SL Pediatrics & Therapeutics

SCIENTIFIC LITERATURE

Case Report

# Non Ketotic Hyperglycinemia: A Case Report

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**ARTICLE INFO**

Received Date: September 23, 2020
Accepted Date: December 20, 2021
Published Date: December 21, 2021

**KEYWORDS**

Non-ketotic hyperglycinemia
Glycine level
Diagnosis
Hypotonia



**Citation for this article:** Deepak Kumar, Ashu Sawhney, Minal Singh, Shweta Pagare and Arvind Sindwani. Non Ketotic Hyperglycinemia: A Case Report. SL Pediatrics & Therapeutics. 2021; 4(1):118

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## ABSTRACT

Non-ketotic hyperglycinemia is a rare autosomal recessive trait caused by deficiency of glycine cleavage enzyme system, resulting in high level of glycine in all tissue including the brain. Neonatal hyperglycinemia is the most common form of NKH. Between 6 hours to 8 days after birth neonate develops poor feeding, failure to suck, lethargy, and profound hypotonia which may progress rapidly to a deep coma, apnea, convulsions, especially myoclonic seizure often associated with hiccups . Diagnosis is based on the detection of elevated glycine levels in the plasma and cerebrospinal fluid and high peak of glycine level on MRS. Mutation analysis can help in providing prenatal diagnosis in subsequent pregnancies in affected families.

## INTRODUCTION

Non-Ketotic Hyperglycinemia (NKH) is inherited as a rare autosomal recessive trait, and is caused by deficiency of glycine cleavage enzyme system, resulting in high level of glycine in all tissue including the brain. The prevalence is not known, but high frequency of the disorder has been noted in northern Finland [1-3]. Non-ketotic hyperglycinemia is the one of the commonest amino acid disorder found in India [4]. Four forms of this condition have been identified: Neonatal, Infantile, Late onset and Transient of which neonatal hyperglycinemia is the most common form. Clinical manifestations develop in the 1st few days of life (usually within 6 hours to 8 days after birth). Poor feeding, failure to suck, lethargy, and profound hypotonia may progress rapidly to a deep coma, apnea, convulsions, especially myoclonic seizure and hiccups are common. Diagnosis is based on the detection of elevated glycine levels in the plasma and cerebrospinal fluid and MRSA. Mutation analysis can help in providing prenatal diagnosis in subsequent pregnancies in affected families. We are reporting 2 cases of neonatal NKH in our unit.

## CASE HISTORY

A 48 hours old baby was admitted to our Neonatal Intensive Care Unit with lethargy and poor feeding. The baby was born to nonconsanguineous parents after a full-term uneventful pregnancy by normal vaginal delivery at our hospital. He cried immediately after birth (APGAR 7,8,9) and discharged the following day on full breast feeds. The next day, he presented with lethargy and poor feeding to our neonatal intensive care unit. At admission baby was lethargic, had shallow respiration. Baby had intermittent apneas and bradycardias and was intubated and ventilated immediately. He subsequently developed myoclonic seizures lasting approximately

for 1-2 minutes per episode and protracted hiccups, necessitating treatment with loading dose of phenobarbitone at 20 mg/kg. He was very hypotonic with depressed reflexes. The investigations revealed a normal arterial pH and normal septic screen done repeatedly. Chest X-Ray showed bilateral clear, well expanded lung fields. His cranial ultrasound scan was normal. Blood ammonia and lactate were in normal range. In view of, clinical feature of suspected metabolic disease (highly Non-Ketotic Hyperglycinemia), Tandem Mass Spectrometry, Cerebrospinal fluid glycine and Plasma glycine was sent and MRI, EEG were done. As diagnostic test usually take days, hence magnetic resonance spectroscopy was also done. Magnetic resonance spectroscopy analysis suggest elevated glycine metabolic peak at 3.5 ppm (Figure 1), MRI showed areas of diffusion restriction in bilateral posterior limb of internal capsule, dorsal pons white matter tract and bilateral cerebellar white matter with loss of T1 hyperintensity in bilateral posterior limb of internal capsule.


