Clinical variability in glycine encephalopathy

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Glycine encephalopathy (GCE) is an autosomal recessive error of glycine degradation, resulting in a poor outcome with severe mental retardation, intractable seizures and spasticity. Milder variants with a significantly better outcome have been reported, but an early prediction of the long-term outcome is not yet possible. With regard to the long-term outcome, the data reported in the literature of children with different GCE forms were compared. Determination of cerebrospinal fluid and plasma glycine concentrations at the time of diagnosis were not useful in differentiating mild and severe outcomes. By contrast, several clinical parameters correlate with a poor outcome: spastic quadriparesis, truncal hypotonia, typical electroencephalography patterns, congenital and cerebral malformations (e.g., corpus callosum hypoplasia). Hyperactivity, behavioral problems and choreiform movement disorders are associated with a milder outcome. Thus, prediction of the outcome of GCE may be facilitated by searching for selected clinical parameters. In addition, early neuroimaging may be a valuable tool in predicting the outcome of GCE.

Glycine encephalopathy ([GCE]; synonym: nonketotic hyperglycinemia; Online Mendelian Inheritance in Man [OMIM] 605899) is an autosomal recessive inborn error of glycine degradation resulting in an excessive accumulation of glycine in all tissues, particularly in the CNS. Patients may be diagnosed biochemically by the typical combination of an increase of glycine in plasma and cerebrospinal fluid (CSF), with an increased CSF–plasma glycine ratio. The underlying defect is a deficiency of the glycine cleavage system (GCS), an intramitochondrial enzyme complex made up of four different protein components: the P-protein (a pyridoxal phosphate-dependent glycine decarboxylase [GLDC]), the T-protein (a tetrahydrofolate-dependent protein [AMT]), the H-protein (a lipoic acid containing hydrogen-carrier protein [GCSH]), and the L-protein (lipoamide dehydrogenase) [1]. Approximately 65–80% of children with GCE have a defect in the P-protein, with the rest having a defect in the T-protein. A defect in the H-protein has been described in one single patient. Abnormalities in the L-protein have not been reported in GCE [1–4].

Glycine functions both as an inhibitory and excitatory neurotransmitter. It acts as a neuromodulator with an excitatory effect at the N-methyl-D-aspartate (NMDA) receptor channel complex located in the cortex and the forebrain. GCS deficiency causes an accumulation of glycine in the synaptic cleft, leading to an overstimulation of the NMDA receptor at the glycine modulatory site. This causes an increased intracellular free calcium accumulation resulting in neuronal injury, with subsequent cell death and intractable seizures [1,5]. Furthermore, glycine is a neurotransmitter on the glycinergic receptors, located in the spinal cord and the brain stem. Stimulation of these receptors has an inhibitory effect due to an enhanced chloride permeability in the postsynaptic neurons, and is likely to be involved in muscular hypotonia, neonatal apnea and hiccupping in children with GCE [1]. The excitatory effect of these receptors on neural progenitor cells could be involved in the malformations sometimes observed in patients with GCE [6].

As far as is predictable, the prevalence of GCE seems to be approximately 1 in 60,000 [1,7]. Most patients suffer from the severe neonatal form (classic GCE), presenting in the first few days of life with muscular hypotonia, seizures, lethargy and apnea, leading to an early death or severe global mental retardation, intractable seizures and spastic quadriparesis. Patients with milder forms of GCE show variable degrees of mental retardation and seizures, behavioral problems and choreoiform movement disorders. Patients with transient GCE have rarely been described, mimicking the clinical and biochemical features of classic GCE during the neonatal period, but resulting in a good neurological outcome with no, or only slight, neurological sequelae [1,4]. An early prediction of the outcome of GCE at the time of manifestation is not yet possible. In addition, an effective treatment does not exist. Current therapy is directed at decreasing the glycine concentration

Keywords: atypical nonketotic hyperglycinemia, glycine cleavage system, glycine decarboxylase, glycine encephalopathy, hydrogen carrier protein, nonketotic hyperglycinemia, outcome, symptoms, tetrahydrofolate-dependent protein

future medicine

and at blocking the effect of glycine at neurotransmitter receptors. Glycine plasma concentrations may be reduced by benzoate treatment and by a low protein diet. The optional treatment with NMDA receptor agonists includes dextrometorphane, ketamine and felbamate. Additionally, combined anticonvulsive treatment is necessary in most children with GCE, mainly in those with classic GCE. To facilitate the classification and prognosis of children with GCE findings on clinical symptoms, laboratory results, electroencephalography (EEG) and neuroimaging of all patients with a mild or transient form of GCE reported in the literature were compared with surveys on children with classic GCE, this was mainly the survey performed by our group [8].

