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Neonatal Nonketotic Hyperglycinemia: A Severe Case With Prenatal Indicators and Comprehensive Review of Recognition and Management

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ABSTRACT

Nonketotic hyperglycinemia (NKH), also known as glycine encephalopathy, is a rare inherited neurometabolic disorder caused by a deficiency in the glycine cleavage enzyme system (GCS), leading to the pathological accumulation of glycine in blood and cerebrospinal fluid (CSF). This case report details a neonate presenting with central apnea, profound hypotonia, and refractory seizures, alongside prenatal findings of polyhydramnios and hiccup-like fetal movements, all strongly suggestive of severe NKH. Diagnostic evaluation confirmed markedly elevated glycine levels in serum and CSF, with a CSF-to-plasma glycine ratio exceeding 0.08, and ruled out alternative causes of hyperglycinemia. Brain MRI revealed characteristic malformations, corroborating the diagnosis of severe NKH. Treatment included anticonvulsants for seizure management, sodium benzoate for glycine reduction, and NMDA receptor antagonists (ketamine and dextromethorphan) to modulate neurotoxicity. Despite these therapies, the patient demonstrated poor neurodevelopmental outcomes, with rapid progression to severe impairment. This case highlights the significance of early identification, precise diagnosis, and a comprehensive care strategy in managing NKH, aiming to enhance patient outcomes and quality of life.

1 | Introduction

Neurotransmitters, which are endogenous chemical messengers, facilitate synaptic communication between neurons, playing crucial roles in regulating physiological and psychological processes [1]. Inherited neurotransmitter disorders (NTDs), a group of rare neurometabolic disorders, are caused by genetic defects that impair neurotransmitter synthesis or the production of essential co-factors [1]. One such disorder, nonketotic hyperglycinemia (NKH), also known as glycine encephalopathy, results from an inadequate function of the glycine cleavage enzyme system (GCS), leading to pathological accumulation of glycine in serum and cerebrospinal fluid (CSF) [2].

NKH is estimated to affect between 1 in 63,000 and 1 in 12,000 live births [3, 4]. This condition results from the inadequate function of the glycine cleavage enzyme system (GCS), leading to the accumulation of excess glycine in the serum and tissues [2]. While this condition is rare, its nonspecific and early-onset symptoms may contribute to delayed recognition or potential underdiagnosis in some cases. In neonates with NKH, glycine levels are significantly elevated in both serum and CSF, with a CSF-to-plasma glycine ratio exceeding 0.08, which is a critical diagnostic threshold. Conversely, perinatal factors such as sodium valproate use, congenital intrauterine infections, and neonatal asphyxia can also cause elevated glycine levels; however, these cases typically exhibit normal CSF glycine levels, distinguishing them from NKH [2].

Summary

- Early recognition of neonatal nonketotic hyperglycinemia is critical, aided by prenatal indicators such as hiccup-like movements.
- Treatment involves antiepileptic drugs, sodium benzoate, and ketamine for NMDA receptor modulation.
- However, prognosis remains challenging, emphasizing the importance of holistic care and therapeutic advancements.

Glycine functions as an excitatory neurotransmitter in the brain, acting on NMDA receptors in regions like the hippocampus, cortex, and cerebellum. This overstimulation can result in intractable seizures and neurotoxicity [5]. In contrast, glycine's role as an inhibitory neurotransmitter in the spinal cord and brainstem can lead to symptoms such as central apnea, persistent hiccups, and profound hypotonia [5]. This dual effect contributes to the varied and severe clinical presentations associated with NKH, which often emerge within the first days of life. Without timely diagnosis and intervention, affected neonates may rapidly progress to severe neurodevelopmental impairment or early mortality [5].

Although research has elucidated NKH's pathophysiology and diagnostic criteria, gaps remain in our understanding of optimal management approaches and long-term outcomes for affected patients. This report presents a case that highlights these challenges and underscores the importance of early diagnosis, differential diagnosis, and a multidisciplinary approach to managing NKH.

