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Clinical Evaluation and Outcome of Patients with Severe Non-ketotic Hyperglycinemia: Single Center Experience

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Abstract

Introduction: Severe non-ketotic hyperglycinemia may present with clinical signs such as lethargy, hypotonia, apnea, hiccups and persistent convulsions in the newborn period. It is aimed to be determine the clinical characteristics, treatments, cranial MRI and EEG findings, prognoses of patients with non-ketotic hyperglycinemia in this study.

Materials and Methods: Eight patients with severe non-ketotic hyperglycinemia who were followed between January 2016 and November 2024 were included in the study. Initial clinical findings, laboratory results, EEG findings, MRI and MRS findings, molecular genetic analyses, drugs, dietary treatments, treatment results and prognosis were evaluated from patient hospital files.

Results: Levels of plasma and cerebrospinal fluid glycine were 868.3 ± 259.0 µmol/l and 137.7 ± 36.0 µmol/l, respectively. The ratio between cerebrospinal fluid and plasma glycine was above 0.08 in all eight patients. Cerebrospinal fluid/plasma glycine ratio was measured after treatment in three patients. Although a decrease in cerebrospinal fluid glycine levels was observed in two patients, no decrease was detected in cerebrospinal fluid/plasma glycine ratio after treatment. Seizure frequency decreased during periods of mild elevated glycine levels in seven patients. Although plasma glycine levels remained normal in one patient, seizures continued in this patient. The c.1784dupT mutation was identified as a novel mutation in GLDC gene. Six patients died, two patients live with severe neurodevelopmental problems.

Conclusions: Non-ketotic hyperglycinemia is a life-threatening inborn error of amino acid metabolism. Although CSF and plasma glycine levels are reduced with medication, unfortunately seizures decrease but continue. We observed that seizures may continue even when plasma glycine levels are normal. Currently, there is no specific treatment for non-ketotic hyperglycinemia. However, new potential curative therapies should be explored for this debilitating disorder, particularly for its severe form.

Key words: Children; encephalopathy; glycine; treatment; prognosis.

Introduction

Non-ketotic hyperglycinemia (NKH) (OMIM# 605899), also called as glycine encephalopathy, is occurred due to the defect in the glycine cleavage system, resulting in the accumulation of glycine in the central nervous system (1). This system comprises four proteins: dihydrolipoamide dehydrogenase, hydrogen carrier protein, amino methyltransferase (AMT) and glycine decarboxylase (GLDC) (2). The disease is caused by mutations in the genes of *GLDC* and *AMT* in general (3,4). NKH can be classified into two groups as classic and variant. Classical NKH is categorized into severe and attenuated NKH based on clinical outcome. Variant NKH refers to glycine encephalopathy with elevated glycine levels and deficient GCS activity without GLDC and AMT mutations. It occurs most commonly due to deficiencies in the metabolism of GCS cofactors including lipoate deficiency and pyridoxal phosphate deficiency (5). The severe NKH may present with clinical signs such as lethargy, hypotonia, apnea, hiccups and persistent convulsions in the newborn period. Seizures, nutritional and behavioral problems, spastic paraplegia, optic atrophy, psychomotor retardation, leukodystrophy, cardiomyopathy, and cortical involvement can be seen in attenuated types. Eighty-five % of the neonatal forms are severe forms, 15% are attenuated forms (6-8). Typically, cerebrospinal fluid (CSF) glycine/plasma glycine ratio is higher than 0.08 for NKH (9). Corpus callosum agenesis, cerebellar vermis hypoplasia, white matter abnormalities, hydrocephalus, diffusion restriction and cortical involvement of infra and supratentorial structures can be seen (10-11). Glycine peak in magnetic

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resonance spectroscopy and burst suppression pattern in electroencephalography (EEG) are significant for the disorder (12). Sodium benzoate, NMDA receptor blockers (dextromethorphan, ketamine), diet (low-protein, glycine free or ketogenic) and antiepileptic therapy are treatment methods. A curative treatment for NKH has not been discovered, and there are no established guidelines for managing the disorder (5). We aimed to obtain clinical characteristics, treatments, cranial MRI and EEG findings, prognoses of the patients with NKH in this study.

Materials and Methods

Patients and data collection: Severe NKH who were followed in Kayseri City Hospital between January 2016 and November 2024 were retrospectively evaluated. Initial clinical findings, laboratory results, EEG findings, MRI and MRS findings, molecular genetic analyses, drugs, dietary treatments (glycine free, ketogenic, low protein), duration of diet therapies, treatment results and prognosis were evaluated.