Clinical course

Classic glycine encephalopathy

The typical clinical picture of GCE is that of children with classic GCE, which starts early in the neonatal period with ensuing poor outcome. During the first 3 days of life, at least two thirds of the children present with muscular hypotonia, apnea and coma [8,9]. Seizures may occur during the neonatal period but also later during the first 3 months of life. Some children show congenital malformations, including clump feet, cleft lip/cleft palate, dysplastic ears, congenital hernias and cryptorchism; and children also frequently show brain malformations. The occurrence of these malformations always associates with a poor clinical course [4,10]. Patients develop spastic quadriparesis before 6 months of age, truncal hypotonia, intractable seizures, severe global retardation, frequent hiccuping and microcephaly (**Table 1**). Children with classic GCE show a poor outcome with a developmental quotient (DQ) of less than 10. They have a developmental age of approximately 6 weeks old and may learn to smile, but only occasionally learn to grasp objects and/or to sit [10]. In contrast to children with mild GCE, they seldom show hyperactivity and/or behavioral problems (**Table 1**). Approximately 30% die during the neonatal period [9–10].

Long-term problems in patients with classic GCE variably include feeding difficulties, bile stones, gastroesophageal reflux and esophagitis, some of which represent side effects of treatment [8]. Some children require gastric tube feeding. Further problems involve the skeletal system, including hip dislocation, scoliosis and osteoporosis [1]. Females had been reported to show a more devastating course of the disease [9], which was not confirmed by our data [8].

Mild glycine encephalopathy variants

All children with GCE have an impaired DQ of varying degrees, but 15–20% of them, termed mild GCE, show a significantly better clinical outcome, reaching a DQ of 25–80 [9–10]. They learn to walk and show some motor skills, but predominantly manifest severe speech retardation. In contrast to classic GCE, children with mild GCE are hyperactive and may develop choreiform movement disorders and behavioral problems, mainly aggressive behavior. In the following, the clinical data of all patients with a mild or transient form of GCE reported in the literature are compared with those of surveys on children with classic GCE (**Table 1**). Enzymatic assays have been performed in only some children with mild GCE, these revealed a significantly reduced, but not null activity of GCS in liver

Table 1. Clinical symptoms in different glycine encephalopathy forms, as reported in the literature.

Clinical symptoms	Mild neonatal GCE*		Mild infantile GCE‡		Late onset GCE§		Classic GCE¶	
Mental retardation including speech delay	16/16	100%	23/25	92%	8/13	62%	23/23	100%
Muscular (truncal) hypotonia	13/16	81%	14/25	56%	0/13	0%	23/23	100%
Spasticity#	3/16	19%	1/25	4%	5/13	38%	23/23	100%
Seizures	11/16	69%	11/25	44%	1/13	8%	23/23	100%
Choreoiform movement disorders	7/16	44%	7/25	28%	3/13	23%	3/23	13%
Behavioral problems	10/16	63%	10/25	40%	6/13	46%	4/23	17%

**[8,11–16]; ‡[8,13–15,17–28]; §[14,22,30–36]; ¶[8]; #Spasticity in late-onset GCE is described as a spastic diplegia caused by a progressive spinocerebellar degeneration [30–32].*

Data of all patients with a mild or transient form of GCE reported in the literature are pooled and compared with those of surveys on children with classic GCE.

GCE: Glycine encephalopathy.

tissue in all children tested. Therefore, mild GCE forms seem to be associated with a certain residual GCS activity.

Children with mild neonatal GCE present during the first days of life with the same clinical picture as children with classic GCE, showing muscular hypotonia, seizures, myoclonic jerks, coma and apnea but no congenital malformations. In the course of the disease they develop severe hyperactivity, choreoiform movement disorders and behavioral problems (**Table 1**). Mental retardation is less pronounced than in children with classic GCE, and patients reach certain developmental milestones. Seizures may occur but are less severe than those observed in classic GCE [8,10–16].