2 | Case History

A 3-day-old term male neonate (38 weeks gestation), born via cesarean section (C/S) to a 28-year-old mother (the previous cesarean was due to thick meconium), was brought from home by his parents due to frequent abnormal limb movements and persistent hiccups. The neonate, the second child of the family, had a birth weight of 3700 g, a length of 52 cm, and a head circumference of 35 cm. Apgar scores were 9 at one minute and 10 at five minutes. From birth, the infant exhibited weak crying and sucking ability, which progressively worsened over 3 days.

The infant initially had weak sucking and minimal feeding, which further deteriorated to an inability to breastfeed due to reduced reflexes. Phototherapy had been initiated at another center, and the parents reported normal stool and urine output. Family history was negative for coronary artery disease, ischemic heart disease, congenital heart disease, diabetes, inborn errors of metabolism, and hyperlipidemia. There was no history of genetic consanguinity between the parents. The first child in the family was healthy.

The mother had received appropriate prenatal care, including two ultrasounds that identified polyhydramnios. She reported intermittent fetal movements resembling hiccups in the last 2–3 weeks of pregnancy, which were deemed normal by her obstetrician. She had no history of thyroid disorders, gestational diabetes, urinary tract infections, preeclampsia, or premature membrane rupture, and took only routine prenatal vitamins.

Upon admission, the neonate appeared lethargic, hypotonic, and had a non-syndromic facial appearance. Initial vital signs included a respiratory rate of 40/min, heart rate of 115/min, oxygen saturation of 93%, and blood pressure of 72/35 mmHg. Shortly after admission, the infant exhibited apneustic respiration with oxygen saturation dropping to 85%. Despite initial noninvasive oxygenation, intubation was performed due to persistent low oxygen saturation and metabolic and respiratory acidemia confirmed by arterial blood gas analysis (pH: 6.940, pCO_2: 109.0 mmHg, pO_2: 61.9 mmHg, and HCO_3: 22.2 mmol/L).

Physical examination showed normal skin, head, and neck findings, with normocephaly and normal fontanelles. Eyes and ears were normal without anomalies, and the mouth and pharynx were free of cleft lip or palate. Chest examination was normal, although chest wall movement appeared reduced. The heart and abdomen were unremarkable, with no signs of organomegaly or distension. The limbs were without edema, deformities, cyanosis, or clubfoot. Neonatal reflexes were absent for Moro and sucking, with a diminished grasp reflex and hypotonic extremities, including reduced axial tone.

3 | Methods

3.1 | Differential Diagnosis (DDX)

The neonate presented with seizures, hypotonia, and persistent hiccups, prompting an initial evaluation for potential metabolic disorders, including nonketotic hyperglycinemia (NKH) and organic acidemias such as methylmalonic acidemia (MMA), propionic acidemia (PA), and glutaric acidemia (GA). To assess these conditions, a metabolic panel and serum and CSF glycine levels were requested. A non-contrast brain CT scan was performed as an emergency evaluation, and brain sonography was completed to rule out structural abnormalities.

Given the prenatal history of polyhydramnios, gastrointestinal obstructive diseases were briefly considered, but this was deemed unlikely due to normal NG tube passage into the stomach, normal stool passage, and the absence of abdominal distension or organomegaly on examination.

Additionally, a cardiovascular evaluation via echocardiography was performed, revealing moderate tricuspid regurgitation (TR) and mild mitral regurgitation (MR), findings that did not contribute significantly to the clinical presentation.

3.2 | Investigations

The brain CT scan, conducted in the emergency department, showed evidence of hypoxic changes, including ventriculomegaly, a large cisterna magna, and diffuse cystic changes. Following stabilization, a brain MRI confirmed cortical and

subcortical atrophy, corroborating the CT findings and supporting the clinical suspicion of NKH.

