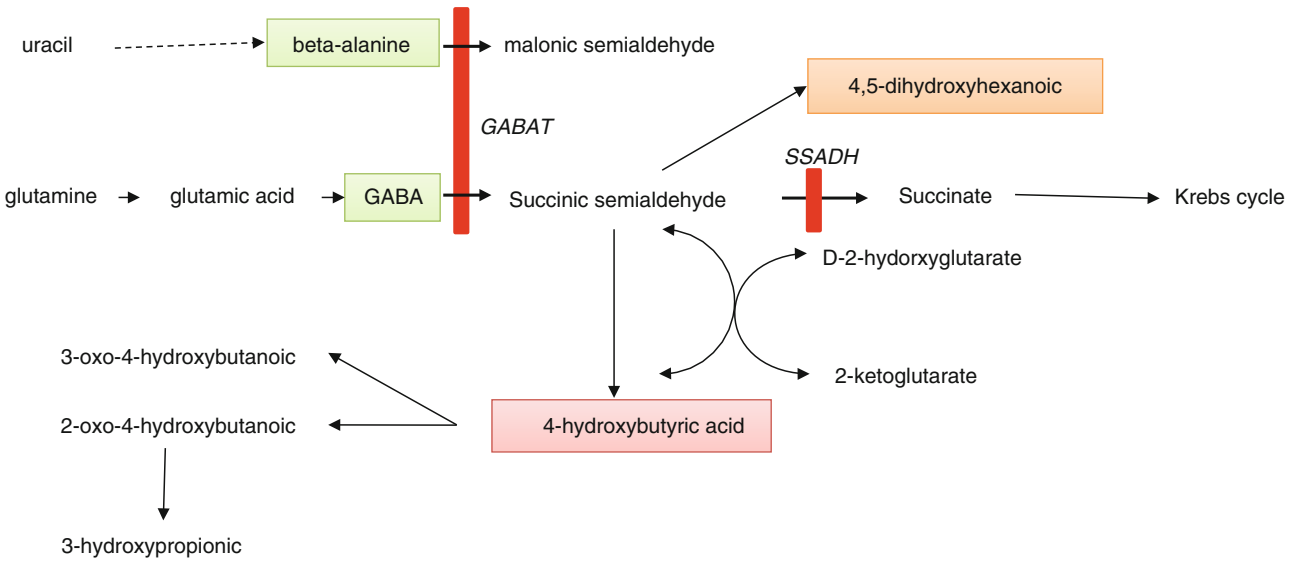

Fig. 5.3 Biochemistry of GABA metabolism. *GABA* is gamma-aminobutyric acid, *GABA-T* is GABA transaminase, *SSADH* is succinic acid semialdehyde dehydrogenase

