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Case Report

Clinical and genetic characterization of neonatal non-ketotic hyperglycinemia: a rare case with SLC6A9 gene mutation

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ABSTRACT

Nonketotic hyperglycinemia (NKH) is a rare autosomal recessive disorder caused by mutations in the glycine cleavage system (GCS), leading to glycine accumulation in cerebrospinal fluid (CSF) and plasma, with an increased CSF-to-plasma glycine ratio. Typically presenting in the neonatal period, symptoms include lethargy, poor feeding, hypotonia, seizures, and encephalopathy, often resulting in severe neurological impairment. Early diagnosis is vital but challenging due to the rarity and nonspecific nature of symptoms, especially in populations with high consanguinity rates. We report a neonate born to consanguineous parents who developed severe encephalopathy within 48 hours of birth despite normal antenatal and perinatal findings. The infant exhibited poor feeding, seizures, and worsening neurological status. NKH was confirmed by elevated CSF glycine levels and genetic analysis identifying a novel SLC6A9 mutation. This case highlights the importance of considering NKH in neonatal encephalopathy and the need for genetic testing and counseling in at-risk groups

Keywords: Nonketotic hyperglycinemia, CSF glycine, SLC6A9 gene

INTRODUCTION

Nonketotic hyperglycinemia (NKH), also known as glycine encephalopathy, is a rare and life-threatening genetic disorder that disrupts the body's ability to metabolize glycine properly.[1] This results in the accumulation of glycine, particularly in the central nervous system (CNS), leading to severe neurological damage. With an incidence of approximately 1 in 55,000 to 1 in 76,000 live births, NKH is an uncommon yet devastating condition that typically manifests in the first few days of life.[2]

NKH is a condition caused by a defect in the GCS, a mitochondrial enzyme complex responsible for breaking down glycine. The GCS operates in various tissues, including the brain, kidney, liver, and testis, and consists of four key proteins: glycine dehydrogenase, aminomethyl transferase, GCS H-protein, and dihydrolipoamide dehydrogenase. Mutations in the genes encoding these proteins, particularly GLDC, AMT, and GCSH, disrupt glycine metabolism, leading to NKH. Notably, GLDC mutations account for 75% of classic NKH cases, while mutations in GCSH and AMT contribute to less than 1% and 20% of cases, respectively.[3]

The most severe and frequent presentation, known as the classic form of NKH, is marked by infantile encephalopathy, respiratory distress, and multifocal myoclonic seizures. Additionally, glycine levels are regulated by glycine transporters GLYT1 and GLYT2, encoded by SLC6A9 and SLC6A5, respectively.

Mutations in SLC6A9, which encodes GLYT1, can also lead to NKH, further highlighting the complexity of the glycine regulation as well as its critical role in this disorder.[4,5]

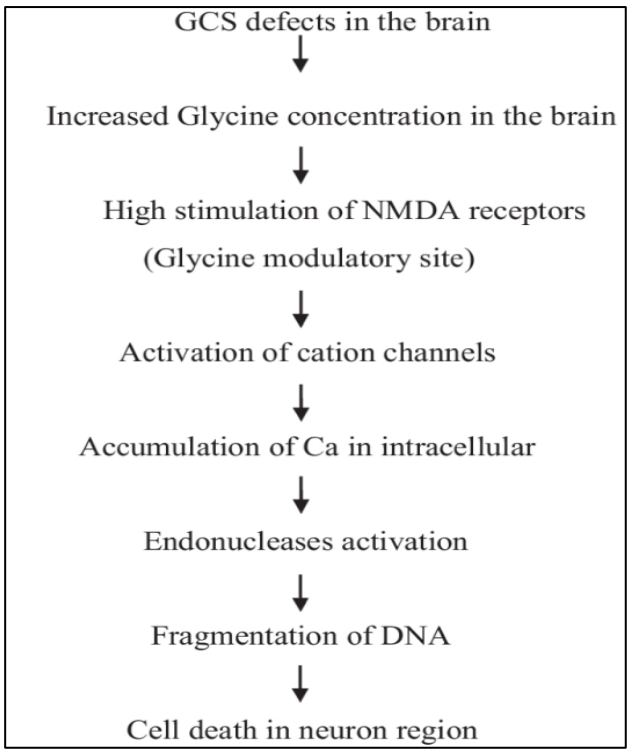

Figure 1: Pathophysiology of non ketotic hyperglycinemia.[3]

