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Case Report

A Novel Mutation Discovered in a Case of Non-Ketotic Hyperglycinemia- A Case Report

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Abstract

Non-ketotic hyperglycinemia (NKH) is a rare and devastating genetic and metabolic condition that affects 1:76,000 live births worldwide. It is an inborn error of glycine (amino acid) metabolism caused by a mutation in the glycine cleavage system resulting in massive increase in glycine in body fluids and its accumulation primarily in the liver and the brain. This eventually results in glycine encephalopathy. We describe a case of classic or neonatal form of NKH. A term infant presented with profound hypotonia, lethargy and progressive respiratory failure along with elevated CSF: plasma glycine ratios, consistent with a diagnosis of NKH. MRI brain with spectroscopy revealed restricted diffusion in the bilateral posterior limb of the internal capsule and elevated lactate, glycine and glutamate levels. EEG revealed burst suppression with severe cerebral dysfunction. Genetic studies revealed a unique novel variant mutation in the AMT gene, which has not yet been reported in the literature. The case report highlights the importance of early recognition of NKH based on history and clinical presentation and a targeted, multidisciplinary approach is essential in improving outcomes of infants with NKH.

Keywords: Non-ketotic Hyperglycinemia; Global hypotonia; Myoclonic seizures; Neonatal hiccoughs; Progressive respiratory failure; Elevated glycine; AMT gene; Neonatal hypotonia

Introduction

Neonatal hypotonia is a commonly encountered clinical presentation in the NICU with varied underlying etiologies including central or peripheral nervous system dysfunction, systemic illnesses, underlying genetic conditions and inborn errors of metabolism. Beyond diagnostic laboratory workup and imaging, the clinical presentation of hypotonia, along with presenting history and relevant family history, play a crucial role in making a differential diagnosis Non-ketotic hyperglycinemia (NKH) is one of many newborn conditions that present as neonatal hypotonia. It is a rare autosomal recessive disorder in which a mutation in the glycine cleavage system (GCS) causes a mitochondrial enzyme deficiency that in turn leads to an accumulation of glycine primarily in the liver and brain [1]. Infants typically present with rapid clinical deterioration in alertness, tone and profound apnea prompting intubation as early as 48 hours of life but usually within the first week of life and can even cause death in many cases. Recurrent hiccoughs have also been reported in some infants. In those that survive, the prognosis is extremely poor. Survivors often

experience intractable seizures (most commonly in the form of myoclonic jerks), may develop profound intellectual disabilities, and experience abnormal brain growth [2].

The case report describes a neonatal presentation of NKH with distinctive characteristics of the disorder and highlights the importance of early recognition and treatment as well as underlines the importance of early institution of a multidisciplinary team for management for best possible outcome.

Case Presentation

A 2.77 kg, male infant was born vaginally at 36 6/7 weeks to a 34-year-old African American woman (Gravida 7, Para 3, uncomplicated pregnancy) with three previous pregnancy losses. The delivery was otherwise uneventful with APGAR score of 7 and 9 at 1 and 5 minutes respectively. Birth examination was unremarkable except for bilateral clubbed feet. Within first 24 hours of life, the infant exhibited increasing hypotonia, lethargy, and a decline in oral feeding skills. Through the course of next 12 hours, he developed shallow respiratory efforts requiring respiratory support in the form of intubation and mechanical ventilation. A sepsis workup was performed for initial evaluation and empiric antibiotics were initiated. By 48 hours of life, the infant experienced a rapid decline in alertness, respiratory effort, and tone. Spontaneous movement progressively diminished, accompanied by profound global hypotonia. The infant was transferred to a level IV NICU for evaluation and management. Significantly, the infant's first cousin on the maternal side (from the mother's half-sister) experienced poor muscle tone and developed feeding difficulties at one year of age, necessitating the use of a gastric tube (G-tube) for feeding. The differential diagnosis included causes of encephalopathy such as hypoxic ischemic encephalopathy, sepsis, inborn errors of metabolism, spinal muscular atrophy, perinatal stroke, myotonic dystrophy, and subdural hematoma among others.

Upon admission, a comprehensive multidisciplinary team was formed consisting of a pediatric neurologist, a pediatric geneticist along with the neonatology team to guide workup and evaluation of the infant. Serum levels of ammonia, lactate, creatinine kinase, carnitine and urine organic acids were assessed and found to be within normal ranges. Cranial ultrasound showed no abnormalities. Subsequent MRI revealed restricted diffusion within the bilateral posterior limb of the internal capsule. Additionally, spectroscopy demonstrated elevated levels of lactate, glycine, and glutamate in the left basal ganglia and the left posterior limb of the internal capsule, suggestive of glycine encephalopathy. Blood and cerebrospinal fluid (CSF) glycine levels were assessed. Based on clinical history, physical examination findings and imaging results, the multidisciplinary team decided to initiate treatment. By day of life (DOL) 3, sodium benzoate, dextromethorphan, and carnitine were started. Blood and CSF cultures yielded negative results. Echocardiography (ECHO) showed normal findings. Electroencephalogram (EEG) demonstrated background burst suppression consistent with severe cerebral dysfunction. Newborn screen results were negative for inborn errors of metabolism.