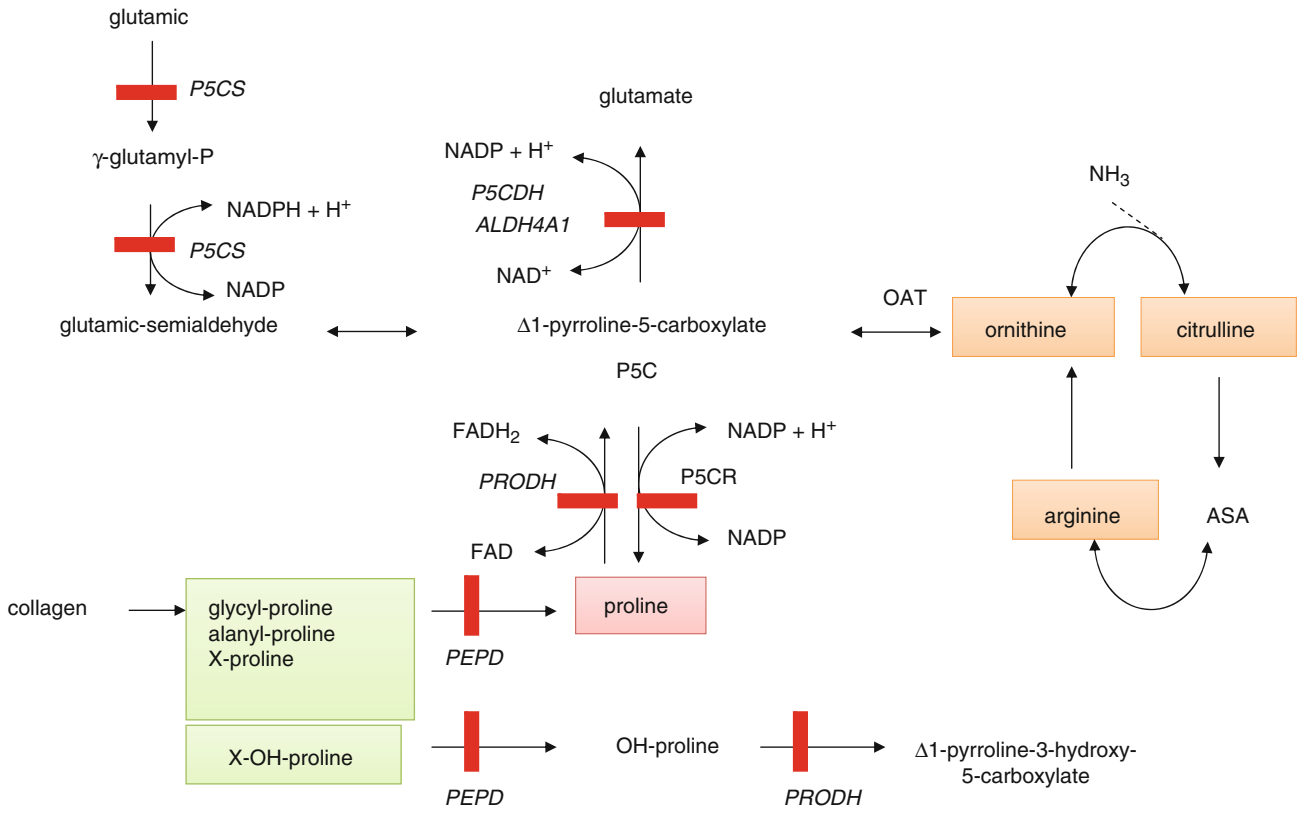

Fig. 5.4 Biochemistry of proline and hydroxyproline. *P5CS* is **Δ**-1-pyrroline-5-carboxylate synthetase, *P5CR* is **Δ**-1-pyrroline-5-carboxylate reductase, *P5C* is **Δ**1-pyrroline-5-carboxylate, *PRODH* is proline dehydrogenase, *ASA* is argininosuccinic acid

5.8 Signs and Symptoms

Table 5.1 Nonketotic hyperglycinemia

System	Symptom	Neonatal	Infancy	Childhood	Adolescence	Adulthood
CNS	Apnea	++	n	n	n	n
	Ataxia		±	++	++	++
	Chorea		+	++	++	++
	Hiccups	++	±	n	n	n
	Hydrocephalus	+	+	+	+	
	Hyperactivity	n	+	++	++	
	Hypotonia	+++	+++	++	+	+
	Lethargy	+++	+++	++	+	+
	Neurologic deterioration	±	++	+	+	
	Retardation, psychomotor	+++	+++	+++	+++	+++
	Seizures	+++	+++	+++	++	±
	Spasticity	±	+	++	+++	+++
Digestive	Feeding difficulties	+++	+++	+++	++	+
Eye	Optic atrophy	±	±	±	±	
Routine laboratory	**EEG: burst suppression, abnormal**	+++	++			
	EEG: hypsarrhythmia, abnormal		++			
	EEG: multifocal epilepsy, abnormal	+	++	++	++	+
Special laboratory	Glycine (CSF)	↑↑	↑↑	↑↑	↑↑	↑↑
	Glycine ratio (CSF:P)	↑↑	↑↑	↑↑	↑↑	↑↑
	MRI: agenesis or hypoplasia of the corpus callosum	++	++	++	++	++
	MRI: posterior fossa abnormalities	+	+	+	+	+
	MRI: simplification of the gyral pattern	+	+	+	+	+