Laboratory investigations included ammonia, lactate, and plasma and urine organic acids. Plasma and CSF amino acid analysis, conducted using tandem mass spectrometry (MS/MS), revealed elevated glycine levels, confirming a CSF-to-plasma glycine ratio of 0.24 (normal < 0.08), consistent with NKH (Table 1).

An EEG could not be performed due to resource limitations at the center; however, a neurologist was consulted, and anticonvulsant therapy was initiated to manage seizures until further diagnostic evaluation, including EEG, could be conducted after discharge.

3.3 | Treatment

The patient was initially treated with levetiracetam (5 mg/kg q12h) and vitamin B6 for seizure activity. Despite persistent seizures, additional anticonvulsant therapy with phenobarbital (3 mg/kg/day in one to two divided doses) and topiramate (25 mg q12h) was administered. Due to ongoing seizure activity, a midazolam drip was initiated.

Arterial blood gas analysis revealed mixed metabolic and respiratory acidemia (pH: 6.940, pCO_2: 109.0 mmHg, pO_2: 61.9 mmHg, and HCO_3: 22.2 mmol/L), necessitating intubation following a trial of noninvasive oxygenation. Intravenous albumin was administered to address albumin levels, which were decreased.

Given the confirmed elevation of serum and CSF glycine levels, treatment specific to NKH was initiated, including sodium benzoate (250 mg/kg/day over 24 h) to lower glycine levels and dextromethorphan (2.5 mg/day divided into two doses) to modulate NMDA receptor activity. Additionally, vitamin A and D drops (five drops daily) and L-carnitine (50 mg/kg/day PO, divided q8–12 h) were administered for supportive care and metabolic optimization, following standard neonatal guidelines.

3.4 | Result: Outcome and Follow-Up

After stabilization and a 7-day course of mechanical ventilation, the patient was extubated and transitioned to maternal milk feeding via nasogastric (NG) tube during intubation, with direct breastfeeding initiated after extubation.

Further metabolic evaluations ruled out propionic acidemia and methylmalonyl-CoA mutase deficiency based on normal levels of organic acids, ammonia, lactate, homocysteine, uric acid, and plasma acylcarnitines. A diagnosis of nonketotic hyperglycinemia (NKH) was confirmed with a CSF-to-plasma glycine ratio of 0.24 (normal < 0.08).

The patient was discharged in good general condition with stable vital signs and was tolerating breastfeeding. The following treatment regimen was prescribed:

- Sodium benzoate: 250 mg/kg/day in divided doses
- Dextromethorphan: 2.5 mg/day in two divided doses
- Topiramate: 25 mg q12 h
- Phenobarbital: 3 mg/kg/day in one to two divided doses
- Levetiracetam: 5 mg/kg q12 h
- Vitamin A and D drops: five drops daily
- L-carnitine: 50 mg/kg/day PO divided q8–12 h

The patient was advised to follow-up with a neurology clinic for EEG evaluation, a pediatric endocrinology and metabolism clinic, and undergo audiometry for hearing assessment. Genetic testing and counseling were offered after discharge, but the family did not complete the follow-up appointments.

4 | Discussion

Nonketotic hyperglycinemia (NKH) is a rare autosomal recessive inborn error of metabolism caused by a deficiency in the glycine cleavage system (GCS), resulting in the accumulation of glycine in the body's tissues, including the brain and spinal cord. The GCS comprises mitochondrial enzymes responsible for breaking down glycine into carbon dioxide, ammonia, and one-carbon units, with activity reported in the brain, liver, kidneys, and testes of vertebrates. This system consists of four distinct proteins: glycine dehydrogenase (decarboxylating), aminomethyltransferase, GCS H-protein, and dihydrolipoamide dehydrogenase, encoded by the GLDC, AMT, GCSH, and DLD genes, respectively [6].