CSF glycine levels were elevated at 314 µmol/L (normal range: 3-26 µmol/L) on admission. Subsequently, glycine levels decreased to 153 µmol/L, five days after starting treatment. Unfortunately, serum glycine levels were not available upon admission. The first serum glycine measurement was obtained after five days of initiating treatment and was mildly elevated at 429 µmol/L (normal range: 133-409 µmol/L). The CSF/serum glycine ratio was 0.36 (normal <0.02), consistent with the diagnosis of NKH. Molecular gene testing confirmed the diagnosis and identified heterozygosity in the AMT gene for a variant (c.339+1G>A) expected to be pathogenic secondary to aberrant splicing (Alamut Visual v2.11; this variant has not been reported in literature yet). Additionally, the infant was heterozygous for an undocumented intronic variant (c.551-8G>A), which strongly predicts alter splicing but remains of uncertain clinical significance.

Within the first week of treatment initiation, the infant showed gradual improvement in tone and alertness, coinciding with appearance of spontaneous respiratory efforts and intermittent hiccoughs. By DOL 7, seizures manifested in the form of myoclonic jerks but were effectively controlled using phenobarbital and clobazam. Extubation occurred by the second week of life. Serum glycine levels were obtained biweekly to follow response to treatment. Sodium benzoate was titrated up to 400 mg/kg twice daily based on increasing glycine levels (reaching 758 µmol/L; Table.1). The titration aimed to maintain serum glycine levels between 120-300 µmol/L. Upon discharge, the infant continued breathing in room air without needing respiratory support and ad lib feeding, with scheduled follow-ups at the developmental clinic, pediatric neurology and pediatric genetics departments (Figure 1).

Table 1: Table showing cerebrospinal fluid (CSF) and serum glycine levels during the clinical course of the infant.

CSF and Serum Glycine Levels During Clinical Course					
	DOL 3	***DOL 7***	***DOL 21***	***DOL 35***	***DOL 48***
CSF Glycine (µMol/L)	314	153			
Serum Glycine(µMol/L)	Insufficient Specimen	429	635	758	250
CSF: Serum ratio		0.36			

