International Journal of Contemporary Pediatrics
Narendra CK et al. Int J Contemp Pediatr. 2025 Sep;12(9):1588-1591
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: https://dx.doi.org/10.18203/2349-3291.ijcp20252618

Case Report

Neonatal glycine encephalopathy diagnosed by genetic sequencing: a case report

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Received: 22 July 2025
Accepted: 12 August 2025

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ABSTRACT

Non-ketotic hyperglycinemia (NKH), also known as Glycine encephalopathy, is a rare inborn error of metabolism (IEM) inherited in an autosomal recessive manner. Homozygous or compound heterozygous mutations in GLDC gene, a component of the mitochondrial glycine cleavage system that encodes the P protein, cause Glycine encephalopathy 1(GCE1). Whereas, mutation in the AMT gene, which codes for the T protein of the mitochondrial glycine cleavage pathway, results in glycine encephalopathy 2 (GCE2). In severe cases, symptoms can include lethargy, poor feeding, seizures, breathing difficulties and death. We report the case of a term neonate who presented with lethargy, poor feeding, hypotonia and seizures. Newborn metabolic screening was negative. Whole Exome Sequencing (WES) was done, which identified, a homozygous 1 base pair deletion in exon 7 of the GLDC gene, which is classified as likely pathogenic, for glycine encephalopathy. Baby was treated with sodium benzoate, dextromethorphan and supportive measures. A normal TMS does not exclude the possibility of glycine encephalopathy. The above case highlights the importance of genetic tests like WES in the diagnostic evaluation of suspected metabolic disorders. Early diagnostic confirmation through genetic studies is necessary for timely and accurate management, prognostication as well as for genetic counseling.

Keywords: Glycine**,** Encephalopathy, Genetic, Non-ketotic Hyperglycinemia

INTRODUCTION

Non-ketotic hyperglycinemia (NKH), also known as glycine encephalopathy, is a rare metabolic disorder characterized by the excessive accumulation of the amino acid glycine in the body, particularly in the brain. This condition is caused by a deficiency in the enzyme system responsible for breaking down Glycine, leading to its buildup in various tissues and fluids.[1] The excessive glycine which is accumulated causes stimulation of glycine receptors and N-methyl-D-aspartate receptors, leading to neuronal excitation and neuronal injury.[2]

NKH is a rare inborn error of metabolism (IEM) with an incidence of 1:55000 globally.[3,4] NKH is inherited in an autosomal recessive manner. The GLDC gene (238300), a component of the mitochondrial glycine cleavage system that encodes the P protein, is located on chromosome 9p24. Homozygous or compound heterozygous mutations in this gene cause Glycine encephalopathy 1 (GCE1).[5] Whereas, mutation in the AMT gene (238310), which codes for the T protein of the mitochondrial glycine cleavage pathway, results in Glycine Encephalopathy 2 (GCE2).[6] The signs and symptoms of NKH can vary widely depending on the severity of the enzyme deficiency and the age of onset. The classical type which presents in the neonatal period is usually fatal compared to the atypical NKH, which is a milder form that manifests later in infancy or childhood.[7] In severe cases, symptoms can include lethargy, poor feeding, hypotonia, seizures, breathing difficulties and death.[8] In less severe cases, symptoms may not become apparent until later and may include intellectual disability, speech delay, behavioral problems, and

movement disorders. Diagnosis of NKH typically involves a combination of clinical evaluation, biochemical testing, and genetic analysis. Elevated levels of glycine in the blood, urine, and cerebrospinal fluid are characteristic findings in individuals with NKH.[9] Genetic testing can confirm the diagnosis. EEG in NKH usually shows burst suppression pattern and progresses to hypsarrhythmia. MRI Brain may show corpus callosal dysgenesis or agenesis, hypomyelination and cerebral atrophy.[10]

Management of NKH is primarily supportive and aimed at minimizing symptoms and complications. Treatment may include dietary modifications, such as glycine-restricted diets and supplementation with special formulas designed to reduce glycine intake. Medications to help control seizures and other symptoms may also be prescribed. Sodium benzoate is commonly used to reduce serum glycine levels. In severe disease, high doses upto 750mg/kg/day have also been tried. N-methyl-D-aspartate antagonists like Dextromethorphan or ketamine have also been tried for symptomatic improvement.[11,12] Early intervention with therapies such as physical therapy, occupational therapy, and speech therapy can help optimize developmental outcomes for affected individuals.

Prognosis for individuals with NKH varies depending on the severity of the condition and the effectiveness of treatment. In severe cases, NKH can be life-threatening, particularly if left untreated. Even with treatment, individuals with NKH may experience refractory seizures, developmental delays and neurological complications that can impact quality of life. NKH cases are rarely reported in India likely due to diagnostic constraints. Here we report a case of a NKH admitted in a tertiary care NICU in Western India.