Children with mild infantile GCE present during infancy, but only after the neonatal period. The neonatal period often seems to be uneventful, but muscular hypotonia may already occur postnatally. In most children with mild infantile GCE, muscular hypotonia is the first symptom, followed by seizures and coma. Apnea is often absent. The clinical course is comparable to those of children with mild neonatal GCE, presenting with hyperactivity, choreoiform movement disorders, behavioral problems, less-severe mental retardation and less-frequent seizures [8,10,13–15,17–28].

Patients with infantile onset, but rapid decline, have seldom been reported [8,10,29]. These children present after the neonatal period at 1–3 months of age with muscular hypotonia, and subsequently develop seizures, occasionally coma and rarely apnea. The outcome is as severe as in children with classic GCE, resulting in spasticity, intractable seizures and profound mental retardation.

Late-onset GCE seldom occurs. Children with this form of GCE present after 2 years of age with a different clinical picture showing cognitive decline and behavior problems. In some patients, the leading symptom is a progressive spinocerebellar disease resulting in spastic diplegia of the lower extremities [30–32]. Muscular hypotonia has not been reported in this patient group and seizures rarely occur (**Table 1**) [22,30–36]. Bilateral optic atrophy has been reported in two patients with late-onset GCE, but not in any other GCE patients [30,35]. In one child with classic GCE, an abnormal retinography was described [37], moreover we detected pathological visual evoked potentials in two out of five children with classic GCE. It has been speculated that optic atrophy may be caused by glycine's toxicity affecting the retina or the optic nerve directly [35]. In conclusion, late onset GCE appears to display a different clinical entity of GCE, but GCS deficiency has never been proved by enzymatic or genetic analysis in any of the patients described.

Transient glycine encephalopathy

Children with transient GCE have rarely been reported. These children mimic the characteristic clinical and biochemical features of classic GCE but progress mainly to a good outcome with slight, or no, neurological sequelae. Currently, 13 children with transient GCE have been described [38–46]. The outcome of these children has been reported to result in six normal children, one death at 3 months of age, one with mild retardation and four with more severe mental retardation. Three children with transient symptoms of GCE and homozygosity for a missense mutation in the P-protein resulting in impaired GCS enzyme activitiy have recently been described [16]. In these children, biochemical parameters did not normalize and their data were not included with those of transient GCE. The pathomechanism(s) of transient hyperglycinemia still remain unexplained. It has been speculated that transient GCE may be caused by heterozygosity for a GLDC mutation, an immaturity in one of the GCS components, a deficiency of any of the GCS cofactors, the presence of an infantile isoenzyme, the temporary presence of an inhibitor of GCS or the transient lack of an activator of GCS [2,39,42]. Nevertheless, a follow-up of glycine measurements in CSF and plasma was not performed in the children with transient GCE. Three children described by Kure and colleagues were only heterozygous for a GLDC or GCSH mutation [46], which does not explain precisely the pathomechanism for transient GCE, as no further heterozygous carrier for GCE has been reported so far. However, the description of transient GCE has highlighted the problem for deciding ongoing life-saving treatment in neonatal GCE manifestation. However, it may still be considered that transient hyperglycinemia in most of these children could have been the result of secondary factor(s) and may not be caused by GCS deficiency.

Biochemical findings

Increased concentrations of glycine in serum and CSF with an increased CSF–plasma ratio are pathognomonic for GCE. The CSF–plasma ratio has been indicated to be the most important diagnostic parameter in GCE [1]. Data on

glycine measurements at the time of diagnosis in the different GCE forms are presented in Table 2. The data from all patients with a mild or transient form of GCE reported in the literature are compared with those of surveys on children with classic GCE [9–28,30–36,38–43,47–48]. A significant increase of glycine in plasma and CSF in addition to an increase of the CSF–plasma ratio has been found in all children with GCE, but the determination of CSF and plasma glycine concentrations at the time of diagnosis is not useful in differentiating transient, mild or severe GCE forms. Children with a neonatal onset of GCE demonstrate the highest glycine CSF and plasma concentrations, independently of the outcome, whereas children with onset in infancy show lower values for both parameters. The CSF–plasma ratio is slightly, but not significantly, higher in children with classic GCE than in those with mild or transient GCE. The CSF–plasma glycine ratio decreases with age; therefore, it is not a useful parameter in predicting the long-term outcome of GCE. Furthermore, there is a broad range of glycine values, mainly in children with classic GCE, and glycine elevation in children with GCE may only be demonstrable in CSF and not in plasma [3].