Diagnostic criteria: Clinical findings, corpus callosum agenesis, hydrocephalus, diffusion restriction, cortical involvement in MRI, glycine peak in MRS, burst suppression pattern in EEG and CSF/plasma glycine ratio above 0.08 were the diagnostic criteria. CSF glycine levels between 3-23mmol/L were evaluated as normal (13).

Including criteria: Eight patients with NKH and followed up were included in the study.

Excluding criteria: Potential causes of ketotic hyperglycinemia, including organic acidemias, as well as conditions like bloody CSF, neonatal ischemia, and prolonged seizures that could disrupt the blood-brain barrier have been ruled out.

Laboratory investigations: Levels of plasma glycine and CSF were assessed by liquid chromatography/mass spectrometry by non-derivative method, deutero standard (Sciex 5500 qtrap device, immuchrom kit, U.S.A). The urine organic acid profile has been examined using gas chromatography-mass spectrometry by single internal standard, ethyl acetate carrier phase, derivative method (Sımadzu 2010SE device, Japan). Molecular genetic testing was carried out on genomic DNA using next-generation sequencing (NGS). The sequencing process was performed using the Miseq-Illumina platform with NGS technology. Variants were evaluated by ACMG criteria. EEG recordings were carried out using a 32-channel EEG machine (Neurowerk, Germany) in a dark room, during both sleep and awake. Sagittal and axial T1W, T2W, and FLAIR brain images have been obtained by using a 1.5-tesla MRI device (Siemens, Germany). MRS was conducted at 3.5 ppm (TE =135 ms) to capture the glycine signal.

Statistical analysis: Statistical process has been realized by using SPSS version 26 (SPSS Inc., Chicago, IL, USA). Shapiro-Wilk normality tests, histogram and q-q graphs have been used to evaluate the distribution of data. Normally and non-normally distributed data are given as mean ± SD and median (min-max), respectively. Categorical variables have been specified as numbers and percentages.

Ethical approval: The study has taken into account following the principles of the Declaration of Helsinki and adhering to good clinical practice guidelines. Informed consent has been taken from the parents of all participants. This study has been approved by the local ethics committee of Kayseri City Hospital (279/24.12.2024)

Results

There were eight patients diagnosed with NKH. Four (50%) of the patients were female and 4 (50%) were male. The diagnosis age was median 27.5 (3-420) days. Patients 1 and 4, patients 2 and 3 were siblings. Patient 8 and patients 1 and 4 were cousins. Clinical findings of 8 patients from 5 families were evaluated. All patients had hypotonia and seizures. Additional anomalies were present in 3 patients. There were no physical examination abnormalities in other patients. Cranial MRI findings were diffusion restrictions in 37.5 % (n: 3/8), corpus callosum dysgenesis in 37.5 % (n: 3/8), ventricular dilatation in 25 % (n: 2/8), cytotoxic edema in 12.5 % (n: 1/8). All of the patients had a glycine peak in MRS. Clinical and laboratory characteristics of the patients with NKH are given in Table 1 and Table 2. The mutations were c.1784dupT (p. Arg596ProfsTer4), c.284T>A (p. Val95Asp), c.1270C> T (p. Arg424Ter) and c.851A>C (p. His284Pro) in the GLDC gene. The c.1784dupT (p. Arg596ProfsTer4) mutation is a novel mutation that leads to a frameshift in the GLDC gene. (A frameshift mutation is a genetic mutation caused by a deletion or insertion in a DNA sequence that shifts the way the sequence is read) Three related patients had the same novel mutation. Different mutations were detected in each of the three unrelated patients. Only AMT gene mutation could be examined in other two related patients. The first EEG recording times were between 5 days and 14 months. The background activity consisted of burst suppression pattern and accompanying sharp waves in seven patients. Since one patient had a history of sibling death, an EEG was performed at the age of 5th day, and discontinuous traced and accompanying centrotemporal sharp waves were detected.