Table 5.2 Phosphoglycerate dehydrogenase deficiency

System	Symptom	Neonatal	Infancy	Childhood	Adolescence	Adulthood
CNS	Ataxia	±	±	±	+	+
	Axonal sensory motor polyneuropathy, chronic	±	±	±	+	++
	Hyperexcitability	+	++	++	++	
	Retardation, psychomotor	++	+++	+++	++	+
	Seizures	+++	+++	++	++	+
	Spastic tetraplegia	+	+++	+++	+++	
Endocrine	Hypogonadism	+	+	+	+	
Eye	Cataract	+	+	+	+	
	Nystagmus	++	++	++	+	
Hematological	**Anemia, megaloblastic**	+	+	+	+	
Musculoskeletal	Adducted thumbs	+	++	++	++	
	Microcephaly	+++	+++	+++	+++	
Routine laboratory	**EEG: hypsarrhythmia, abnormal**		+++	++		
	EEG: Lennox-Gastaut syndrome, abnormal		++	++	+	
	EEG: multifocal epilepsy, abnormal	+++	+++	+++	+++	
Special laboratory	Serine (CSF)	↓↓↓	↓↓↓	↓↓↓	↓↓↓	↓↓↓
	Serine (P) – fasting	↓	↓	↓	↓	↓
	5-Methyl-THF (CSF)	↓	↓	↓	↓	↓
	Glycine (CSF)	↓	↓	↓	↓	↓
	Glycine (P) – fasting	↓	↓	↓	↓	↓
	MRI: cortical and subcortical atrophy	++	+++	+++	+++	
	MRI: delayed to absent myelination	+++	+++	+++	+++	
	MRS: decreased *N*-acetylaspartate/creatine ratio	+	+	+	+	
	MRS: increased choline/creatine ratio	+	+	+	+	

Table 5.3 Phosphoserine aminotransferase deficiency

System	Symptom	Neonatal	Infancy	Childhood	Adolescence	Adulthood
CNS	**Retardation, psychomotor**		++	++	++	
Musculoskeletal	Growth retardation		++	++	++	
Special laboratory	Serine (CSF)		↓↓	↓↓	↓↓	
	Serine (P)		↓-n	↓-n	↓-n	

Table 5.4 Phosphoserine phosphatase deficiency

System	Symptom	Neonatal	Infancy	Childhood	Adolescence	Adulthood
CNS	Hypertonia	+	++	++		
	Seizures, intractable	++	++	++		
Musculoskeletal	Microcephaly	n	++	++		
Special laboratory	Glycine (CSF)	↓	↓	↓		
	Glycine (P)	↓	↓	↓		
	MRI: cerebellar vermis hypoplasia	+	++	++		
	MRI: generalized atrophy	+	++	++		
	Serine (CSF)	↓↓	↓↓	↓↓		
	Serine (P)	↓	↓	↓		

Table 5.5 GABA transaminase deficiency

System	Symptom	Neonatal	Infancy	Childhood	Adolescence	Adulthood
CNS	Hypotonia	++	++	++		
	Lethargy	++	+	+		
	Pitched cry, high	++	++	+		
	Retardation, psychomotor	+	+++	+++		
	Seizures	+++	+++	+++		
	Spasticity	±	+	++		
	Tendon reflexes, increased	++	++	++		
Digestive	Feeding difficulties	++	++	++		
Other	Accelerated growth	+	++	++		
Routine laboratory	Growth hormone		↑	↑		
Special laboratory	Beta-alanine (CSF)	↑	↑	↑		
	GABA-free (CSF)	↑↑	↑↑	↑↑		
	Homocarnosine (CSF)	↑	↑	↑		
	MRI: diffusion restriction in the internal and external capsule and subcortical white matter	+	+	+		
	MRS: GABA	↑	↑	↑		

Table 5.6 Succinic semialdehyde dehydrogenase deficiency

System	Symptom	Neonatal	Infancy	Childhood	Adolescence	Adulthood
CNS	Anxiety		+	++	++	
	Ataxia		+	++	++	
	Attention disorder		+	++	++	
	Behavior, aggressive		+	++	++	
	Hyperactivity		+	++	++	
	Hypotonia	++	++	++	+	
	Language difficulties		++	++	++	
	Oculomotor dyspraxia		+	++		
	Retardation, psychomotor	+	++	++	++	
	Seizures		++	++	++	
	Sleep disturbances	+	++	++	++	
	Tendon reflexes, decreased	+	++	++	+	
Digestive	Feeding difficulties	+	+	+		
Eye	Strabismus		+	+	+	
Routine laboratory	**EEG: spike wave discharges and generalized slowing, abnormal**	+	++	++	++	
Special laboratory	4-Hydroxybutyric acid (U)	↑↑	↑↑	↑↑	↑↑	↑
	MRI: cerebellar and cerebral atrophy	+	+	+	+	
	MRI: increased T2 signal in the globus pallidus, cerebellar dentate nucleus, brain stem, and subcortical white matter	+	++	++	++	

