Review

Nonketotic hyperglycinemia: Pathophysiological studies

By Keiya TADA*),**),†) and Shigeo KURE ***)
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Abstract: Recent study on nonketotic hyperglycinemia, an inborn error of glycine metabolism, is reviewed from clinical, metabolic, molecular, and neuropathological points of view. This disorder is caused by an inherited deficiency of the mitochondrial glycine cleavage system (GCS), which causes accumulation of glycine in such body fluids as plasma, cerebrospinal fluid, and urine. There are four disease types: neonatal, infantile, late-onset, and transient types. The genetic backgrounds of the neonatal and infantile types have been largely clarified by a comprehensive mutational screening of genes encoding three components of the GCS, while the molecular pathogenesis of the late-onset and transient types are largely unknown. In the central nervous system of vertebrates, the GCS has been identified in astrocytes and neural stem cells. The GCS in astrocytes is co-localized with N-methyl-D-aspartate receptors, and is thought to maintain the glycine level around the receptors, while the physiological and pathological roles of the GCS in neural stem cells remains to be elucidated.

Key words: Nonketotic hyperglycinemia; glycine encephalopathy; glycine cleavage system (GCS); mutational analysis; glycine decarboxylase (GLDC); neuropathogenesis.

Introduction. Nonketotic hyperglycinemia (NKH), also termed as glycine encephalopathy, is an inborn error of glycine metabolism, which is characterized by various neurological symptoms and accumulation of a large amount of glycine in the body.[1),2)] Glycine levels in cerebrospinal fluids (CSF) are elevated to a much greater extent than in the plasma; hence, the abnormally high value of the CSF/plasma glycine ratio, which is used as a biochemical marker of NKH. NKH is inherited as an autosomal recessive trait.[2)] The incidence of NKH is estimated as approximately one in 250,000 births. The incidence is unusually high in the following countries: Finland (1/12,000 births),[3)] British Colombia (1/63,000 births),[4)] and Israel.[5)-7)] Molecular cloning of the glycine cleavage system (GCS) genes has enabled us to diagnose many patients by mutational analysis, which reveals atypical clinical symptoms of NKH. In this review we summarize the advances in the study of NKH, especially focusing on the phenotypic heterogeneity of this disorder.

Identification of the metabolic lesion for NKH. Glycine is a nonessential amino acid, which has many metabolic pathways, as shown in Fig. 1. Glycine loading to NKH patients results in a higher peak of glycine and a delay in the return to the preloading level, indicating a block in the main route of glycine degradation.[8)] The main route for glycine catabolism had been thought to be its conversion to serine by serine hydroxymethylase, followed by its conversion by serine dehydratase to pyruvate, which enters the tricarboxylic acid cycle. However, Tada *et al*. found that the activities of serine hydroxymethylase and serine dehydratase were normal in the liver of NKH patients. On the contrary, the mitochondrial glycine cleavage system (GCS, EC2.1.2.10) was found to be markedly diminished in the liver of the patients with NKH.[9)] These findings indicate that GCS plays the major route of glycine degradation.

Glycine cleavage system. The mechanism of glycine breakdown by the glycine cleavage system (GCS) has been studied by the research group of Motokawa and Kikuchi.[10)] The GCS catalyzes the conversion of glycine and tetrahydrofolate to CO_2, NH_3, and

*) Emeritus Professor of Tohoku University School of Medicine (Department of Pediatrics), Sendai 980-8575, Japan.
**) Recipient of the Japan Academy Prize in 1993.
***) Department of Medical Genetics, Tohoku University School of Medicine, Sendai 980-8575, Japan.
†) Correspondence to: K. Tada.