Table 1: Clinical and laboratory characteristics of the patients with NKH

Patient no	1	2	3	4	5	6	7	8
Gender	Male	Male	Female	Female	Male	Female	Female	Male
NKH type	Severe	Severe	Severe	Severe	Severe	Severe	Severe	Severe
Ethnicity	Turkish	Syrian	Syrian	Turkish	Turkish	Turkish	Turkish	Turkish
Clinical findings	Seizure, hypotonia	Seizure hypotonia	Seizure, poor sucking, hypotonia	Seizure, poor sucking, hypotonia	Poor sucking, hypotonia, seizure	Hypotonia, seizure	Poor sucking, lethargy hypotonia, seizure hiccups	Hypotonia, seizure hiccups
Consanguinity	(-)	(+)	(+)	(-)	(+)	(+)	(+)	(-)
Malformation	(-)	(-)	Pes equinovarus	ASD	(-)	(-)	(-)	Cleft palate
MRI/MRS findings	Corpus callosum agenesis/ Glycine peak (+)	Ventricular dilatation / Glycine peak (+)	Lateral ventricle asymmetrically dilated/ Glycine peak (+)	Corpus callosum agenesis / Glycine peak (+)	Diffusion restrictions in corticospinal tract, central tegmental tract, middle cerebellar peduncle and dentate nuclei/ Glycine peak (+)	Diffusion restrictions in corticospinal tract, mesencephalon and cerebello-pontin peduncle Glycine peak (+)	Cytotoxic edema in internal capsule, corticospinal tract, central tegmental tract, optic radiation, middle cerebellar peduncle and cerebellar white matter+/ Glycine peak (+)	Diffusion restrictions in internal capsule Thin corpus callosum. Glycine peak (+)

Abbreviations; NKH: Non-ketotic hyperglycinemia, MRI: Magnetic resonance imaging, MRS: Magnetic resonance spectroscopy, ASD: Atrial septal defect

Seizures were fragmented or erratic myoclonic seizures seen in the extremities in the early period. They started to appear as myoclonic-tonic and generalized myoclonic jerks over time. Vigabatrin, benzodiazepines, levetiracetam, topiramate and phenobarbital were used as antiepileptic therapy in all patients at different times of their lives. Seizure-free period was not observed in any patient despite antiepileptic treatment. The average follow-up time all of the patients was 16.7 ± 14.8 months. Six patients died. Two patients are still being followed up. Seizures continue in these patients and they had nutritional intolerance. Clinical and laboratory characteristics are given in Table 1 and Table 2. The average plasma glycine levels were 868.3 ± 259.0 mmol/l, CSF glycine levels were 137.7 ± 36.0 mmol/l, respectively. The ratio between CSF and plasma glycine was above 0.08 in all eight patients. Plasma and CSF glycine levels, CSF/plasma glycine ratio of the patients at diagnosis are given in Table 3. The daily seizure frequency and duration of the seizures were obtained from families and/or doctors during their hospitalization. A reduction in repetition and time of seizures was observed in two patients following a glycine-free diet. Seizure frequency decreased during periods of mildly elevated glycine levels except one patient in our study. Although plasma glycine levels remained normal, seizures continued in this patient. CSF/plasma glycine ratio was measured after treatment in three patients. Plasma glycine levels decreased in all three patients. Although a decrease in CSF glycine levels was observed in two patients, no decrease was detected in CSF/ plasma glycine ratio after

Table 2: Clinical and laboratory characteristics of the patients with NKH (continued)

Patient no	1	2	3	4	5	6	7	8
Mutation	c.1784dupT (p. Arg596 ProfsTer4) in GLDC gene	AMT gene mutation (-)	AMT gene mutation (-)	c.1784dupT (p. Arg596 ProfsTer4) in GLDC gene	c.1270C>T (p. Arg424Ter) in GLDC gene	c.284T>A (p. Val95Asp) in GLDC gene	c.851A>C (p. His284Pro) in GLDC gene	c.1784dupT (p. Arg596 ProfsTer4) in GLDC gene
Age at diagnosis	39-day-old	14-month-old	25-day-old	1-month-old	18-day-old	2-month-old	3-day-old	7-day-old
Follow up time	3 months	2 years	10 months	6 months	23 months	4 years	14 months	6 months
Medication	Sodium benzoate	Sodium benzoate	Sodium benzoate	Sodium benzoate	Sodium benzoate Dextromet-horphan Ketamine	Sodium benzoate Dextromet-horphan	Sodium benzoate Dextromet-horphan	Sodium benzoate
Antiepileptic treatment	Phenobarbital Clonazepam Levetiracetam	Phenobarbital Clonazepam Levetiracetam	Phenobarbital Levetiracetam Clonazepam	Phenobarbital Levetiracetam	Phenobarbital Levetiracetam Clonazepam	Phenobarbital Levetiracetam Clobazam	Phenobarbital Levetiracetam Topiramate, Vigabatrin Synacten	Phenobarbital Levetiracetam Clonazepam
Diet therapy	Low protein	Low protein	Low protein	Low protein Ketogenic	Glycine free Low protein	Glycine free Ketogenic Low protein	Low protein Glycine free	Low protein
Prognosis	Died	Died	Died	Died	Died	Severe cognitive impairment, central hypotonia, nutritional intolerance, tube feeding	Died	Severe cognitive impairment, central hypotonia