Table 5.7 Hypoprolinemia

System	Symptom	Neonatal	Infancy	Childhood	Adolescence	Adulthood
CNS	Behavior difficulties		+	++	++	
	Dystonia		+	+	+	
	Hypotonia	+	++	++		
	Neuropathy, axonal motor			++	+	
	Pyramidal signs			+	++	
	Retardation, psychomotor		+	++	+	
	Seizures	+	+	+	+	
Dermatological	**Cutis laxa**	++	+++	+++	+	
	Sparse hair		+	++	+	
Digestive	Feeding difficulties	++	++	++		
Eye	Cataract	+	++	++	++	
	Corneal clouding		++	++		
Musculoskeletal	Hernias	+	+	+		
	Hip dislocation	+	++	+		
	Joint contractures	+				
	Joint laxity	++	++	++	+	
	Laxity	+	++	++	+	
	Microcephaly	++	++	++	++	
	Osteopenia		+	+	+	
	Osteoporosis		+	++	++	
	Pes planus		+	++	+	
	Rhizomelia		+	+		
	Stature, short		+	++	++	
	Wormian bones	+	+	+		

(continued)

Table 5.7 (continued)

System	Symptom	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Special laboratory	Pro, Cit, Arg, Orn, fasting (P)	↓-n	↓-n	↓-n		
	Ammonia, fasting (P)	±	±	±		
	MRI: paucity of white matter		+	+		
	MRI: thin corpus callosum		+	+		
	MRI: tortuous blood vessels		+			
	MRS: creatine	↓-n	↓-n	↓-n		

Table 5.8 Prolidase deficiency

System	Symptom	Neonatal	Infancy	Childhood	Adolescence	Adulthood
CNS	**Retardation, psychomotor**		+	+	+	+
Dermatological	**Erythematous, papular eruptions**		++	+	+	+
	Itching, eczematous lesions		++	+	+	+
	Lymphedema		+	+	+	+
	Malar flush		+	+	+	+
	Skin ulceration		+	++	+++	+++
	Telangiectasia		+	++	++	++
Ear	Recurrent otitis media		++	++	+	
Hematological	Anemia		+	+	+	+
	Splenomegaly		+	++	++	++
	Thrombocytopenia		+	+	+	+
Musculoskeletal	**Dysmorphic features**	+	+	+	+	+
Respiratory	**Respiratory infections**		++	++	++	+
Special laboratory	Alanylproline (U)	↑↑↑	↑↑↑	↑↑↑	↑↑↑	↑↑↑
	Glycylproline (U)	↑↑↑	↑↑↑	↑↑↑	↑↑↑	↑↑↑
	Proline, after acid hydrolysis (U)	↑	↑	↑	↑	↑
	Anti-DNA antibodies			±	±	±

