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Nonketotic Hyperglycinemia: Newborn with Hiccups and Specific Radiological Findings (A Case Report)

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Case Report

Keywords: Nonketotic hyperglycinemia, hiccups, restricted diffusion, sodium benzoate, glycine

Posted Date: November 19th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11149118/v1

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Additional Declarations: No competing interests reported.

Abstract

Background

Nonketotic hyperglycinemia (NKH) is a rare autosomal recessive metabolic disorder resulting from a defect in the glycine cleavage system. This case emphasizes the importance of early recognition of NKH through characteristic clinical and radiological findings, complemented by genetic confirmation.

Case presentation:

A term male neonate of Caucasian origin presented on day five of life with hypotonia, poor feeding, and rhythmic hiccups. Sepsis and initial metabolic workup were unremarkable. Brain MRI showed restricted diffusion in the cerebellar white matter and posterior limbs of the internal capsules, suggestive of NKH. Plasma amino acid analysis revealed elevated glycine, and whole-genome sequencing identified a pathogenic AMT variant. CSF studies could not be performed due to a hemorrhagic lumbar puncture, representing a diagnostic limitation. The patient was treated with levetiracetam, sodium benzoate, and a ketogenic diet, resulting in partial improvement.

Conclusions

Rhythmic hiccups may serve as an early clue to NKH. Early recognition based on integrated clinical, radiological, and genetic findings allows timely initiation of targeted therapy and family counseling

Background

Nonketotic hyperglycinemia (NKH) is a rare autosomal recessive inborn error of metabolism with an incidence of approximately 1 in 76,000.[1] It results from defective glycine degradation, leading to glycine accumulation, particularly in neural tissues.[1, 2] Glycine has both inhibitory and excitatory roles, resulting in symptoms ranging from hypotonia to seizures.[3, 4] NKH can be categorized into two forms severe and attenuated NKH based on outcome. Most cases occur during the neonatal period with more than 80% of neonates presenting with the severe form characterized by early onset lethargy, hypotonia, respiratory distress, myoclonus, and generalized convulsions. [5] Diagnosis relies on elevated plasma and cerebrospinal glycine levels, an increased CSF:plasma glycine ratio, and genetic confirmation. [6] Magnetic resonance imaging (MRI) often reveals diffusion restriction in the infratentorial region before the age of three months in addition to many possible malformations. [7] Diagnosis can be confirmed by molecular genetic testing or enzymatic liver tissue analysis of the glycine cleavage system obtained by biopsy. Recently, enzymatic assays were only performed in select cases. [4][6] There is no presence of a standard treatment for NKH till date. However, multiple therapies targeted at alleviating the consequent effect of elevated glycine levels are in use. [8] Cerebral malformations detected by Magnetic resonance imaging (MRI) of the brain correlate tightly with prognosis. [3]

Case presentation

We describe the case of a 5-day-old Caucasian male infant, product of term gestation transferred to our institution with hypotonia, decreased oral intake and brief intermittent hiccups with vocalization. The patient's name and identifying details have been removed, and the parents provided informed consent for publication of this case report and the accompanying images. The reporting of this case conforms to the CARE guidelines.

The patient was born at term by C-section due to failure to progress. Mother had an uncomplicated pregnancy, negative serologies, and a normal morphological scan. The delivery was uneventful, no cord prolapse or placental abruption. Apgar scores were 9 and 10 at 1 and 5 minutes respectively without any reported perinatal insult. On the fifth day of life, he became somnolent with decreased activity, poor crying, and sluggish sucking requiring admission to the Neonatal Intensive Care Unit. He was calm and hypoactive, afebrile, normotensive, with no respiratory distress. His neurological exam was remarkable for significant hypotonia, decreased deep tendon reflexes in upper and lower extremities with bilateral clonus, and absent primitive reflexes. Ophthalmologic assessment was normal. He developed frequent hiccups and episodes of eye twitching with tachycardia, reaching 190 bpm. Initial laboratory evaluation for sepsis was negative with normal white blood count 14100 with neutrophils 35% and lymphocytes 41%, normal platelets count, and negative C-reactive protein (CRP). Blood and urine cultures were negative, as well. Electrolytes and liver enzymes were unremarkable. Basic work-up for hypotonia was normal, including Creatinine phosphokinase (CPK) level at 169 IU/L, arterial lactic acid 1.98 mmol/L and ammonia 25 µmol/L.