Excessive glycine in the brain overstimulates NMDA receptor channels, leading to intractable seizures and brain damage. In the spinal cord and brainstem, glycinergic receptor activation causes central apnea, hiccups, and diffuse hypotonia. Elevated glycine levels increase NMDA receptor stimulation, cation channel activity, intracellular calcium accumulation, endonuclease activity, DNA fragmentation, and subsequent neuronal cell death [1].

Four types of NKH have been identified [4]. The neonatal form is the most common, with symptoms appearing within the first few days of life (6 h to 8 days), including poor feeding, failure to suck, lethargy, and profound hypotonia, which can rapidly progress to deep coma, apnea, and death. Convulsions, particularly myoclonic seizures and hiccups, are common. Laboratory findings diagnostic of NKH include hyperglycinemia, hyperglycinuria, unequivocal elevation of CSF glycine concentration, and a high CSF-to-plasma glycine ratio (> 0.08, normal < 0.02). Urine assays in these patients are negative for organic acids [4].

Infantile NKH develops signs and symptoms after 6 months of age in previously normal infants but is milder than the neonatal form [4]. Late-onset NKH manifests as progressive spastic diplegia, optic nerve atrophy, and choreoathetotic movements, with onset ranging from 2 to 33 years. Symptoms of delirium, chorea, and vertical gaze palsy may occur episodically during intercurrent infections. Mental development is usually normal,

TABLE 1 | Analysis of plasma and CSF amino acids.

	Amino acids profile by LC–MS/MS					
	CSF			Plasma		
Amino acid	Result (μM)	Normal value	Description	Result (μM)	Normal value	Description
Alanine	25.2	24–124	Normal	100.6	139–474	Abnormal
Allo-isoleucine	0	< 3	Normal	0.1	< 2	Normal
Alpha-aminobutyric acid	0.1	< 15	Normal	0.3	< 4	Normal
Arginine	8.5	5–39	Normal	18.5	12–94	Normal
Argininosuccinic acid	0	< 1	Normal	0	< 0.2	Normal
Asparagine	10.9	8–34	Normal	29.4	25–91	Normal
Aspartic acid	1.7	< 3	Normal	12.8	< 20	Normal
Beta-aminoisobutyric acid	0	< 1	Normal	0.4	< 5	Normal
Beta-alanine	2.1	< 26	Normal	3.8	< 28	Normal
Citrulline	3.2	< 11	Normal	13.3	7–42	Normal
Cystathionine	0	< 1	Normal	0	< 2	Normal
Cystine	0.2	< 2	Normal	6.9	2–25	Normal
Gamma-aminobutyric acid	0.1	< 1	Normal	0.2	< 1.5	Normal
Glutamic acid	7.9	< 12	Normal	84.2	31–202	Normal
Glutamine	345.8	467–1832	Abnormal	222.5	316–865	Abnormal
Glycine	152.7	5–41	Abnormal	633.7	111–426	Abnormal
Glycylproline	0	< 1	Normal	0	< 0.5	Normal
Histidine	15.9	11–70	Normal	69.9	10–116	Normal
Homocitrulline	0	< 3	Normal	0.1	< 1	Normal
Homocystine	0	< 1	Normal	0	< 0.2	Normal
Hydroxylysine	0	< 1	Normal	0.1	< 0.5	Normal
Hydroxyproline	1.5	< 7	Normal	17.5	8–61	Normal
Isoleucine	3.9	< 27	Normal	9.3	24–105	Abnormal
Leucine	18.8	12–41	Normal	49.0	48–205	Normal
Lysine	36	11–80	Normal	97.7	49–283	Normal
Methionine	2.9	< 43	Normal	9.9	11–44	Abnormal
Ornithine	6.6	< 24	Normal	43.9	20–130	Normal
Phenylalanine	9.6	7–40	Normal	31.0	28–122	Normal
Proline	2.4	< 17	Normal	61.5	85–303	Abnormal
Serine	38.4	26–136	Normal	205.4	69–271	Normal
Sulfocysteine	0	< 3	Normal	0.2	< 1	Normal
Threonine	63.6	32–143	Normal	123.4	47–237	Normal
Tryptophan	2.4	< 12	Normal	19.1	17–135	Normal
Tyrosine	10.6	8–83	Normal	27.4	26–139	Normal
Valine	18.8	14–61	Normal	97.5	83–312	Normal