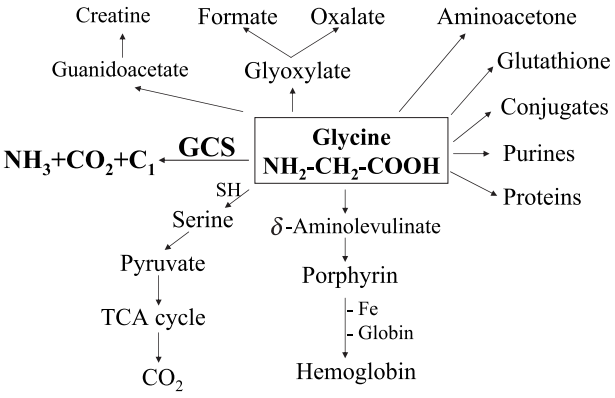

Fig. 1. Metabolic pathways of glycine. Abbreviations: TCA, tricarboxylic acid; SH, serine hydroxymethylase; and GCS, glycine cleavage system.

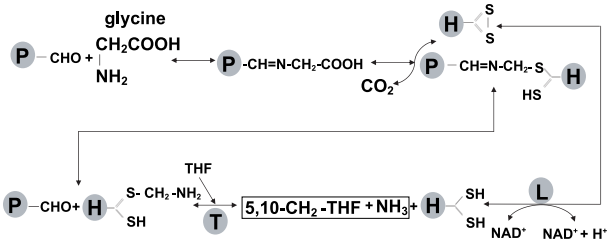

Fig. 2. Glycine breakdown by components of the GCS. The circled P, T, H, and L represent the components of the GCS.

Table I. The GCS components

component	abbreviation	gene	number of coding exons	amino acid	chromosome
glycine decarboxylase	P-protein	*GLDC*	25	1,020 a.a.	9p24
aminomethyltransferase	T-protein	*AMT*	9	403 a.a.	3q21
hydrogen carrier protein	H-protein	*GCSH*	5	173 a.a.	16q24
dihydrolipoamide dehydrogenase	L-protein	*GCSL*	14	509 a.a.	7q31

methylene-tetrahydrofolate. The GCS is a mitochondrial complex enzyme system that consists of four individual proteins: glycine decarboxylase (EC 1.4.4.2, abbreviated as P-protein); aminomethyltransferase (EC 1.8.1.4, T-protein); hydrogen carrier protein (H-protein); and dihydrolipoamide dehydrogenase (EC 1.8.1.4, L-protein) as illustrated in Fig. 2. Glycine forms a Schiff base with the pyridoxal phosphate bound to P-protein, and then the disulfide form of H-protein combines with this complex, generating CO_2 from the carboxyl moiety of glycine. This step is coupled with the reaction of the disulfide group of H-protein. The α-carbon of glycine binds immediately to the H-protein to form an S-C bond without loss of hydrogen atoms that attach to the α-carbon. The H-protein with the intermediate is then decomposed to yield methylene tetrahydrofolate and ammonia. The H-protein becomes a dithiol form. The dithiol form of the H-protein is reoxidized to the disulfide form by L-protein and NAD^+.

L-protein is a housekeeping enzyme that serves as an E_3 component of other α-keto acid dehydrogenase complexes, such as pyruvate dehydrogenase (Table I). A deficiency of dihydrolipoamide dehydrogenase causes progressive neurological deterioration with lactic acidosis, but not hyperglycinemia.[11] In this review we will discuss three GCS specific components, P-, T-, and H-proteins that are encoded by different genes (Table I). P-protein consists of 1,020 amino acids [12),13)] and is encoded by the glycine decarboxylase (*GLDC*) gene [14)] on chromosome 9p24.[15)] T-protein has 403 amino acids [16)] and is encoded by the aminomethyltransferase (AMT) gene on chromosome 3q21.[17)] H-protein consists of 173 amino acids [18)] and is encoded by the glycine cleavage system H-protein (GCSH) gene on chromosome 16q24.[19)]

Clinical symptoms. NKH is classified into four types based on the onset of disease: neonatal, infantile, late-onset, and transient types.[1)]

Neonatal type. This is the most common subtype of NKH. Most patients are products of uncomplicated, full-term pregnancies. Recent brain imaging studies have revealed that patients with NKH frequently have brain malformation such as hypogenesis or agenesis of the corpus callosum, gyral malformation, ventricular enlargement, and cerebellar hypoplasia.[20),21)] An MRI scan