EEG showed a burst suppression pattern suggestive of an inborn error of metabolism vs hypoxic ischemic encephalopathy. Brain Magnetic Resonance Imaging (MRI) / Magnetic Resonance Venography (MRV) revealed delayed myelination with restricted diffusion along the posterior limb of the internal capsules extending to the corona radiata and peri Rolandic area and restricted diffusion in the cerebellar white matter and the brain stem. Which may point out to either a perinatal insult or nonketotic hyperglycinemia. Corpus Callosum was normal with no gyral malformation (Fig. 1). Plasma amino acid analysis revealed markedly elevated glycine levels, establishing with the MRI results the biochemical suspicion of NKH.

A genetic study by whole genome sequencing confirmed the diagnosis of autosomal recessive glycine encephalopathy type 2 (Amino methyltransferase AMT variant). CSF glycine and CSF:plasma glycine ratio could not be assessed because the lumbar puncture was hemorrhagic, precluding accurate CSF analysis. The patient was maintained on levetiracetam for seizure control and initiated on sodium benzoate (250 mg/kg/day) and a ketogenic diet to reduce glycine levels, leading to partial clinical improvement. Biochemical and metabolic findings are summarized in Table 1.

Table 1
Summary of biochemical and metabolic investigations

Test	Result	Reference Range	Interpretation
Plasma glycine	1275 µmol/L	140–420 µmol/L	Elevated
CSF glycine	Not available	5–20 µmol/L	—
CSF:Plasma glycine ratio	Not calculated (hemorrhagic sample)	< 0.04	—
Ammonia	25 µmol/L	10–47 µmol/L	Normal
Lactic acid	1.98 mmol/L	0.5–2.2 mmol/L	Normal
CPK	169 IU/L	24–195 IU/L	Normal

Discussion

This case illustrates a classic neonatal presentation of NKH characterized by hypotonia, feeding difficulty, and distinctive rhythmic hiccups. The picture of our patient is remarkable because, despite the absence of overt signs of metabolic disorder, the occurrence of repetitive rhythmic hiccups is strongly linked to nonketotic hyperglycinemia. [7][9]

Early suspicion was raised by MRI findings showing restricted diffusion in the cerebellar white matter and internal capsules; features considered pathognomonic in the early phase of NKH. [10–12] In the differential diagnosis of neonatal encephalopathy, several metabolic and structural disorders were considered. Hypoxic-ischemic encephalopathy (HIE) was excluded due to normal perinatal history and absence of basal ganglia or cortical injury on MRI. Urea cycle defects were ruled out by normal plasma ammonia levels. Organic acidemias were excluded based on normal metabolic screening, absence of acidosis, and negative urinary ketones. Mitochondrial disorders were considered unlikely given normal lactate levels and lack of characteristic imaging changes. Congenital infections were excluded by negative TORCH serologies and absence of inflammatory markers. Structural brain malformations were ruled out by normal MRI anatomy. Collectively, these findings supported a diagnosis of metabolic encephalopathy secondary to NKH. A significant limitation of this case was the inability to measure CSF glycine or determine the CSF:plasma glycine ratio due to a hemorrhagic lumbar puncture. Nevertheless, the diagnosis was strongly supported by clinical presentation, MRI features, elevated plasma glycine, and confirmatory genetic testing.