5.9 Diagnostic Flow Charts

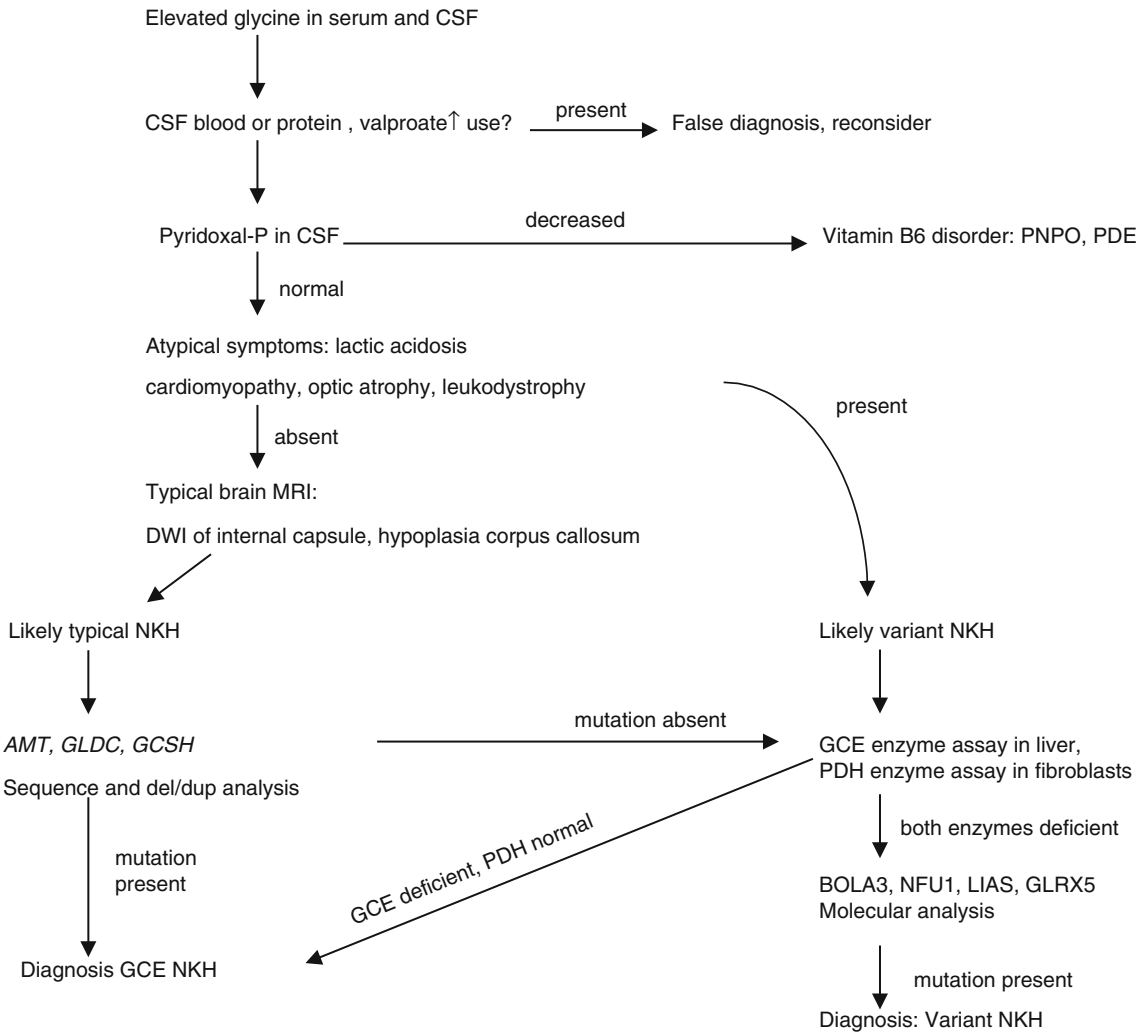

Fig. 5.5 Diagnosis of glycine disorders. *GCE* is glycine cleavage enzyme, *DWI* is diffusion-weighted images, *PDE* is pyridoxine-dependent epilepsy, *PNPO* is pyridox(am)ine phosphate oxidase, *NKH* is nonketotic hyperglycinemia, *PDH* is pyruvate dehydrogenase