Molecular basis

All four protein components of GCS map to different chromosomes. Mutation analysis reveals predominantly private mutations. With the exception of Finnish patients, no common or founder mutations are described. Therefore, a genotype–phenotype correlation could not yet be established in patients with GCE.

GLDC, located on 9p24, is the product of a 25-exon gene spanning over 135 kb. A processed pseudogene of *GLDC*, designated φ*GLDC*, sharing 97.5% homology with the *GLDC* cDNA, has been identified recently [49]. More than 80 *GLDC* mutations have currently been described, three of them occuring more frequently: S564I, G761R (both in the Finnish population) and R515S in 5% of Caucasian patients [50–53]. The gene for T-protein, *AMT*, is located on 3q21.1–21.2 and consists of nine exons spanning over 6 kb [54]. More than 20 AMT mutations have been identified, four of which were reported in more than one family: R320H, IVS7–1G>A, H42R and M1T, the latter two found in an Israeli–Arab kindred [53,55–56]. The H-protein gene, *GCS*, is encoded on 16q24 and consists of five exons spanning over 13.5 kb, revealing only one abnormal splicing mutation in heterozygosity in a single patient with transient GCE [2,57]. A recently performed mutation screening analysis in patients with GCE revealed mutations in *GLDC* and in *AMT*, both in patients with classic and mild GCE, but no mutations in *GCSH* [52–53]. Seven patients with late-onset GCE also underwent mutation screening, but no mutations in *GLDC*, *AMT* or *GCSH* were identified [53]. This underlies the possibility of a different pathomechanism of late-onset GCE.

Electroencephalogram changes

Typical electroencephalogram (EEG) patterns occur in children with GCE. During the neonatal period a burst suppression pattern, which may also be found in children with hypoxia, is

Table 2. Biochemical investigation at the time of diagnosis in different glycine encephalopathy forms, as reported in the literature.

Laboratory data	Mild neonatal GCE*	Mild infantile GCE‡	Late onset GCE§	Transient GCE¶	Classic GCE	Normal newborn
Glycine in plasma (μmol/l)	1241 (675–2800)	660 (325–1100)	633 (354–961)	1013 (240–2285)	1110 (420–4090)# 920–1827** 780 ± 276‡‡	154–515
Glycine in CSF (μmol/l)	130 (70–567)	53 (7.4–163)	30 (7.4–68)	125 (16–463)	160 (40–1440)# 83–280** 88 ± 41‡‡	3–23¶¶
CSF–plasma ratio	0.094 (0.058–0.307)	0.084 (0.017–0.250)	0.046 (0.020–0.073)	0.116 (0.047–0.882)	0.15 (0.05–0.43)# 0.136 (0.09–0.25)§§	0.012–0.04

**[8,11–16]; ‡[8,13–15,17–28]; §[14,22,30–36]; ¶[38–46]; #[8]; **[20]; ‡‡[47]; §§[48]; ¶¶[78]*

Data of all patients with a mild or transient form of GCE reported in the literature are pooled and compared with those of surveys on children with classic GCE. Values are given in median, with minimum and maximum in brackets.

CSF: Cerebrospinal fluid; GCE: Glycine encephalopathy.

commonly seen in GCE. This pattern usually disappears after the neonatal period and then often changes to the pattern seen in typical hypsarrhythmia [1,58]. In some children, EEG reveals multifocal spike discharges. The EEG data of all patients with a mild or transient form of GCE reported in the literature are compared with those of surveys on children with classic GCE and are shown in **Table 3**. Burst suppression is a frequent pattern in children with neonatal manifestation of GCE, but among those children it is more common in classic GCE. Hypsarrhythmia has not been described in children with late-onset or transient GCE, and only in a few children with other mild GCE forms. By contrast, hypsarrhythmia is described frequently in classic GCE. Therefore, this EEG pattern often seems to be associated with a poor disease outcome.