Abbreviations; NKH: Non-ketotic hyperglycinemia, GLDC: Glycine decarboxylase, AMT: aminomethyl transferase

Table 3: Plasma and CSF glycine levels, CSF/plasma glycine ratio of the patients at diagnosis

Patient	Gender	Age at diagnosis	Plasma glycine level (μmol/l)	CSF glycine level (μmol/l)	CSF/plasma glycine ratio
1	Male	39 days old	1054	175	0.16
2	Male	14-month-old	776	120	0.15
3	Female	25 days old	803	145	0.18
4	Female	1 month old	705	102	0.14
5	Male	18 days old	1187	114	0.09
6	Female	2-month-old	1200	130	0.1
7	Female	3 days old	772	206	0.26
8	Male	7 days old	450	110	0.24

Abbreviations: CSF: cerebrospinal fluid. Reference values: Plasma glycine level (N: 111-426μmol/l) CSF glycine level (N: 3-23μmol/l (15). CSF/plasma glycine ratio over 0.08 is consistent with NKH.

treatment. CSF/plasma glycine levels, EEG findings, duration and frequency of seizures before and after therapy are given in Table 4.

Discussion

NKH is an amino acid metabolism disorder that the world-wide incidence is 1/76.000 (3). NKH is quite frequent in Tunisia. Kairouan region has the highest NKH incidence rate. Predicted incidence is 1/55.641 (14). Also, the incidence has been estimated at 1:55000 newborns in Finland, 1:63000 in British Columbia (15). The prevalence of the disease in our country is unknown. The disease is caused by mutations in the GLDC gene in 80% of cases. Nonsense or missense mutations are the major mutations. The remaining mutations include large deletions, splicing mutations, small deletions, and small insertions. De novo mutations occur in approximately 1% of individuals (16). Four mutations were identified in six patients, including one novel mutation in GLDC gene in our study similar to the literature. Only AMT gene mutation could be examined in our other two patients. Bayrak et al. (17) observed a higher frequency of AMT gene variants in our country reported than other countries. Unfortunately, it was not possible to perform a genotype-phenotype correlation in our study. Although clinical findings of case 7 appeared in the neonatal period, she had resistant seizures, and she had serious neurodevelopmental problems, a longer surveillance was obtained. It can be said that the c.851A>C (p. His284Pro) mutation in the GLDC gene of the patient showed a more favorable course. Mohammad et al. reported that the topographic distribution of diffusion restriction in MRI is not limited to the areas of myelination expected at a certain age, and there are differences

Table 4: CSF /plasma glycine levels, EEG findings, duration and frequency of seizures before and after therapy

Patient	Diet	CSF/plasma glycine ratio before treatment	CSF/plasma glycine ratio after treatment	Pre-treatment EEG	Post-treatment EEG	Seizure frequency after treatment	Seizure duration after treatment
1	Low protein	0.16	-	Burst suppression	Burst suppression	No change	No change
2	Low protein	0.15	0.28	Burst suppression	Thorn-sharp slow wave activities accompanied by suppressed areas	No change	No change
3	Low protein	0.18	-	Burst suppression	Sharp-slow wave activities, ground activity irregularity	No change	No change
4	Low protein Ketogenic	0.14	0.22	Burst suppression	Sharp slow wave activities followed by attenuation in ground activity	No change	No change
5	Glycine free Low protein	0.09	0.16	Burst suppression	Sharp-slow wave activities, ground activity irregularity	Decreased	Decreased
6	Glycine free Ketogenic Low protein	0.1	-	Burst suppression	Sharp-slow wave activities, ground activity irregularity	Decreased	Decreased
7	Low protein Glycine free	0.26	-	Burst suppression	Burst suppression	No change	No change
8	Low protein	0.24	-	Burst suppression	Burst suppression	No change	No change

Abbreviations; NKH: Non-ketotic hyperglycinemia, **EEG:** Electroencephalography, **CSF:** cerebrospinal fluid

between patients with NKH. Basal ganglia such as globus pallidus, thalamus, red nucleus and dentate can be affected (18). Corpus callosum agenesis, ventricular dilatation, diffusion restrictions in corticospinal tract, central tegmental tract, mesencephalon, middle cerebellar peduncle and

dentate nuclei were seen in our study. There were differences between patients. Glycine peak is evident in the MR spectroscopy of patients with severe NKH also may be low and sometimes difficult to detect glycine peak in attenuated types (19). Glycine peak was observed in all of our eight patients. Hennermann et al (20) reported club feet in three, unilateral ptosis in two, micrognathia and dysplastic ears in one, hemangioma localized in the liver in one, congenital hernias in three, and cryptorchism in seven patients with severe NKH. Pes equinovarus, cleft palate and atrial septal defect are some anomalies seen in our patients.