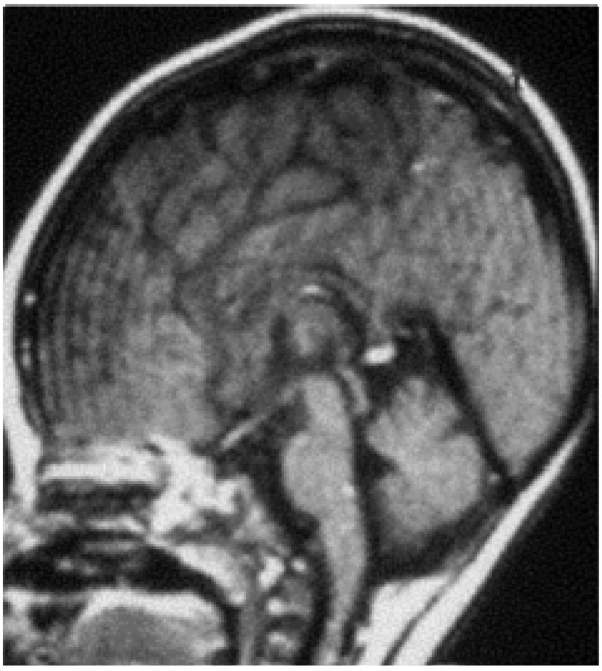

Fig. 3. MRI scan image of a patient with neonatal NKH. Note hypogenesis of the corpus callosum, gyral abnormality, and hypoplasmic cerebellum.

image of a patient with neonatal NKH is shown in Fig. 3. Neonates with NKH are average for gestational age in all growth parameters at birth. Within the first week such patients develop rapidly progressing neurological symptoms such as muscular hypotonia, depressed Moro response, convulsive seizures, apneic episodes, and lethargy or coma.[22] A third of such patients die within a few weeks of life. Survivors have severe psychomotor retardation and rarely achieve such developmental milestones as head control, sitting, and walking. Convulsive seizures range in severity from myoclonic seizures to grand mal convulsions. Hiccupping is often observed. During the first weeks of life, a characteristic EEG pattern is seen with bursts of high complex waves of 1-3 seconds, arising periodically from a hypotonic background. This so-called burst-suppression pattern disappears at the end of the first month and subsequently changes to hypsarrythmia. Muscular hypotonia is prominent in the neonatal period, but thereafter spasticity proceeds gradually, resulting in opisthotonus. Recently, we encountered two patients with typical neonatal presentation who showed far better developmental outcomes. The *in vitro* expression analysis of the identified *GLDC* mutations revealed considerable residual enzyme activity, suggesting prognostic and enzymatic heterogeneity even in neonatal-onset nonketotic hyperglycinemia.[23]

Infantile type. Patients with infantile NKH are asymptomatic in the neonatal period.[24] They tend to present seizures, are spared coma and profound hypotonia, and have a longer life expectancy with milder psychomotor retardation.[25] The GCS activities in the liver were measured in nine patients with neonatal type and three patients with infantile type. The range of GCS activities was 0-0.7 nmoles of CO_2 formed/mg protein/hr in the neonatal type, in contrast with 0.7-1.4 in the infantile type, control range was 3.9-5.2,[26),27] suggesting that patients with infantile type tend to have higher residual activities than patients with the neonatal type although there is some overlap between the two types. The diagnosis of infantile NKH is, however, sometimes difficult because the CSF and plasma glycine level are not so high as compared with the situation in neonatal NKH. Recently, we have reported several patients with infantile NKH whose diagnosis was confirmed by the identification of *GLDC* mutations.[25),28),29] The clinical pictures of the three patients are described below.