CASE REPORT

Baby boy was born to 20-year-old primi gravida with third degree consanguineous marriage. There was no other significant antenatal history, past history and obstetrical history. Baby was delivered by spontaneous vaginal delivery at term gestation. Baby had a weak cry at birth. Baby was resuscitated and required positive pressure ventilation for 30 seconds, following which cry and activity had improved. The birth weight was 2.7 kg (15th to 50th percentile), the length was 49 cm (15th to 50th percentile) and the head circumference was 34.0 cm (15th to 50th percentile).

At 6 hours of life, baby presented with lethargy and poor feeding. On examination, baby was noted to have hypotonia, depressed sensorium, poor sucking and seizures. Considering probable sepsis, antibiotics were initiated after sending blood culture. Septic screen and CSF analysis turned out to be negative for sepsis. Blood culture and CSF culture were sterile. Hypoglycemia and dyselectrolytemia were ruled out. Renal function test and liver function tests were normal. Lactate and arterial blood gas reports were noted to be within normal limits. Urine ketones were negative. Cranial ultrasound was normal.

Subsequently, during the evaluation for Inborn errors of metabolism, three consecutive blood samples were reported to be non-recordable for ammonia levels. Considering hyperammonemia as cause for encephalopathy, peritoneal dialysis was started. Hyperammonemia with normal blood gases pointed towards urea cycle defect. So baby was kept nil per oral and started on sodium benzoate, arginine and carnitine supplementation. Further ammonia levels were recorded between 90 to 200 mcg/dl which were close to normal limits. Peritoneal dialysis was omitted after performing for 60 hours. Further there was no increase in ammonia levels after stopping peritoneal dialysis. Newborn metabolic screening (TMS) for urea cycle defects, organic acidemias and fatty acid oxidation disorders turned out to be negative.

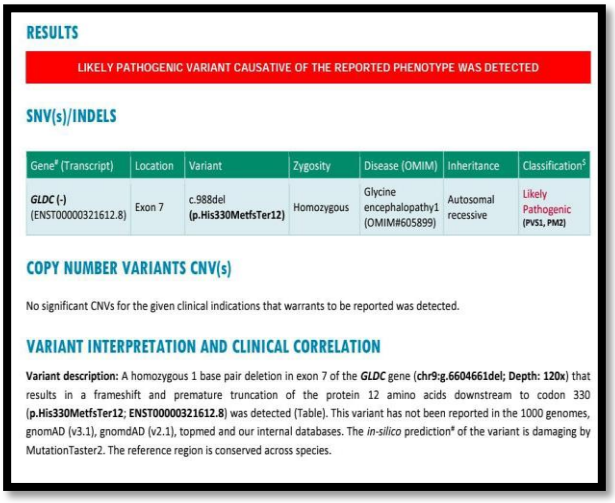
By day 3 of life, baby developed seizures, hiccups and continued to have persistent encephalopathy. So, baby was started on antiepileptic drug phenobarbitone. Levetiracetam was also added and increased up to 60 mg/kg/day to control seizures. EEG showed bilateral epileptiform discharges. Baby was intubated and started on conventional ventilation because of repeated seizures, poor respiratory efforts, persistent encephalopathy and respiratory acidosis in blood gas analysis.

In view of persistent encephalopathy, seizures, hypotonia and hiccups, possibility of Non ketotic hyperglycinemia (NKH) was strongly considered. Newborn metabolic screening was negative. CSF, Serum and urinary glycine levels (quantitative) were not done because of technical constraints. Dextromethorphan supplementation was started at 15 mg/kg/day considering NKH as an important differential diagnosis. Whole Exome sequencing was done which revealed, a homozygous 1 base pair deletion in exon 7 of the GLDC gene (chr9: g.6604661del), which is classified as likely pathogenic, for Glycine encephalopathy (Figure 1).

Sodium benzoate doses were increased up to 600 mg/kg/day and Dextromethorphan supplementation at 15 mg/kg/day was continued. CT imaging of brain revealed diffuse confluent hypodensity in bilateral white matter with minimal ventricular prominence, subarachnoid enhancing and inadequately visible corpus callosum. Baby was continued on ventilator support till third week of life in view of persistent encephalopathy and poor respiratory efforts. Very slow improvement in the sensorium and movements were noted. No further seizures were noted. Baby developed Ventilator Associated Pneumonia and was treated with 3rd line antibiotics. Gradually ventilator parameters were tapered and baby was started on CPAP support by 28 days of life. By day 32 of life, baby was off respiratory support.

Spoon feeds of expressed breast milk was started by 5th week of life. Baby was discharged on day 40 of life, on oral feeds.

On follow up, baby was noted to have global developmental delay. MRI Brain done at 4 months of life showed delayed myelination involving bilateral internal capsules and cerebellum. Marked diffuse thinning of corpus callosum was also noted. Baby was continued on neurodevelopmental follow up and started on early interventional therapy. Genetic counseling was given to parents regarding future pregnancies.



RESULTS

LIKELY PATHOGENIC VARIANT CAUSATIVE OF THE REPORTED PHENOTYPE WAS DETECTED

SNV(s)/INDELS

Gene# (Transcript)	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification$
GLDC (-) (ENST00000321612.8)	Exon 7	c.988del **(p.His330MetfsTer12)**	Homozygous	Glycine encephalopathy1 (OMIM#605899)	Autosomal recessive	Likely Pathogenic **(PVS1, PM2)**

COPY NUMBER VARIANTS CNV(s)

No significant CNVs for the given clinical indications that warrants to be reported was detected.