CSF/plasma glycine ratio was measured in three patients after treatment in our study. Although plasma glycine levels decreased in all of the patients, CSF/ plasma glycine ratio increased after treatment. The increase in the CSF/plasma ratio can be explained as follows. Plasma glycine levels decrease with treatment, but since a sufficient decrease in CSF glycine levels is not observed, the rate is determined to be higher. Hennermann et al (20) defined a positive treatment effect as a decrease in plasma glycine levels to ≤300 μmol/L. Positive effects were defined as increased alertness, decreased seizures, and decreased number of anticonvulsants. Currently, the therapy is based on sodium benzoate and the N-Methyl-D-aspartate (NMDA) receptor antagonists. Sodium benzoate reduces plasma glycine concentration by conjugation with glycine and was found to have the most frequent positive effect in both initial and long-term treatment across all forms of NKH. Also, they reported that dextromethorphan therapy showed a good response in all NKH forms, but it was most effective for long-term treatment in children with attenuated NKH. Zammarchi et al. (21) reported that treatment with NMDA receptor antagonists such as dextromethorphan and ketamine may not have long-term efficacy even if it is started too early due to irreversible prenatal brain damage. Bjoraker et al. (22) reported that the sodium benzoate dose is customized for each patient, with the goal of maintaining plasma glycine levels between 120 and 300 μmol/L. All patients in our study received sodium benzoate (250mg/kg/day) treatment. Three patients received sodium benzoate (250mg/kg/day) and dextromethorphan (5-10mg/kg/day) treatment together. While no change was observed in EEG findings after treatment in three patients, improvement was observed in EEG findings in five patients. A relative decrease in seizure frequency was detected during periods of mild elevated glycine levels in all patients except case 8. Although plasma glycine levels remained normal with sodium benzoate treatment, seizures continued in this patient. Ketogenic diet induce ketosis and helps to regulate the neurotoxic cascade initiated by NMDA receptor activation. It has been shown to reduce the glycine, resulting in improved seizure control (23-27). No change was detected in the frequency and duration of the seizures in one patient after ketogenic diet. This situation explained by the short diet period. She could only receive ketogenic diet therapy for one month. Swanson et al. (28) reported that onset of clinical findings at the first month of life, CSF glycine level>230mM, presence of brain malformations was associated with poor prognosis. Hydrocephalus, thin and short corpus callosum has been also shown to indicate severe NKH. Kuseyri Hübschmann et al. (29) reported that CSF glycine concentration ≥ 116.5μmol/l and CSF/plasma glycine ratio ≥ 0.15 are specific for severe forms of the disorder. In contrast to these findings, Zhou et al. (27) reported distinct disease processes and outcomes in 20 Chinese NKH patients. They found that CSF glycine levels and the CSF to plasma glycine ratios are not reliable indicators of prognosis. Although CSF glycine level<230mM in all patients, prognosis was very poor in our study. Our patients present with poor sucking, lethargy, hypotonia, seizure and hiccups in newborn period. They didn't have developmental progress and have intractable epilepsy. Therefore, they were classified as having severe NKH.

Study limitations: Limitations of our study consist of the retrospective nature of the patient evaluation and the small sample size. Further studies involving larger patient cohorts are necessary to gather more comprehensive data on the optimal treatment duration, the differences between medications, and the effectiveness of non-pharmacological treatments for epilepsy.

Conclusion

Although CSF and plasma glycine levels have been reduced by medication, seizures were decreased but continued, unfortunately. Also, we observed that seizures may continue even when plasma glycine levels were normal in one patient. This situation may contribute to treatment follow-up guidelines. In addition, the c.1784dupT mutation was detected as a new mutation in the GLDC gene.

Ethical approval and informed consent: This study has been approved by the local ethics committee of Kayseri City Hospital (279/24.12.2024). Written informed consent was

obtained from patients who participated in this study.

Conflict of interest: The authors have no conflict of interest to declare.

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