Patient 1. Pregnancy and delivery of patient 1 were uneventful. He had a normal neonatal period. He sat without support at 10 months, walked at 2 years, talked at 3 years, and he had bowel and bladder control at 4 years of age. He was evaluated at four years and found to have mild psychomotor delay, appendicular ataxia, and choreoathetoid movements. His plasma glycine was elevated at 1,100 μmol/L (normal 186-431 μmol/L) and CSF glycine was 55 μmol/L (normal 1-9.8 μmol/L); hence the CSF glycine/plasma glycine ratio was 0.05 (normal < 0.03). Analysis of urine organic acids was normal, and the patient was diagnosed as having atypical NKH. Apart from the mild delay he manifested no significant neurological problems except for frequent outbursts of aggressiveness between ages 5 and 12. He attended special education classes at school and graduated from high school. He worked for two years as a department store greeter. He never had a seizure. His EEG at of 21 years age old was normal.

Patient 2. Patient 2 was born after full term pregnancy with a birth weight of 2,900 g. He was hypotonic after birth without respiratory problems and developed seizures during the first week of life. He walked at 5 years, had bowel and bladder control at 8 years. He still has expressive language problems at the age of 21. Seizures were difficult to control initially but currently are fairly well controlled with valproate. Since age 12 he

Table II. Mutations in three disease types of NKH

mutated gene	total	disease type		
		neonatal	infantile	late onset
GLDC	30	27	3	0
AMT	11	11	0	0
GCSH	0	0	0	0
No mutation	27	17	2	8
detection rate	41/68 (60%)	38/55 (69%)	3/5 (60%)	0/8 (0%)

has occasionally exhibited uncontrolled aggressive behavior. He has severe mental retardation. Plasma glycine at age 15 years was elevated at 1,670 μM (normal 186-431 μM) and CSF glycine was 150 μM (normal 1-9.8 μM). The CSF glycine/plasma glycine ratio was thus 0.09. An EEG at 20 of age years showed moderate generalized slowing. MRI analysis revealed central volume loss with mildly prominent ventricles. He attended special education classes and graduated from high school.

Patient 3. The mother described decreased fetal movements during pregnancy. His birth weight was 3,600 g. He had a normal neonatal period. At 6 months he was found to be mild hypotonia, and metabolic screening revealed persistent glycinuria. Plasma glycine was elevated to 637 μmol/L (normal 186-431 μmol/L) and CSF glycine was 36 μmol/L (normal 1-9.8 μ mol/L). The CSF glycine/plasma glycine ratio was thus 0.056 (normal < 0.03). Analysis of urine organic acids was normal, excluding a secondary ketotic hyperglycinemia. His development was mildly delayed with impaired expressive language (Verbal IQ 70, Performance IQ 59, Full Scale IQ 59). During childhood he was diagnosed as having attention deficit hyperactivity disorder. During adolescence he had outbursts of aggressiveness and sexual impulsivity. He attended special education classes at school, and is currently works.

The three patients had *GLDC* mutations, which showed 5-8% of residual *GLDC* activity in the *in vitro* expression analysis,[28] suggesting that slight higher percent of residual activity results in a marked difference in clinical symptoms between neonatal and infantile NKH.

Late-onset type. Mild neurological symptoms develop in preschool, school, or in adolescence.[30),31] Clinical presentations of late onset NKH are heterogeneous; two families had no seizures nor mental retardation, but progressive paraplegia and optic atrophy.[32),33] Another family presented mental retardation and choreoathetosis.[34]

Transient type. Several patients have been described with the peculiar phenotype of transient neonatal hyperglycinemia.[35),36] At presentation, the patients with transient NKH were clinically indistinguishable from patients with neonatal type, with elevated CSF glycine/plasma glycine ratios diagnostic of NKH and a burst-suppression pattern on EEG. By 2-8 weeks of age, their elevated plasma and CSF glycine levels returned to normal. Most patients showed normal psychomotor development while some had severe neurologic symptoms.[37] The etiology of transient NKH remains unknown.