Findings by cerebral magnetic resonance imaging and magnetic resonance spectroscopy

Various brain abnormalities and malformations have been described in GCE: hypoplasia or aplasia of the corpus callosum, enlarged ventricles, hydrocephalus, brain atrophy, gyral malformation, cerebellar hypoplasia, delayed myelination, posterior fossa cysts and intracranial hemorrhage [1,59]. Histolopathological examinations reveal a spongy myelinopathy in myelinated areas [1]. The magnetic resonance imaging (MRI) data of all patients with a mild or transient form of GCE reported in the literature are compared with those of surveys and reports on children with classic GCE, as shown in **Table 4**. Children with classic GCE frequently show brain abnormalities, whereas they are less common in children with mild or transient GCE. Hypoplasia of the corpus callosum has been described in one single child with late-onset GCE and in one child with transient GCE [31,44], not in any other patient with mild GCE, but in two-thirds of children with classic GCE. In the majority of cases, all other MRI changes are more frequent in classic GCE than in mild GCE, for example, enlarged ventricles, delayed myelination, hydrocephalus and posterior fossa cyst. Thus, hypoplasia of the corpus callosum and other congenital brain malformations are associated with a poor outcome of GCE. This emphasizes the need for an early cerebral imaging to predict the clinical course and outcome of the disease.

Magnetic resonance spectroscopy (MRS) may easily detect increased cerebral glycine concentrations. On long echo time, elevated glycine peaks are found in white and grey matter of children with GCE [68]. The measured glycine concentrations and the glycine ratios correlate well with the clinical course [69]. By contrast, in mild GCE elevated cerebral glycine peaks are not detectable by MRS [13]. Therefore, MR spectroscopy may be a valuable, but expensive, tool in the diagnosis and monitoring of GCE.

Therapy

There is currently no effective treatment for GCE. Intervention is aimed at decreasing the glycine concentration and blocking the effect of glycine at neurotransmitter receptors. The goal of glycine reduction is to obtain glycine plasma levels of 250 μM or less. The most effective treatment is that of high dose benzoate with 250–750 mg/kg/day [1,70]. Benzoate is activated by the intramitochondrial butyryl CoA synthase to benzoyl CoA. It binds to glycine and is then excreted as hippurate in urine. Benzoate treatment does not ameliorate developmental delay but it reduces seizure frequency and improves alertness in patients [70]. Higher doses of benzoate are often required in classic GCE. As higher benzoate doses are associated with renal toxicity, plasma benzoate levels must be monitored regularly. Therapeutic plasma levels of benzoate are less then 5 mM and toxic levels are greater than 8 mM [70]. In addition to a renal dysfunction syndrome [71], signs of benzoate toxicity may also include gastrointestinal disturbances and esophagitis. Therefore, prophylaxis with an H2-blocker is recommended in all children receiving benzoate intervention. Dietary

Table 3. Electroencephalogram patterns in different glycine encephalopathy forms, as reported in the literature.

EEG pattern	Mild neonatal GCE*		Mild infantile GCE‡		Late-onset GCE§		Transient GCE¶		Classic GCE#	
Burst suppression	4/10	40%	1/17	6%	0/4	0%	5/12	42%	20/26	77%
Hypsarrhythmia	2/10	20%	2/17	12%	0/4	0%	0/12	0%	14/19	74%

**[8,11–16]; ‡[8,12,14–15,17,19–28]; §[14,22,32–36]; ¶[38–46]; #[8].*

Data of all patients with a mild or transient form of GCE reported in the literature are pooled and compared with surveys on children with classic GCE.

EEG: Electroencephalogram; GCE: Glycine encephalopathy.

Table 4. Magnetic resonance imaging changes in different glycine encephalopathy forms.