but mild cognitive impairment and infrequent seizures have been reported. Laboratory findings are similar to neonatal NKH but less pronounced [4]. Transient NKH is indistinguishable from the neonatal form but resolves clinically and biochemically by 2–8 weeks of age after cessation of glycine-lowering medication [4].

The severity and prognosis of NKH are related to the residual activity of the GCS, with two defective alleles resulting in worse outcomes compared to a single defective allele [7]. NKH severity is also classified based on developmental milestones, with higher CSF glycine concentrations associated with severe forms. However, low glycine levels do not preclude severe NKH [7]. Irreversible brain damage due to glycine can begin in utero, linked to poor prognosis, as suggested by pre-birth hiccup-like movements in our case [8]. It should be noted that polyhydramnios, cervical cysts, fourth ventriculomegaly, hydrops (abdominal wall and scalp edema), and bone defects in the perinatal period can be early indicators of the disease, as observed in our case [9]. Paying attention to these prenatal symptoms can facilitate the early diagnosis of the disease.

Early symptoms, CSF glycine levels $> 230\,\mu M$, brain MRI malformations, and two non-missense mutations indicating nonfunctional GCS are associated with severe NKH [10, 11]. Farris et al. introduced a quantitative Weighted Multiparametric Mutation Score (WMMS) for accurately predicting NKH severity based on clinical and genetic evaluations [12]. In the absence of molecular and genetic testing, MRI abnormalities, particularly corpus callosum agenesis, should be considered for severity assessment [13].

Our patient underwent metabolic and imaging evaluations that confirmed NKH, but follow-up was incomplete. Genetic counseling was offered, although the family did not return for follow-up genetic testing. No developmental milestones were assessed due to the lack of follow-up visits.

Despite efforts, most patients with neonatal and infantile NKH do not survive beyond these stages, with only two cases reaching childhood. However, the transient form may normalize glycine levels and continue without developmental issues, indicating possible underdiagnosis and study bias [4, 9]. The survival of two patients from neonatal and infantile stages to childhood without ventilation raises the hypothesis that glycine transporter 1 function may be critical in early life [9].

Follow-up evaluation with EEG was advised to monitor seizure control, although this could not be completed at our facility due to resource limitations. The absence of follow-up findings, including current age, EEG, and developmental milestones, limits the depth of our discussion.

Diagnosis is based on clinical features (seizures, muscle hypotonia, and lethargy) unexplained by infection, trauma, hypoxia, or other causes, elevated plasma and CSF glycine levels, absence of urinary organic acids, burst suppression pattern on EEG, brain MRI abnormalities, 13C glycine breath test, multiplex ligation-dependent probe amplification (MLPA) for DLD gene deletion, and genetic tests for SLC6A9 [9]. Genetic testing is definitive but may be normal in transient NKH.

No standard or effective treatment exists. Current management focuses on anticonvulsants to control seizures, sodium benzoate to reduce plasma glycine, and NMDA receptor antagonists like ketamine or oral dextromethorphan [2]. Sodium benzoate can reduce glycine levels but may cause gastrointestinal issues (gastritis, reflux, and esophagitis), renal tubular dysfunction, and carnitine depletion. Excessive use may lead to sodium benzoate toxicity, coma, metabolic acidosis, hypokalemia, and hypocalcemia, necessitating regular monitoring of glycine, sodium benzoate, and carnitine levels to minimize side effects [7]. NMDA antagonists can reduce seizures, normalize EEG, and positively impact muscle hypotonia and apnea. Ketamine, although superior to other NMDA antagonists, may cause increased sleepiness, agitation, or involuntary movements [14, 15]. Dextromethorphan has shown good clinical response in all NKH types, particularly in children with milder forms, improving alertness, reducing seizures, and decreasing the need for anticonvulsants [13]. Perampanel, an AMPA receptor antagonist, is suggested for patients unresponsive to combined sodium benzoate and NMDA antagonist therapy [16].