Genetic background of NKH. In patients with neonatal NKH, 3 and 10 mutations have been reported in the *GLDC* and AMT genes, respectively. The *GLDC* mutations include one missense mutation,[38),39] one micro-deletion,[40] and one large deletion,[14] while the *AMT* mutations consist of eight missense mutations,[5),39),41)-44] one micro-deletion,[42] and one splicing mutation.[39] Two *AMT* mutations, R320H and IVS7-1G > A, and one *GLDC* mutation, R515S, have been found to account for 5-7% of Caucasian mutant alleles,[43] whereas each of the other mutations have been detected in only a single family. Mutational analysis was performed in one family with infantile type, which revealed that the patient was a compound heterozygote of the *AMT* mutations, G47R and R320H.[41]

Recently, we have undertaken comprehensive mutational screening of the *GLDC*, *AMT*, and GCSH genes in 55 patients with the neonatal type of NKH, 5 patients with infantile type, and 8 patients with the late-onset type (Table II).[45] No mutation has been identified in the eight patients with late-onset NKH, suggesting that it may be caused by mutations in genes other than the GCS genes. To elucidate the genetic background of transient

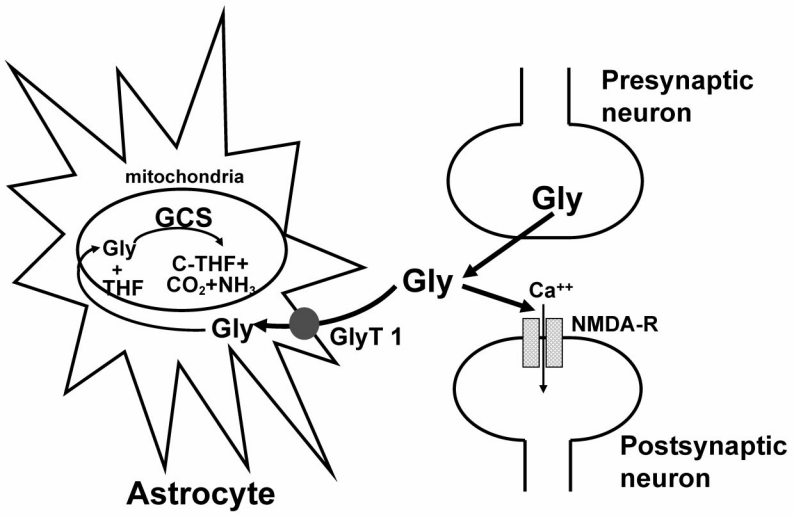

Fig. 4. Schematic drawing of role of the GCS in the central nervous system. Abbreviations: Gly, glycine; NMDA-R, N-methyl-D-aspartate type glutamate receptor; THF, tetrahydrofolate; and GlyT1, glycine transporter type 1.

NKH, we studied three patients with this type by mutational analysis of the *GLDC*, *AMT*, and GCSH genes. As a result, heterozygous *GLDC* and GCSH mutations have been identified in patients with transient NKH.[46] Since transient NKH does not develop in all heterozygous carriers, other genetic and/or environmental factors must participate in the pathogenesis of transient NKH.

Diagnosis. NKH should be considered when neonates or infants develop seizures, muscular hypotonia, and lethargy that are not readily explicable on the basis of infection, trauma, hypoxia, or other commonly encountered pediatric problems. Differential diagnosis between NKH and other diseases with hyperglycinemia is sometimes difficult. The absence of ketoacidosis is indicated by plasma biocarbonate levels and/or blood pH. Exclusion of organic acidemia by gas chromatographic analysis of urine or plasma are crucial.[47] In NKH the glycine level in CSF is elevated and the ratio of CSF to plasma glycine concentration is increased more than 0.09, while in normal and ketotic hyperglycinemia it is below 0.04.[26] An EEG finding of a burst suppression pattern is characteristic for NKH in the first month of life.