Therapeutic options for NKH aim to reduce glycine concentration and modulate its excitatory effects. Sodium benzoate facilitates glycine conjugation and excretion, while dextromethorphan, an NMDA receptor antagonist, can reduce excitatory neurotransmission. [13, 14] There are no recommendations regarding the duration of pharmacotherapy in NKH; however, the attempts to discontinue the use of sodium benzoate resulted in relapse of existing symptoms. [15] Ketogenic diet has also been associated

with improved seizure control and developmental outcomes in select patients.[16] Although treatment does not alter the underlying defect, it may improve alertness and quality of life.

Recognizing repetitive hiccups as an early indicator of NKH can prompt timely neuroimaging and metabolic work-up, facilitating earlier diagnosis and management. Early genetic counseling is essential to guide future reproductive decisions. [17, 18]

Conclusions

Nonketotic hyperglycinemia is a rare cause of neonatal encephalopathy. This case highlights the diagnostic value of combining clinical, radiological, and molecular findings. While no curative therapy exists, early diagnosis enables symptomatic treatment and informed genetic counseling. Continued research into novel therapeutic approaches is essential to improve prognosis and quality of life for affected individuals.

Abbreviations

AMT
aminomethyltransferase
CPK
creatine phosphokinase
CRP
C-reactive protein
CSF
cerebrospinal fluid
EEG
electroencephalogram
HIE
hypoxic–ischemic encephalopathy
MRI
magnetic resonance imaging
MRV
magnetic resonance venography
NKH
nonketotic hyperglycinemia
NMDA
N-methyl-D-aspartate
TORCH
toxoplasmosis,other infections,rubella,cytomegalovirus,and herpes simplex.

Declarations

Consent for publication:

Informed consent for publication of this case report and the accompanying images was obtained from the patient's parents. The patient's name and identifying details have been removed to protect confidentiality.

Competing interests:

The authors declare that they have no competing interests.

Funding:

No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this article.

Author Contribution

M.H and N.H wrote the main manuscript text. M.H did teh supervision and editing. All authors reviewes the manuscript.

Acknowledgements:

Not applicable.

Financial disclosure: The authors have indicated no financial relationships relevant to this article to disclose.

Sources of support: The authors declare no sources of support, including grants, fellowships or gifts of materials.

Availability of data and materials:

The clinical findings supporting this case report are presented in the manuscript and Table 1.

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Figures

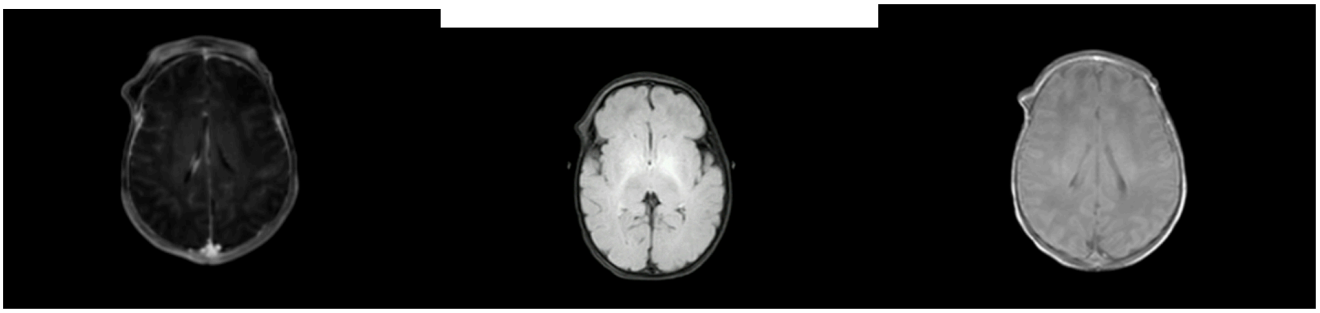


Figure 1

Brain MRI findings in neonatal nonketotic hyperglycinemia. MRI showed restricted diffusion in the posterior limbs of the internal capsules and cerebellar white matter.