Astrocytes in the CNS play a significant role in glycine metabolism as they contain the GCS, indicating that glycine breakdown predominantly occurs in these cells. The GCS is closely linked to N-methyl-D-aspartate (NMDA) receptors in the brain. This association suggests that astrocytes with GCS are involved in NMDA receptor regulation. Excess glutamate exposure leads to neuronal damage by causing DNA fragmentation into nucleosomal-sized fragments, a hallmark of glutamate-induced neuronal death. Elevated intracellular calcium levels, triggered by glutamate overstimulation, are also implicated in this DNA fragmentation, further contributing to neuroexcitotoxicity.[3]

Glycine exerts distinct effects depending on its site of action. It activates glycinergic receptors in the brainstem and spinal cord, producing inhibitory effects that lead to symptoms such as hypotonia and apnea. Conversely, in the cerebral cortex, glycine acts as an excitatory neurotransmitter at the modulatory site of NMDA receptors, which contributes to seizures. In NKH, this excitatory effect underpins the characteristic seizures, while the inhibitory effects account for hypotonia and apnea.[1] NKH typically manifests within the first few days of life, presenting with symptoms such as lethargy, myoclonic jerks, hiccups, and severe encephalopathy. The prognosis is grim, with a mortality rate of approximately 50% in the first week of life. [1]

In this case report, we present the diagnosis of NKH in a neonate, confirmed through a comprehensive CSF study and clinical exome sequencing, emphasizing the importance of considering rare disorders like NKH in the differential diagnosis of neonatal encephalopathy and seizures.

CASE REPORT

We present the case of a 48-hour-old female neonate, born outside our facility, who was admitted with a history of poor feeding, seizures, and encephalopathy. The baby was born to a 26-year-old primigravida mother from a second-degree consanguineous marriage. The mother had a normal pregnancy with no antenatal risk factors, and all ultrasound scans during each trimester showed normal results. The baby was born at term via emergency cesarean section (indicated for non-progressing labor) with a birth weight of 3 kg. The baby cried immediately after birth, and there was no history of perinatal asphyxia. The APGAR scores at 1 minute and 5 minutes were 8 and 9, respectively. Breastfeeding was initiated within half an hour, and the baby was shifted to the mother's side.

At 12 hours of life, the baby developed poor sensorium, followed by seizures at 24 hours, which required treatment with antiepileptic drugs. The baby was referred to our hospital at 48 hours of life for further management. Upon admission, the baby's vital signs were stable, but activity was poor, with hypotonia noted in all four limbs. Neonatal reflexes were absent, and systemic examinations were otherwise unremarkable. Blood glucose levels were normal, and the baby was started on IV fluids, with serum electrolytes also normal. We initially suspected metabolic causes of encephalopathy, such as urea cycle disorder. The first arterial blood gas (ABG) was normal, and initial laboratory investigations revealed normal hemoglobin, white blood cell count, and platelet count, with negative CRP and sterile blood cultures. Given the encephalopathy with no identifiable cause and normal investigations, NKH was considered.

Subsequent testing showed an elevated serum ammonia level of 974.6 µg/dl (normal range: 9-150 µg/dl), while serum lactate levels were within normal limit. A metabolic cocktail was initiated and tandem mass spectrometry was sent for further analysis. A repeated ABG revealed severe respiratory acidosis (pH 6.7, pCO_2 99 mmHg, HCO3 13.8 mmol/l), and EEG showed bi-hemispheric dysfunction. Neurosonogram and brain MRI suggested mild cerebral edema, while an echocardiogram was normal. Despite these interventions, the baby continued to experience persistent hiccups, shallow breathing, hypotonia, and poor sensorium.

Further investigation revealed markedly elevated CSF glycine levels (62.61 µmol/L, normal range: 3-26 µmol/L), with a normal blood glycine level of 519 µmol/L. The CSF to plasma glycine ratio was elevated (0.1 µmol/L, diagnostic value >0.08), confirming the diagnosis of NKH. Parents were counseled regarding the genetic basis of the disease and the recurrence risk for future pregnancies, and they were referred to a clinical geneticist for genetic

counseling. Clinical exome sequencing was performed, and by 72 hours of life, the baby had developed severe encephalopathy. Despite efforts to discuss the possibility of mechanical ventilation, the parents declined due to financial constraints. The child's condition worsened, and by day 3 of admission, the baby developed catecholamine-resistant shock and cardiorespiratory failure, leading to death at 72 hours of life.