VARIANT INTERPRETATION AND CLINICAL CORRELATION

Variant description: A homozygous 1 base pair deletion in exon 7 of the ***GLDC*** gene (**chr9:g.6604661del; Depth: 120x**) that results in a frameshift and premature truncation of the protein 12 amino acids downstream to codon 330 (**p.His330MetfsTer12**; **ENST00000321612.8**) was detected (Table). This variant has not been reported in the 1000 genomes, gnomAD (v3.1), gnomdAD (v2.1), topmed and our internal databases. The *in-silico* prediction# of the variant is damaging by MutationTaster2. The reference region is conserved across species.

Figure 1: Whole exome sequencing report showing deletion in GLDC gene, likely pathogenic for glycine encephalopathy.

DISCUSSION

In our case, we noted a history of consanguineous marriage, which could have resulted in homozygosity of the defective gene. Similar history of consanguinity was noted by Flusser et al and Yu et al.[13,14] However, 3 unrelated people with a mild type of glycine encephalopathy were reported by Dinopoulos et al.[15]

NKH has a classical neonatal form and atypical mild form. Most of the classical neonatal forms of GCE present in the neonatal period with lethargy, myoclonic jerks, hypotonia, hiccups and apnea. Hayasaka et al reported a case of NKH born to unrelated parents which presented with poor sucking, hypotonia, decreased responsiveness and mildly elevated ammonia and markedly elevated Glycine in blood and CSF.[16] Since it is a classical neonatal form which is severe, the baby died at age of 12 days. Autopsy of the liver and brain study revealed defect in P protein suggestive of GCE 1. Our patient had a similar clinical presentation, but had a comparatively better outcome. Hayasaka et al had also reported another case of NKH with T protein deficiency which was similar to case reported by Schutgens et al.[17] Hove et al reported four patients with classical NKH who developed hydrocephalus with brain imaging suggestive of acute hydrocephalus, atrophy of white matter and extremely thin corpus callosum, where findings were similar to our case.[18]

Hayasaka et al reported atypical NKH or mild glycine encephalopathy which is phenotypically heterogeneous and nonspecific.[16] These patients manifest later in the infancy or in the childhood. They can present with features of delirium, chorea, ataxia, mental retardation, ADHD and autism spectrum disorder. Patients with atypical GCE and signs of increasing central nervous system degeneration was reported by Hayasaka et al, Ando et al, Frazier et al and Flannery et al.[19-21]

Over the course of eight years, Tan et al screened 733, 527 newborns, and nine of them had an NKH diagnosis.[22] Two appeared within 72 hours and had neonatal glycine levels over our cut-off and newborn screening was not beneficial. In case of mild or early glycine encephalopathy, standard screening methods like tandem mass spectrometry (TMS) may not be sensitive to detect the disease. Hence even if metabolic screening is normal, additional tests like CSF glycine levels have to be carried out, as CSF to serum glycine level ratio is more diagnostic. In our case, metabolic screening was normal and the clinical index of suspicion was high. Hence genetic testing was done, which revealed the diagnosis of glycine encephalopathy.

A homozygous mutation in the GLDC gene was found by Boneh et al in 8 Arab patients suffering from glycine encephalopathy. Flusser et al and Dinopoulos et al also reported similar finding as seen in our case. Treatment with dextromethorphan and sodium benzoate within 12 days of birth, in a neonate with GCE showed improvements in both clinical and electrophysiologic aspects, according to Hamosh et al, Zammarchi et al started the treatment at 65 hours of life and they saw only temporary improvement on the same regimen.[23,24] High doses of benzoate treatment for GCE patients can lower CSF glycine levels and improve wakefulness and seizure control, which will improve the quality of life for infants who survive. However, even with early initiation of treatment, mental retardation may still develop. Hove et al reported treatment with L-carnitine normalized plasma-free carnitine. Authors had supplemented our patient with dextromethorphan, carnitine and arginine which showed a significant improvement.

CONCLUSION

Overall, non-ketotic hyperglycinaemia is a complex neurometabolic disorder that requires a multidisciplinary approach to management, involving healthcare professionals from various specialties including neonatology, genetics, neurology, nutrition, and developmental pediatrics. A normal TMS does not exclude the possibility of glycine encephalopathy. Whole exome sequencing is an important diagnostic tool for

evaluation of this metabolic disorder. Through early diagnosis, comprehensive care, and ongoing support, individuals with NKH can have the best possible outcomes and quality of life. Early diagnostic confirmation through genetic studies is necessary for timely and accurate management, prognostication as well as for genetic counselling.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Narendra CK, Pallithanam JJ, Sreekumar K, Joshi V. Neonatal glycine encephalopathy diagnosed by genetic sequencing: a case report. Int J Contemp Pediatr 2025;12:1588-91.