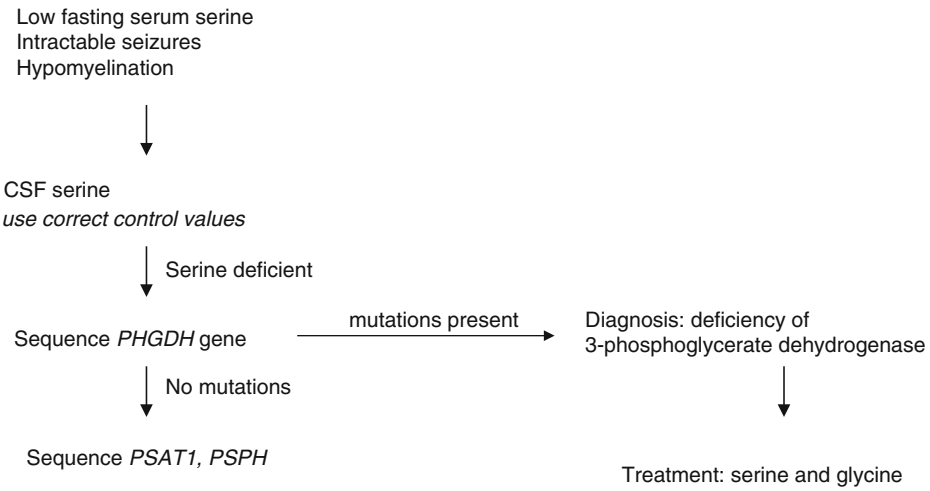

Fig. 5.6 Diagnosis of serine deficiency disorders

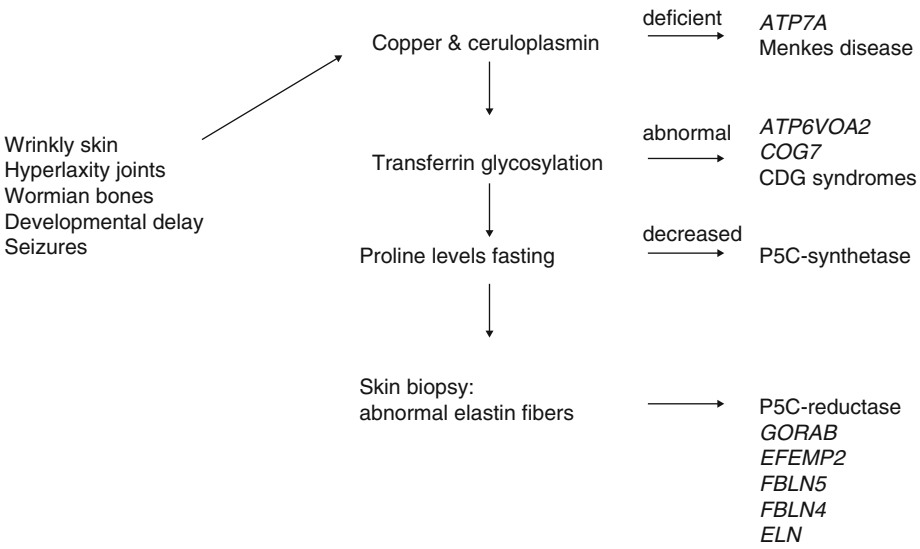

Fig. 5.7 Differential diagnosis of proline deficiency disorders. *CDG* is congenital disorder of glycosylation

5.10 Specimen Collection and Interpretation Pitfalls

Metabolite	Material	Handling	Pitfalls
Glycine	Serum	Serum or plasma. Store frozen	Do not use tubes containing thrombin ↑ Valproate ↑ Kwashiorkor ↑ Irrigation fluids with glycine ↑ IV immunoglobulins with glycine buffer ↑
Glycine	CSF	Store frozen; tap without blood or protein; use age-appropriate reference range	Spinal fluid containing blood or serum ↑ Valproate ↑↑ Other anticonvulsants vigabatrin ↗ Hypoxic-ischemic brain injury ↑ Pyridoxine responsive seizures, pyridoxal-P-responsive encephalopathy ↑

Metabolite	Material	Handling	Pitfalls
Glycine	CSF/plasma ratio	Obtain blood and CSF glycine simultaneously	Valproate ↑ CSF containing blood or serum ↑ Hypoxic-ischemic encephalopathy ↑
Glycine	Urine		Infant Hyperprolinemia Immaturity of transporter or polymorphism in transporter
Serine	Serum/plasma	Freeze at −20 °C	Obtain sample after overnight fast to identify deficiency
Serine	CSF	Freeze at −20 °C; tap without blood or protein	Use age-appropriate reference intervals (Moat et al. 2010)
GABA	Serum	Freeze immediately; store at −70 °C	Vigabatrin ↑
GABA	CSF	Freeze immediately; store at −70 °C	Vigabatrin↑ Hyperprolinemia Immaturity of transporter or polymorphism in transporter
4-Hydroxybutyric acid	Urine	Freeze at −20 °C	Treatment with 4-hydroxybutyric acid ↑ Vigabatrin ↓
4-Hydroxybutyric acid	CSF	Freeze at −20 °C	Treatment with 4-hydroxybutyric acid ↑ Vigabatrin ↓
Proline	Serum	Obtain fasting	Hypoprolinemia in P5CS only present in fasting state
Proline-containing dipeptides	Urine		Confirmation by large increase in proline and hydroxyproline after acid hydrolysis
Prolidase enzyme activity	Red blood cells, leucocytes, fibroblasts		Red blood cell requires preincubation with Mn