CSF: Cerebrospinal fluid; DOL: Day of life

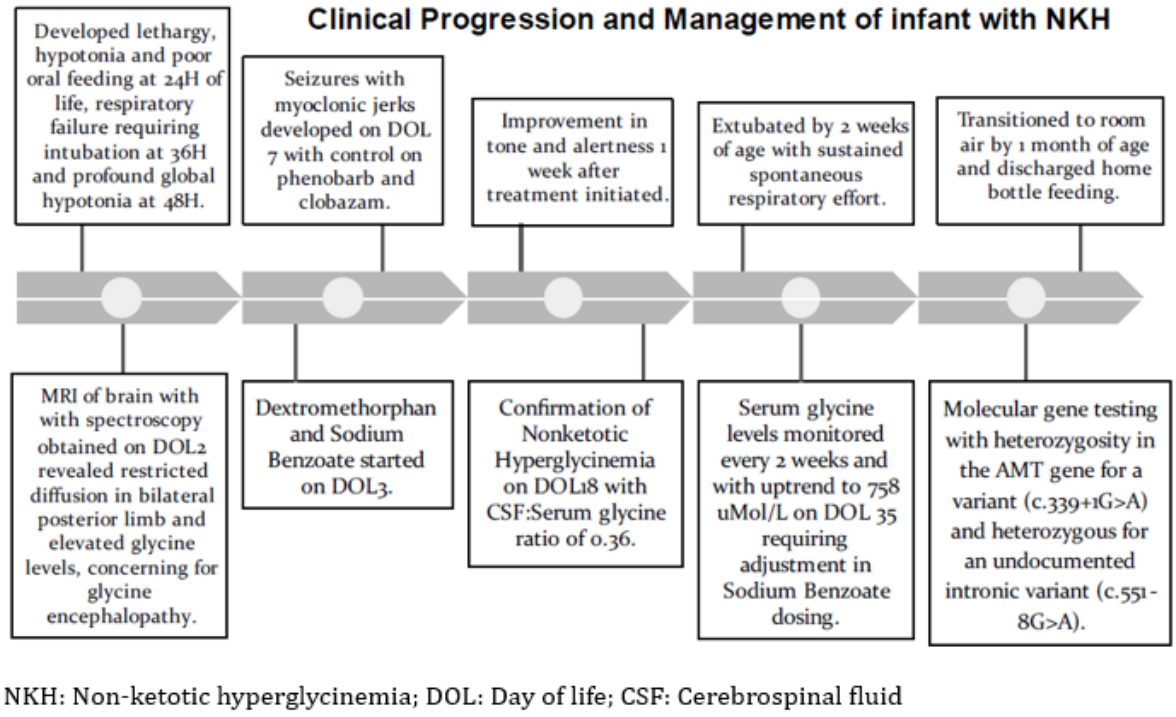

Figure 1: Clinical progression and management during hospital stay.

Discussion

Non-ketotic hyperglycinemia (NKH) is a rare but devastating condition that affects 1:76,000 live births [1], however global incidence of NKH has not been fully investigated, yet there have been several sporadic cases reported throughout the world most notable in Finland, British Columbia and lower incidences in Saudi Arabia, Philippines, Iran, and India. We report heterozygosity in the AMT gene for a variant (c.339+1G>A) that is likely pathogenic due to aberrant splicing (Alamut Visualv2.11). Notably, this specific variant has not been previously reported in the literature.

Glycogen undergoes breakdown into serine via the activity of 3-phosphoglycerate, which is subsequently converted in to glycine. When circulating glycine levels are elevated, glycine enters the glycine cleavage system to help break down glycine at the mitochondrial level [3]. Glycine consists of T, L, P and H proteins, which when broken down, weakly interact to degrade glycine into chloride, CO2 and ammonia [4]. Excessive circulating glycine accumulates in the brain and spinal cord, leading to disease manifestation and progression. In the brain, glycine accumulation activates glycine receptors causing an inhibitory postsynaptic potential, contributing to central apnea symptoms. In the spinal cord, glutamate and glycine cause an excitatory postsynaptic potential at the NMDA receptor, resulting in intractable seizures. Additionally, glycine accumulation leads to extensive neuronal injury, that contributes to global hypotonia [2].

The classical (neonatal) form of non-ketotic hyperglycinemia is commonly associated with a mutation in the GLDC (P protein) accounting for approximately 80% cases and AMT gene (T protein), which contributes to about 20% of cases [4]. Atypical forms of NKH may present later in life [3]. A study conducted by the NKH Network in 2004 involving 65 patients revealed that 33% of the participants died, with an average age at death of 2.6 years for boys and <1 month for females. Additionally, 67% of infants required intubation and 90% developed confirmed seizures [5].

There is currently no cure for non-ketotic hyperglycinemia, and discussions for redirection of care often being at the time of diagnosis due to the poor prognosis and compromised quality of life. Research by experts have identified pharmacological agents, including sodium benzoate and dextromethorphan, which can lower glycine levels and alleviate symptom severity. However, these treatments do not improve long-term neurodevelopmental outcomes [4]. Sodium benzoate binds to glycine in the blood, forming hippuric acid that is excreted in urine. Dextromethorphan, crossing the blood brain barrier, acts as a glutamate antagonist at the NMDA receptor. Inhibition of glycine activity in the brain can lead to better seizure control and improved alertness [6]. One study suggests employing serial electroencephalograms (EEGs) to assess efficacy of treatment [7]. However, other studies indicate

varying clinical response to early treatment initiation, highlighting the potential impact of genetic variants with differing enzymatic activity levels and variations in dextromethorphan metabolism on treatment outcomes [8,9].

During the management of this case, our multidisciplinary team facilitated early and prompt detection of NKH even before a definitive diagnosis was made. Despite the family not considering re-direction of care, early treatment led to relative symptom stabilization. Challenges included determining the most effective medication titrations to achieve desired serum glycine levels for symptom alleviation, underscoring the need for additional research.

Conclusion

Non-ketotic hyperglycinemia (NKH) in its severe and classical form is a devastating genetic and metabolic condition. The incidence of NKH may be underestimated due to rapid deterioration and death in the neonatal period. A multidisciplinary approach facilitates early diagnosis, prompt treatment, and potentially improves outcomes. Providing accurate long-term prognostic information during early neonatal phase is crucial in setting realistic expectations while counseling parents. Although rare, transient or infantile forms of NKH introduce uncertainty in predicting clinical outcomes. Early diagnosis, often during ventilator dependence, may provide compassionate weaning options and re-direction of care for families of infants with advanced disease states.

Acknowledgment

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Conflict of Interest

None.

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