Changes in cerebral imaging*	Mild neonatal GCE		Infantile GCE		Late-onset GCE		Transient GCE		Neonatal classic GCE	
Hypoplasia of the corpus callosum	0/12	0%	0/9	0%	1/4	25%‡	1/10	10%	35/57	61%
Enlarged ventricles	0/12	0%	2/9	22%	0/4	0%	1/10	10%	22/57	39%
Delayed myelination	0/12	0%	0/9	0%	0/4	0%	3/10	30%¶	22/44	50%
Brain atrophy	2/12	17%	1/9	11%	1/4	25%‡	2/10	20%	20/54	37%
Posterior fossa cyst	0/12	0%	0/9	0%	0/4	0%	0/10	0%	9/57	16%
Hydrocephalus	0/12	0%	0/9	0%	0/4	0%	0/10	0%	7/57	12%
Cerebellar hypoplasia	1/12	8%	0/9	0%	1/4	25%‡	0/10	0%	7/57	12%
Intracranial hemorrhage	0/12	0%	0/9	0%	0/4	0%	1/10	10%	2/57	4%

**[8,11–15,17,22,24–26,30–31,34–35,59–67].*

‡Percentage may not be useful as the total of four children is too small.

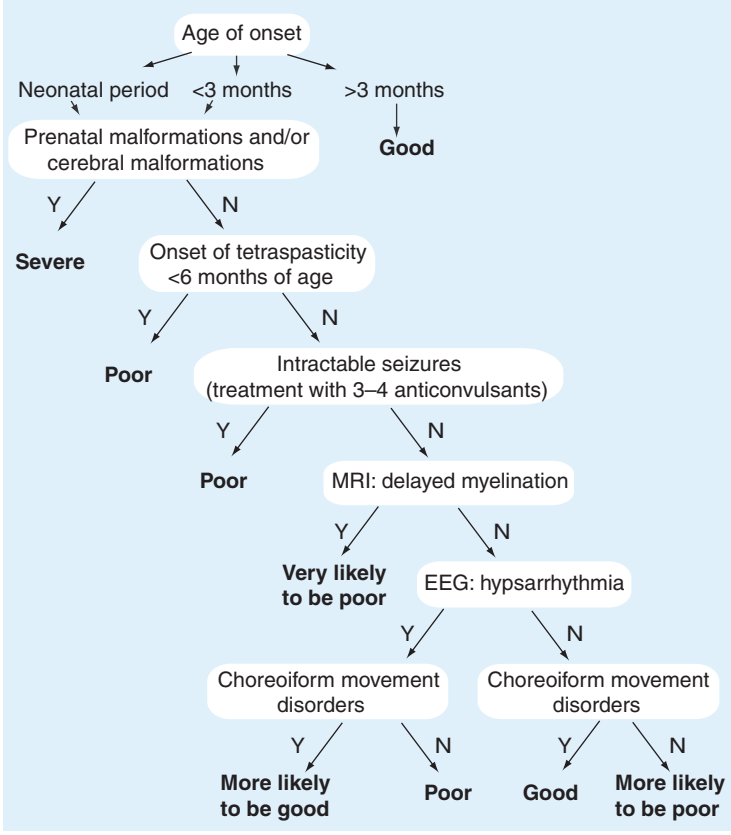
¶In two children retarded myelination normalized or was only very slight.

Data of all patients with a mild or transient form of GCE reported in the literature are pooled and compared with surveys on children with classic GCE.

GCE: Glycine encephalopathy.

glycine and serine restriction combined with benzoate therapy may be effective in classic GCE. The glycine balance as a new parameter for the prognosis of the outcome of GCE has recently been described by Van Hove and colleagues [72]. After normalizing glycine values by benzoate treatment in children with GCE, the glycine balance was calculated as the amount of glycine ingested by food and compared with the amount of glycine excreted as urinary hippuric acid. Glycine balance values of less than 2 mmol glycine/kg/day have been demonstrated to be associated with a good outcome, but glycine balance values of more than 3 mmol glycine/kg/day are associated with a poor outcome [72].

Figure 1. Flowsheet for facilitating the classification and prognosis of the different glycine encepalopathy forms.



EEG: Electroencephalogram; MRI: Magnetic resonance imaging.

Receptor antagonists block the effect of glycine at the neurotransmitter receptors. Dextromethorphan blocks the glutamate binding-site of the NMDA receptor. Dextromethorphan reduces seizures and improves alertness primarily in mild GCE, but is less effective in classic GCE [1,73–74]. Other NMDA-receptor antagonists have been employed as well, mainly tryptophan and ketamine, both targeting the glycine allosteric site of the NMDA receptor [75–76]. The inhibitory effect of glycine is blocked by strychnine, which is effective in apneoic infants but may have deleterious side effects on long-term use [1]. Diazepam also blocks the inhibitory effect of glycine, but its effect is transient and tachyphylactic [77].