Other treatments include additional anticonvulsants for refractory seizures, avoiding valproate due to its inhibitory effect on GCS and potential to induce seizures [17]. Non-pharmacological treatments for refractory seizures are also recommended [18]. The ketogenic diet, a high-fat, low-carbohydrate, moderate-protein diet used for drug-resistant epilepsy and epileptic encephalopathy (e.g., Dravet syndrome and Lennox–Gastaut syndrome), has shown promise in controlling refractory seizures in classic NKH [2]. Vagus nerve stimulation may reduce anticonvulsant use, improve seizure control, and decrease myoclonic and tonic seizures [7].

NKH patients require multidisciplinary care, including neurological, metabolic, gastrointestinal, cardiovascular, and orthopedic support. Gastrointestinal care addresses feeding problems, gastroesophageal reflux, esophagitis, and gallstones. Cardiovascular care includes echocardiography for cardiac anomalies (e.g., mitral valve defects, patent ductus arteriosus, patent foramen ovale, and dilated cardiomyopathy). Also, pulmonary hypertensive vascular disease (PHVD) may be an initial NKH manifestation [7]. Orthopedic care is needed for early-onset progressive neuromuscular scoliosis and hip dislocations [7].

Given the rarity of nonketotic hyperglycinemia (NKH) and the potential for underdiagnosis, it is crucial to thoroughly evaluate patients presenting with relevant symptoms. Early diagnosis is imperative to mitigate further damage, prevent complications, and reduce mortality rates. Determining the specific form of NKH can provide valuable insights into the prognosis. Additionally, addressing associated comorbidities can further prevent complications and improve patient outcomes.

5 | Conclusion

NKH should be considered in neonates presenting with persistent hiccups, seizures, hypotonia, reduced reflexes, poor breastfeeding tolerance, abdominal distension, and swallowing difficulties. A history of pre-birth hiccup-like movements can suggest severe NKH due to intrauterine glycine accumulation. Prenatal findings such as polyhydramnios and abnormal fetal

movements may facilitate earlier recognition of the disease. Brain MRI abnormalities, including cortical atrophy or agenesis of the corpus callosum, can help indicate disease severity.

This case highlights the importance of early diagnosis and appropriate management pathways for NKH. Suboptimal management, including limited access to EEG, genetic testing, and long-term follow-up in this case, underscores the need for adherence to standard protocols. Optimal management includes early initiation of anticonvulsants, glycine-lowering agents such as sodium benzoate, and NMDA receptor antagonists like dextromethorphan. Furthermore, a multidisciplinary care approach involving neurology, genetics, and metabolic specialists is essential to address the complex needs of these patients.

Regular follow-up to monitor developmental milestones, seizure control, and glycine levels is crucial to improving outcomes. Genetic counseling and testing should be offered to all families, as identifying mutations in NKH-related genes can guide prognosis and management. Attention to gastrointestinal, cardiovascular, and orthopedic complications is also critical to comprehensive patient care.

Author Contributions

Samaneh Parviz: data curation, investigation, methodology, project administration, supervision, validation. **Dariush Hooshyar:** data curation, writing – original draft, writing – review and editing.

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Ethics Statement

In accordance with the patient journal's consent policy, written informed consent was obtained from the patient's family for the publication of this report. The authors received a waiver for ethical approval from the institutional review board committee.

Consent

Written informed consent for publication was obtained from the patient's family, in line with the patient journal's consent policy.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data available on request due to privacy/ethical restrictions.

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