There is a special demand for prenatal diagnosis, since no effective treatment has been established for NKH to date. We examined the GCS activity in tissues from an aborted fetus at risk for NKH. Activity of the GCS in liver, brain, and placenta were extremely low in the fetus as compared to controls, suggesting the feasibility of antenatal enzymatic diagnosis of NKH using chorionic villi tissues obtained by biopsy.[48),49] A number of fetuses at risk has been diagnosed by this method.[50)-52] Prenatal DNA diagnosis is also possible if the causative mutation is identified.[52]

Neuropathogenesis of NKH. Glycine plays two distinct functions in the central nervous system. In the brain stem and spinal cord, glycine is an inhibitory neurotransmitter,[53] while, in the cerebral cortex, hippocampus, and cerebellum, glycine is an excitatory co-agonist of the *N*-ethyl-D-aspartate(NMDA)-type glutamate receptor-channel complex. It has been reported that the specific activity of GCS is high in the telencephalon and low in the spinal cord in the central nervous system of the adult rat.[54] The authors also reported an inverse relationship between the GCS activity and glycine content in various regions of the rat brain. In immunohistochemical and *in situ* hybridization studies of P-protein, astrocytes in the telencephalon and cerebellum were strongly labeled, while the labeling of the spinal cord and brain stem was faint.[55),56] These data suggest the GCS may make little contribution to inhibitory glycine transmission, but modulate NMDA-mediated responses by removal of excessive synaptic glycine in adult rat brain as illustrated in Fig. 4.

Neuroradiological examinations have revealed frequent association of brain malformation in patients with NKH[20] but the neuropathogenesis of prenatal brain damage in NKH remains unclear. We identified the functional GCS in embryonic neuroepithelial stem cells

and neural stem cells prepared by neurosphere culture.[57] The GCS in neural stem cells may play a role distinct from that in adult astrocytes. Congenital malformations reported in NKH are parenchymal volume loss, thin corpus callosum (including agenesis), gyral malformation, ventricular enlargement, and cerebellar hypoplasia.[20] These hypoplastic abnormalities suggest the deterioration of cellular proliferation in prenatal NKH brains. Recently, it has been demonstrated that folate deficiency affects the proliferation of neural stem cells.[58] The GCS provides one carbon unit (C_1), which is used for folate metabolism. Brain malformation associated with NKH may be attributed to impaired folate metabolism caused by GCS deficiency.

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Profile

Keiya Tada was born in 1930 and graduated from Tohoku University School of Medicine in 1954. In 1958 he had the opportunity to go abroad for study as a research fellow of Pediatrics, University of Maryland Medical School Baltimore. He studied metabolic derangement of phenylketonuria, a representative disorder of amino acid metabolism under Prof. Samuel P. Bessman. It was 1958 when the Nobel Prize in Physiology or Medicine was awarded to George Beadle and Edward Tatum who proposed the "one gene, one enzyme theory". Therefore, an ardent interest in inborn errors of metabolism was pervasive among young researchers in the field of pediatrics on the east coast of USA. He was deeply impressed with their vigorous activity. At that time in Japan, nutritional problems such as dystrophy and vitamin deficiencies or infectious diseases such as dysentry in summer and pertussis in winter were major subjects of pediatrics. No attention was paid to inborn errors of metabolism in those days. As soon as he returned to Japan in 1960, he started screenig of aminoaciduria by paper-chromatography, thin-layer chromatography and aminoacid analyzer and subsequently made many studies on inborn errors of aminoacid metabolism during his academic life. Among them studies on nonketotic hyperglycinemia required his great effort. He was promoted to Professor of Pediatrics, Osaka City University Medical School in 1971 and then moved to Tohoku University School of Medicine as Professor and Chairman of Department of Pediatrics. He was awarded Noel Raine Prize (Society for the Study of Inborn Errors of Metabolism, UK) in 1982, the Vitamin Society of Japan in 1983, the Japan Society of Human Genetics Prize in 1983, Prize of Medicine (Japan Medical Association, 1985), Takeda Prize (Takeda Scientific Foundation, 1989), Uehara Prize (Uehara Life Science Foundation, 1993), The Japan Academy Prize, 1993. He was appointed as a member of Science Council of Japan during 1997 to 2003.