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# A Newborn Infant With Poor Feeding: Non-ketotic Hyperglycinemia

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**Abstract**
Non-ketotic hyperglycinemia (NKH) is a rare autosomal recessive disorder affecting glycine metabolism that is a rare metabolic disorder in infants. The clinical manifestations of poor sucking, hypotonicity, lethargy, hiccups, and seizures develop within six hours to eight days of the birth of an otherwise healthy newborn. The present study introduced a newborn girl with poor feeding and hypotonia in the first day after birth with NKH. In addition, the patient was evaluated regarding hypotonia and poor feeding. The neonatal-onset NKH was diagnosed based on a markedly elevated cerebrospinal fluid/plasma glycine ratio of 0.32 and confirmed by the genetic test. It is extremely rare that NKH is manifested with poor feeding and hypotonia thus considering this diagnosis in infants with poor feeding and hypotonia is highly important.

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## Background

Non-ketotic hyperglycinemia (NKH) is considered as a rare autosomal recessive disorder that affects glycine metabolism with a reported prevalence of 1:60 000-100 000. The biochemical defect is in the glycine cleavage system which consists of a mitochondrial enzyme complex.[1,2] Glycine encephalopathy includes neonatal, infantile, transient, and late types. The clinical manifestations of poor sucking, hypotonicity, lethargy, hiccups, and seizures develop within six hours to eight days of the birth of an otherwise healthy newborn. The symptoms of children with NKH begin at infancy, including lethargy, coma, and hypotonia. Among the children whose symptoms initiate at infancy, 85% have a severe form of the disease and the remaining 15% have an attenuated form of the disease. However, hypotonia is regarded as the most common symptom and the severe and attenuated forms of the disease are 50% each if the symptoms occur from 2 weeks to three months. In addition, patients whose symptoms develop after three months of age have an attenuated form of the disease.[3] Acute neurological deterioration rapidly progresses to coma and often leads to death in a short period. Further, patients suffer from severe mental and developmental retardation and seizures if they survive the ventilator-dependent period.[4,5] According to previous evidence,[6] the changes in the biochemical index in patients with NKH resulted in elevated plasma glycine and cerebrospinal fluid (CSF) concentrations, which increased the CSF to plasma glycine ratio above the normal level (0.04). Standard treatment strategies include the reduction of the plasma concentration of glycine, the use of *N*-methyl-D-aspartate (NMDA) receptor site antagonists, and the symptomatic care to control intractable seizures in addition to antiepileptic drugs.[7] The current study presented a new case of NKH.

## Case Presentation

The present study introduced a neonate (girl) with poor feeding and hypotonia in the first day after birth. She was the result of a normal vaginal delivery at 38 weeks of age. Her mother was 32 years old and her obstetrics history was G5, P4, and Ab1 that the last child was a boy who died 25 days after birth. The patient was evaluated in terms of hypotonia and poor feeding. In primary lab dates, the obtained data were as follows:

The blood sugar, creatinine, and blood urea nitrogen were normal, white blood cell = 15 000 $\times 10^3/mm^3$, hemoglobin = 18.3 mg/dL, and platelet was 270 $\times 10^3/mm^3$. Serum sodium, potassium, magnesium, and calcium concentrations were normal as well. The neonatal-onset NKH was diagnosed based on a noticeably elevated CSF/plasma glycine ratio of 0.32 (the normal ratio is less than 0.08) with a CSF glycine of 162 mol/L (normal range = 1.6-19.5 mol/L) and plasma glycine of 1136 mol/L (normal range = 224-514 mol/L). Urine glycine levels were also markedly elevated at 41,752 mol/g creatinine (normal range = 0-7047 mol/g creatinine).

The diagnosis was confirmed by mutation testing that demonstrated the homozygous mutation of the glycine decarboxylase (GLDC) gene encoding for the P-protein of the glycine cleavage system complex. Unfortunately, despite the patient's admission to the neonatal intensive care unit and supportive care, the patient died on the 14th day after birth.

## Discussion and Conclusion

As it is known, the NKH is an uncommon metabolic disorder in children. It is caused due to a defect in the glycine cleavage system, which is a multi-enzyme complex of four proteins like P, H, T, and L-protein included a pyridoxal phosphate-dependent glycine decarboxylase, a lipoic acid-containing protein, a tetrahydrofolate-requiring enzyme, and a lipoamide dehydrogenase, respectively. The code for these proteins is located in *GLDC*, *GCSH*, and *AMT* genes, respectively. Further, the P-, T-, H- and L-protein genes are on chromosome nine and its short arm. The defects in any of these enzymes can lead to NKH, but P protein deficiency is considered as its most common form that is observed in 80% of patients.[8] The accumulation of glycine in the CNS and other body fluids is the characteristic of this syndrome. The glycine function as an inhibitory neurotransmitter in the brain stem and spinal cord, as well as stimulatory effects through NMDA receptors. Infants developing this syndrome experience neurological symptoms due to high levels of glycine in their cerebrospinal fluid. It seems that apnea and hiccups in these infants are due to the inhibitory effects of glycine in the spinal cord and brain stem. On the other hand, refractory seizures in these patients are attributed to the effects of the activation of NMDA receptors by glycine. In some patients, hypotonicity, decreased neonatal reflexes, myoclonic seizures, and hiccups are reported as well.[9] In 2011 a newborn was identified by the diagnosis of NKH and MRI and MR spectroscopic was done for the patient at six days of age, followed by investigating the radiologic findings in this patient.[10] Furthermore, Kaźmierczuk-Skubis et al introduced a neonate diagnosed with NKH, who was presented with seizures in the first 24 hours of life. To diagnose NKH in this patient, all other causes of seizure were rolled out, and the diagnosis of NKH was proved with high concentrations of glycine in the blood and the symptoms of the patient such as hypotonicity, as well as the imaging of the central nervous system.[11] Moreover, Chang et al reported a newborn baby with a classic neonatal form of NKH that included hiccups and muscle tone reduction and then used genetic testing to confirm the diagnosis.[12] Similarly, Panayiotou et al reported a newborn with respiratory problems who needed intubation and mechanical ventilation during the treatment. The examination of respiratory data showed that the patient had multiple hiccups during mechanical ventilation. NKH was diagnosed during further studies and metabolic screening for the patient.[13] In another study, Chiu et al evaluated the NKH of the infants in Taiwan, including 11 infants and 2 neonatal NKH infants had a mutation in the *GLDC* gene,[14] which is similar to a mutation that we found in our patient. In the other case report in Iran, Danaei et al provided data about a 4-day-old girl with hypotonia, lethargy, seizures, and poor sucking and high levels of glycine in blood and urine were reported in more evaluations, confirming the diagnosis of NKH.[15] The current study also presented a newborn girl with neonatal-onset NKH with poor feeding and hypotonia, therefore, it is very important to consider this diagnosis in infants with poor feeding and hypotonia.

### Authors' Contributions

AJM interpreted the patient data. MG contributed to writing the manuscript. All authors read and approved the final manuscript.

### Ethical Approval

Written consent was obtained from the patient's parents.

### Conflict of Interest Disclosures

The authors declare that they have no conflict of interests.

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