Conclusion & future perspective

For facilitating the classification and the prognosis in children with GCE, a flow sheet with the most important clinical hallmarks has been developed (**Figure 1**).

Determination of CSF and plasma glycine concentrations may not allow to distinguish between the different GCE forms. However, several parameters seem to correlate with the clinical

course. Late manifestation appears to associate with a better outcome, whereas congenital malformations, mainly cerebral malformations, associate with a poor clinical course. Spastic quadriparesis, truncal hypotonia, intractable seizures, and typical EEG changes with hypsarrhythmia associate with a poor clinical course, whereas hyperactivity, behavior problems and choreoiform movement disorders associate with a mild outcome. A new parameter for the prognosis of the outcome of GCE has been found by determining the glycine balance. Predicting the outcome of GCE may currently be facilitated by searching for selected clinical parameters. Early neuroimaging may be a further valuable tool in prognosticating the outcome of GCE.

As the pharmacology of the inhibitory glycine receptor and the excitatory NMDA receptors continue to be described, newer treatments for GCE may become available in the near future.

Executive summary

Introduction

- Glycine encephalopathy (GCE), an autosomal recessive inborn error of glycine degradation, results in an excessive accumulation of glycine in plasma and cerebrospinal fluid (CSF), leading to severe neurological impairment.
- Most patients with GCE suffer from the severe neonatal form (classic GCE), but 15–20% of children with GCE show a milder course. An early prediction of the outcome of GCE at the time of manifestation is not yet possible.

Clinical course

- Children with classic GCE develop spastic quadriparesis, truncal hypotonia, intractable seizures, severe global retardation, frequent hiccuping, microcephaly and have partial congenital malformations.
- Children with mild GCE show a significantly improved outcome, reaching a developmental quotient (DQ) of 25–80, however they develop choreiform movement disorders and behavioral problems. The time of manifestation of mild GCE may be in the neonatal period or later in infancy.
- Late-onset GCE seldom occurs, presenting after the second year of life and with a different clinical picture of cognitive decline, behavioral problems and progressive spinocerebellar disease. Late-onset GCE may display a different clinical entity of GCE.
- Rarely, children with transient GCE have been reported who mimic the clinical and biochemical features of classic GCE but who mainly progress to a good outcome with no, or only slight, neurological sequelae. Transient GCE may be the result of secondary factor(s) and may not be caused by GCS deficiency.

Biochemical findings

- Significantly increased concentrations of glycine in serum and CSF with an increased CSF–plasma ratio are pathognomonic for GCE. Determination of CSF and plasma glycine concentrations at the time of diagnosis is not useful in differentiating transient, mild or severe outcome.

Molecular basis

- GCE is mapped to different chromosomes: 9p24, 3q21.1–21.2 and 16q24. As mutation analysis reveals predominantly private mutations, no genotype–phenotype correlation has yet been established.

Electroencephalogram changes

- GCE is associated with typical electroencephalogram (EEG) patterns: a burst suppression pattern during neonatal period, changing then to hypsarrhythmia. This pattern is significantly more frequent in children with a poor outcome.

Findings by cerebral magnetic resonance imaging & magnetic resonance spectroscopy

- Various brain abnormalities and malformations have been described in GCE. In the majority, hypoplasia of the corpus callosum, enlarged ventricles, delayed myelination, hydrocephalus and posterior fossa cysts are associated with a poor outcome.

Therapy

- Currently, there is no effective treatment for GCE. Intervention is aimed at decreasing the glycine concentration and blocking the effect of glycine at neurotransmitter receptors.
- Decreasing glycine concentrations is achieved with the use of sodium benzoate, which binds to glycine, combined with a dietary glycine and serine restriction. Receptor antagonists include dextromethorphan, tryptophan, ketamine, strychnine and diazepam.

Conclusion & future perspective

- Outcome of GCE may be predicted by time of manifestation, typical EEG changes, occurrence of congenital malformations, early onset of tetraspasticity, intractable seizures, choreoiform movement disorders and behavioral problems, and by determining the glycine balance.
- As the pharmacology of the inhibitory glycine receptor and excitatory N-methyl D-aspartate receptors continue to be described, new treatments for GCE may come available in the near future.

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