5.11 Normal and Pathological Values

Nonketotic hyperglycinemia

	Normal	Classic NKH	Attenuated NKH	Variant NKH
Glycine				
Plasma µmol/L	<1 month, 230–450 >1 month, 100–350	261–2,127	324–1,000	445–1,035
CSF µmol/L	5–20 neonate 3–12 older	96–440	43–230	15–180
CSF/plasma ratio	<0.02	0.09–0.49	0.05–0.22	0.02–0.09

Serine deficiency syndromes

	Normal	PHGDH severe	PHGDH mild	PSAT1/ PSPH
Serine				
Plasma µmol/L	<1 month, 230–450 >1 month, 100–350	28–64	63, 58, 33	30–80
CSF µmol/L	<1 month, 31–82 1 month–1 year, 24–70 1–5 years, 20–59 >5 years, 17–44	<2 years, 4–18 >2 years,3–12	9, 13	5–18
CSF glycine	<3 months, 5–20 >3 months, 3–12	1–4	Normal	<1 to normal

GABA disorders

	Normal	SSADH	GABA-T
4-Hydroxybutyric acid			
Urine mmol/mol creatinine	0–7	100–1,200	
Plasma µmol/L	0–3	35–600	
CSF µmol/L	0–2	100–850	
GABA-free			
Serum µmol/L	0.12–0.50		2.9; 2.1
CSF µmol/L	<2 years, 0.017–0.067 >2 years, 0.032–0.167	0.12–2.33	1.26
GABA total			
CSF µmol/L	<2 years, 4.2–13.4 >2 years, 3.3–12.2		38
Beta-alanine			
Plasma µmol/L	<12		23
CSF µmol/L	<0.1		0.48

Proline disorders

	Normal	Hyperprolinemia 1	Hyperprolinemia 2	P5CS	Prolidase
Proline					
Plasma	<1 month, 110–420 >1 month, 50–350	500–2,000	>2,000	91 ± 18; 107 ± 49 120–197 8–20[a]	
Peptide bound Urine µmol/L					
Proline	430–1,250				5,700–27,000
Hydroxyproline	250–725				1,400–2,100

Prolidase enzyme activity: prolidase <10 %
[a]Results from individual patients

5.12 Prenatal Diagnosis

Condition	Prenatal diagnosis	Pitfalls
Nonketotic hyperglycinemia	Mutation analysis	Gene and mutations must be known Intragenic linkage if only one allele is known
	Enzyme assay uncultured CVS	1 % false-negative diagnosis
Variant NKH	Mutation analysis	Gene and mutation must be known
	Enzyme assay of GCS and PDH	Limited experience
Serine deficiency	Mutation analysis	Gene known
GABA-T	Mutation analysis	
SSADH	Metabolite: 4-hydroxybutyric in amniotic fluid	Stable isotope dilution assay
	Enzyme assay in CVS or cultured amniocytes	
	Mutation analysis	
Hyperprolinemia 1	Mutation analysis	
P5CS	Mutation analysis	
P5CR	Mutation analysis	
Prolidase	Mutation analysis	
	Enzyme assay in amniocytes	Prediction of clinical severity not possible

5.13 Treatment

Nonketotic hyperglycinemia (glycine encephalopathy). In the neonatal period during the apneic phase, withdrawal of intensive care should be discussed with the parents (Boneh et al. 2008). Treatment consists of reduction in glycine by using sodium benzoate and inhibition of the action of glycine on the NMDA receptor. The dose of benzoate must be individually adjusted to bring the glycine level down to the therapeutic range of 120–300 μM. Most patients with severe NKH require 500–750 mg/kg/day, whereas most patients with attenuated NKH require much lower doses (250–450 mg/kg/day) (Wolff et al. 1986; Van Hove et al. 2005; Hennermann et al. 2012). Dosing must be divided in at least three doses, more in infants. Secondary carnitine deficiency is possible during treatment with high doses of benzoate in the first year of life. Blocking of the NMDA receptor can be done with dextromethorphan (5–10 mg/kg/day) or with ketamine. Treatment improves lethargy and seizure control. It does not avoid severe mental retardation in patients with severe NKH. However, in patients with attenuated or mild NKH, early treatment improves neurodevelopmental outcome, often suffices for seizure control, and prevents lethargic attacks during intercurrent illness. Valproate must be avoided in such patients. Difficult to control seizures can sometimes benefit from ketogenic diet or from vagal nerve stimulator.