Figure 1: MRS

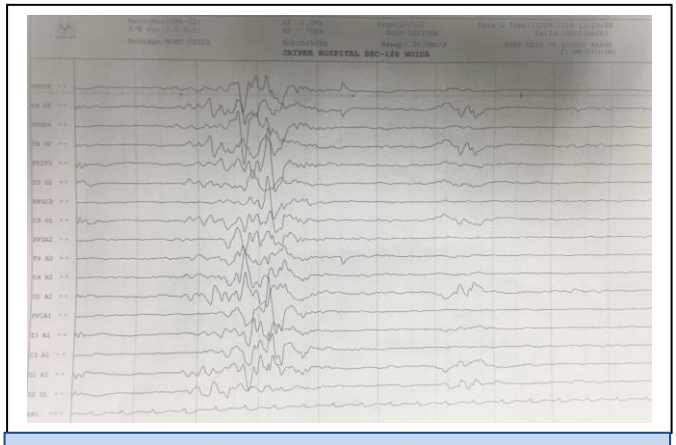

Figure 2: EEG on Day- 9

EEG on day 4 showed epileptic activity over bilateral frontal region and repeat EEG on day 9 suggestive of severe generalised slowing with burst suppression pattern (Figure 2).

Amino acid analysis showed high concentration of glycine in the plasma at 583µmol/L (reference range: 150–560 µmol/L), Cerebrospinal Fluid (CSF) at 75.68 µmol/L (reference range: < 38 µmol/L). The CSF plasma glycine ratio was markedly elevated at 0.13 (reference range: <0.08). The diagnosis of classical NKH was made. Mechanical ventilator was continued and neonate was treated with oral dextromethorphan at 5 mg/kg/day and sodium benzoate at 300 mg/kg/day. The plasma glycine levels normalised over next few days. He continued to have hiccups and myoclonic jerks, which responded well to intravenous levetiracetam & phenobarbitone. He improved clinically showing good spontaneous respiratory effort on day 19 of life was extubated on to Nasal CPAP with PEEP 5 and 21% FiO2. Nasal CPAP was gradually weaned off on day 28th of life. He was discharged home on day 38th of life.

Gene analysis showed GLDC (Glycine decarboxylase) gene heterozygous at Exon 13 (p.Asn543LysfsTer10) and Exon 6(p.Tyr266Ter).

## DISCUSSION

Early diagnosis of NKH is key for adequate management and to give prognosis to parents. Often babies with non ketotic hyperglycinemia are not diagnosed early because presentation is similar to sepsis and initial newborn metabolic screening report in blood usually is reported normal. We had a high suspicion because we had managed another case of NKH a year back whom diagnosis was delayed as urine GCMS report was delayed.

Currently, there is no effective treatment for severe NKH, even when initiated early treatment developed global developmental delay, spasticity, and intractable epilepsy [5]. Oral sodium benzoate administration at doses of 250–750 mg/kg/day is aimed at reducing plasma glycine levels to low normal range (between 120 and 300 µmol/L) to observe beneficial effects, including increased wakefulness and enhanced seizure control in severe phenotypes. However, even early initiation of treatment with high doses of benzoate will not preclude the natural progression towards profound intellectual disability and seizure disorder in classical, severe

NKH. NMDA receptor antagonists including dextromethorphan (5–15 mg/kg/day), levetiracetam (20-80mg/kg/day) have been used to improve seizure control. Ketogenic diet may improve in seizure control, but non availability of Ketogenic diet in developing country is a major disadvantage. Lang et al [2], highlighted the difficulties in the diagnosis of transient cases of this disease. The pathogenesis of NKH is discussed and illustrated to assist in the understanding of the biochemical derangement involved: Glycine is a non-essential amino acid synthesised from combination of serine and threonine. This catabolic process requires glycine cleavage enzyme system. MRS and MRI is very useful tool in suspected case and make diagnosis on right path.

## REFERENCES

1. Applegarth DA, Toone JR, Lowry RB. (2000). Incidence of Inborn Errors of Metabolism in British Columbia, 1969–1996. American Academy of Pediatrics. 105: e10.
2. Lang TF, Parr JR, Matthews EE, Gray RGF, Bonham JR, et al.. (2008). Practical difficulties in diagnosis of transient non-ketotic hyperglycinemia. Developmental Medicine & Child Neurology. 50: 157-159.
3. Bonita F Stanton, Joseph W St Geme III, Nina F Schor, Richard E Behrman. (2012). Nelson Text Book of Pediatrics. Philadelphia: Saunders.
4. Manjeet Kaur, Das GP, Varma IC. (1994). Inborn Errors of Amino Acid Metabolism in India. J. Inher. Metab. Dis, 17: 230-233.
5. Johan LK Van Hove, Curtis Coughlin, Michael Swanson, Julia B Hennermann. (2019). Non Ketoic Hyperglycinemia. Gene Reviews.