Genetic analysis revealed a novel sequence variant, c.454C>T p.(Pro152Ser) in exon 4 of SLC6A9, identified in a homozygous state in the proband. Sanger sequencing confirmed that both parents were heterozygous carriers of this variant. These findings support a diagnosis of glycine encephalopathy despite normal serum glycine levels, emphasizing the importance of considering rare disorders like NKH in the differential diagnosis, especially in neonates presenting with unexplained encephalopathy and seizures.

DISCUSSION

NKH is a rare autosomal recessive metabolic disorder resulting from a deficiency in the glycine cleavage system (GCS). This enzymatic defect results in a spectrum of neurological symptoms due to an abnormal accumulation of glycine in the CSF and plasma. Clinically, NKH is classified into classical and atypical forms. Atypical forms can be further subdivided into neonatal, infantile, and late-onset types.

Clinical presentation

Children with classical NKH typically show symptoms within the first week of life, including lethargy, feeding difficulties, low muscle tone, seizures, and breathing problems.[6] Many survivors experience severe brain damage, leading to developmental delays, seizures, and muscle stiffness. Some may not reach major developmental milestones, and the condition can be life-threatening, with a mortality rate of up to 50% within the first week.[7,8]

Atypical NKH has varying symptoms and outcomes, depending on the age of onset. Late-onset cases can have diverse symptoms, including intellectual disabilities and behavioral problems. NKH can be categorized into severe and attenuated forms, based on the outcome. Severe NKH is characterized by uncontrollable seizures and no developmental progress, while attenuated NKH has variable developmental progress and treatable or no seizures. Onset during neonatal period is typically severe form (85%), while presentations after 3 months are mostly attenuated type.[9]

Diagnosis

Diagnosing NKH involves a combination of biochemical, imaging, and genetic tests. Key indicators include high glycine levels in blood and CSF, an abnormal CSF-to-plasma glycine ratio (>0.08), and brain imaging (MRI) showing restricted diffusion at the posterior limb of the internal capsule and cerebellum.[10,11] Magnetic resonance spectroscopy (MRS) may also detect a prominent glycine peak. [9]Genetic testing confirms the presence of specific gene mutations, such as AMT, GLDC, or GCSH. Selected cases may require enzymatic testing also.

Management

Management of NKH focuses on symptom relief, as there is no cure. For severe NKH, treatment includes sodium benzoate to lower glycine levels and improve alertness and seizure control, as well as NMDA receptor inhibitors like dextromethorphan and ketamine to manage seizures and neurological symptoms.[12] In attenuated NKH, therapy combines glycine reduction with NMDA receptor antagonism to optimize outcomes. Long-term care involves regular developmental and neurological assessments, monitoring for complications like scoliosis and respiratory issues, and avoiding certain medications such as vigabatrin and valproate that can worsen symptoms.[9,10]

Prognosis

There are multiple prognostic markers. Attenuated disease is indicated by a CSF-to-plasma glycine ratio <0.08, whereas severe consequences are predicted biochemically by a CSF glycine >230 µmol/L. A thin and truncated corpus callosum or hydrocephalus are radiological abnormalities that are associated with severe forms. Clinically, reduced NKH is linked to choreatic movements, while prolonged burst-suppression patterns on EEG and early pyramidal tract symptoms imply worse outcomes. Results from MRS and the glycine/creatine ratio, can predict outcomes even more.[9]

Future directions

In families that are at risk, the discovery of harmful mutations facilitates prenatal testing and preimplantation genetic diagnosis. Long-term research and developments in molecular genetics could lead to new therapeutic strategies. To improve the quality of life for those who are impacted, research into early intervention techniques and tailored therapies must continue.

CONCLUSION

NKH is a rare metabolic disorder that can cause serious neurological impairment if it is not identified quickly. The significance of taking NKH into account in neonates with unexplained encephalopathy and seizures-particularly in consanguineous families-is highlighted by this example. NKH poses significant challenges due to its variable presentation, diagnostic complexity, and limited treatment options. Early diagnosis, multidisciplinary care, and continued research are vital to enhancing patient outcomes. Raising awareness among healthcare providers

is crucial to ensure timely recognition and intervention for this rare but impactful disorder.

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