3-Phosphoglycerate dehydrogenase deficiency (PHGDH). Treatment with supplementation with serine and glycine shows improvement in seizures and increased white matter volume and myelination, but little effect on psychomotor development unless treatment is started prenatally (De Koning et al. 2002). Some patients also need folinic acid treatment. Mild patients responded well to treatment with low doses of serine. High-dose serine improved the adult patient subjectively.

Phosphoserine aminotransferase deficiency (PSAT1). Treatment with serine and glycine supplementation resulted in marginal improvement in seizure control and responsiveness in the older patient, but the patient treated from the first day of life has had normal development and has remained symptom-free.

Phosphoserine phosphatase deficiency (PSPH) has been reported in a single patient who also had Williams syndrome (Jaeken et al. 1997). Treatment with L-serine resulted in slow improvement of head growth, but no improvement in height or weight.

GABA transaminase deficiency. There is no effective treatment for this condition.

Succinic semialdehyde dehydrogenase deficiency (SSADH). Treatment is symptomatic. Antiepileptic drugs that are most helpful include carbamazepine and lamotrigine. Valproate is contraindicated since it inhibits the enzyme. Methylphenidate, thioridazine, risperidone, and fluoxetine have been helpful in some patients for psychiatric symptoms (Pearl et al. 2009). Clonidine has been used to improve REM sleep. Vigabatrin has variable clinical responses and is no longer indicated. GABA(B) receptor antagonists are under experimental investigation (Pearl et al. 2009). Although taurine was promising in animal experiments, it did not show efficacy in an open-label clinical trial.

Hyperprolinemia type I. At this moment, a specific treatment is not available. Given the endogenous brain metabolism of proline, a dietary restriction does not seem indicated as a treatment option.

Δ-1-Pyrroline-5-carboxylate synthase (P5CS) deficiency. Treatment with arginine (150 mg/kg/day) corrected the brain MRS creatine levels; improved levels of ammonia, proline, and ornithine; and was associated with improved psychomotor development (Martinelli et al. 2012). Treatment with citrulline and proline has been suggested, but is without data (Baumgartner et al. 2005).

Δ-1-Pyrroline-5-carboxylate reductase (P5CR) deficiency. A specific treatment is not available. Treatment is symptomatic.

Prolidase deficiency. No effective treatment exists. Red blood cell transfusions with manganese incubation to activate the enzyme did not work. High-dose pulsed systemic steroids and growth hormone systemic or topical treatment had a transient improvement on skin ulcers. Ointments with proline, or proline and glycine, have limited benefit. Enzyme replacement therapy is currently under development.

5.14 Treatment Summary

Condition	Treatment	Comments
Nonketotic hyperglycinemia: classic severe	Benzoate 500–750 mg/kg/day (for severe) Glycine restricted diet Dextromethorphan 5–10 mg/kg/day Multiple anticonvulsants	Dosing of benzoate individualized Effect on outcome for seizure control but limited in severe Diet limited impact
Nonketotic hyperglycinemia: attenuated	Benzoate 250–500 mg/kg/day (for attenuated) Dextromethorphan 5–10 mg/kg/day	Avoids neurodepressive episodes Prevents seizures Improves neurocognitive outcome Effect of dextromethorphan persists Benzoate dose individualized to maintain serum glycine <300 μM Effect on outcome in developmental progress in attenuated if started early
Variant nonketotic hyperglycinemia	None known	Theoretical treatment with lipoic acid of limited benefit
Serine deficiency syndromes	Serine 200–600 mg/kg/day Glycine 200–300 mg/kg/day	Improves head growth and myelination Improves seizures Neurodevelopment improved if started prenatal or first day of life Lower doses in mild serine deficiency
GABA transaminase deficiency	None known	
SSADH deficiency	Carbamazepine or lamotrigine; psychotropic drugs, physical and occupational therapy	Most effective anticonvulsants Treatment with vigabatrin or taurine not consistently helpful
Hyperprolinemia type 1	None known	
P5C synthetase deficiency	Arginine 150 mg/kg/day	Improved serum ammonia, proline, ornithine, and brain creatine and development
P5C reductase deficiency	None known	
Prolidase deficiency	None known	Transient and inconsistent improvement with topical proline-containing ointment, steroids, and growth hormone

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