3(1): 005-008; Feb 2024
Pediatric Academic Case Reports
DOI: 10.61107/pacr.2024.090

Case Report

Neonatal nonketotic hyperglycinemia: A case report

Yenidoğanın nonketotik hiperglisinemi: Bir olgu sunumu

Sümeye Özlen[1], Bayram Ali Dorum[1], Murat Tutanç[2]

[1]*Bursa City Hospital, Pediatrics, Bursa, Türkiye*
[2]*Bursa Medicine Faculty, Pediatrics, Bursa, Türkiye*

ABSTRACT

Nonketotic hyperglycinemia (NKH) is an autosomal recessive disorder caused by a defect in the glycine cleavage enzyme. It leads to the accumulation of glycine in the body tissues, blood, and cerebrospinal fluid (CSF). Most NKH cases are diagnosed during the natal period of life and are fatal if not promptly diagnosed and managed. Here, we present a case of a two-day-old child who presented with hypotonia and lethargy. She had reduced tone in all four limbs and a loss of reflexes. The patient was shifted to the neonatal intensive care unit. Metabolic and other tests were sent. She was started on phenobarbital because of a seizure. Keeping a metabolic disease and an infectious etiology in mind, she was started on biotin, Vitamin B complex, ampicillin and gentamicin. Serum amino acid chromatography showed elevated glycine levels, and a diagnosis of NKH was made. The patient was managed symptomatically and discharged on the 14th day. The case emphasizes the significance of diagnosis and management of aminoacidopathies. Nearly all metabolic disorders have similar clinical presentations, and an early diagnosis can improve patient outcomes.

Keywords: *neonates hyperglycinemia, nonketotic hyperglycinemia, metabolic disorders*

ÖZET

Nonketotik hiperglisinemi (NKH), glisin parçalama enzimindeki bir mutasyonun neden olduğu otozomal resesif bir hastalıktır. Vücut dokularında, kanda ve beyin omurilik sıvısında (BOS) glisin birikmesine yol açar. NKH vakalarının çoğu, doğumu takiben ilk günlerde teşhis edilir ve hemen tedavi edilmezse mortalitesi yüksektir. Bu olgu sunumunda hipotoni ve letarji ile başvuran iki günlük bir yenidoğanı ele aldık. Dört ekstremitede tonusu azalmıştı ve refleks kaybı vardı. Hasta yenidoğan yoğun bakım ünitesine yatırıldı. Metabolik ve diğer testler gönderildi. Nöbet nedeniyle fenobarbital başlandı. Metabolik bir hastalık ve enfeksiyöz nedenler düşünülerek biotin, vitamin B kompleksi, ampisilin ve gentamisin başlandı. Serum amino asit kromatografisinde yüksek glisin seviyeleri tespit edildi ve NKH teşhisi kondu. Hasta semptomatik olarak tedavi edildi ve 14. günde taburcu edildi. Vaka, aminoasidopatilerin tanı ve tedavisinin önemini vurgulamaktadır. Neredeyse tüm metabolik bozukluklar benzer klinik tablolara sahiptir ve erken teşhis hastalarda prognoza katkı sağlayabilir.

Keywords: *neonatal hiperglisinemi, nonketotik hiperglisinemi, metabolik hastalık*

INTRODUCTION

Nonketotic hyperglycinemia (NKH) is a rare autosomal recessive metabolic encephalopathy usually presenting in the neonatal period. It may occur because of the accumulation of glycine in all body tissues, especi–

Received: 13.07.2023 · **Accepted:** 20.09.2023 · **Published:** 28.02.2024

Correspondence / Yazışma: Sümeye Özlen · Bursa Şehir Hastanesi, Pediatri Kliniği, Bursa, Türkiye · ozlensumeye@gmail.com

Cite this article as: Ozlen S, Dorum BA, Tutanc M. Neonatal nonketotic hyperglycemia: A case report. Pediatr Acad Case Rep. 2024;3(1):5-8.

ally in cerebrospinal fluid (1). The primary defect lies in the liver enzyme complex, called the glycine cleavage system. NKH is a rare disease with an estimated incidence of 1 per 250,000 (2). NKH has four major forms: neonatal, infantile, transient, and late. The neonatal form is the most common and severe. The patients usually appear normal at birth but within a few hours, may present with hypotonia, lethargy, seizures, myoclonic jerks, hiccups, and apnea, which if left untreated may lead to death (3). In some cases, cortical atrophy, and hypoplasia of vermis along with delayed or deficient myelination have been reported on CT/MRI (4). NKH is associated with poor prognosis, with a high mortality rate of up to 50% during the first week of life (5). Survivors generally have severe psychomotor retardation and uncontrolled seizures. Here, we present a case of a two-day-old female with classical NKH type who was seen hypotonia, hiccups and lethargy.

CASE REPORT

A two-day-old female neonate was seen near her mother with complaints of hypotonia and lethargy for one day. There was no history of fever, fits, vomiting, or diarrhea. She was the second product of consanguineous marriage and was born using normal vaginal delivery at 39 weeks of gestation. The elder sibling who could speak at the age of four were healthy and alive. Then, we learned that her three uncles/aunts died in the first days of their lives.

On examination, she looked hypotonic, lethargic and had no cry. The newborn reflexes were so weak. Moro, rooting, sucking, and grasping reflexes were weak. Her vital signs and percentile were normal. There were not any abnormality signs except lethargy, hypotonia and weak reflexes. She was hospitalized for the purpose of observation and nutritional follow-up. We tried oral nutritional, but she could not have enough oral and her oral intake got worse and worse. She was managed on intravenous (IV) 80 mL 10% dextrose water over 24 hours.

The initial investigations (at the day of admission) revealed a hemoglobin (Hb) of 18.2 g/dL, hematocrit of %51, total leukocyte count of $23x10^3$/µL, platelet count (PLT) of $228x10^3$ /µL, and C-reactive protein of 1 mg/L. level of blood glucose was 72 mg/dL. Serum ammonia was 112 µg/dL (18.7 - 96.8). Sodium benzoate was started for high blood ammonia level. At the same time, serum and CSF amino acid chromatography and urine organic acid chromatography were ordered for aminoacidopathies. Biotin was started for likely biotinidase deficiency. On the second day, the patient had a seizure, so we loaded phenobarbital. She was started ampicilin, gentamicin, biotin and Vitamin B complex. The patient with worsening breathing and had a high carbon dioxide ratio in her blood gas was intubated and put on a ventilator. On the third day, she had hiccups. She was made lumbar puncture. Ultrasound (US) brain was normal, and CSF detailed report showed protein of 507 mg/L, glucose 76 mg/dL, chloride of 122 mmol/L, and no lymphocyte with no red blood cells and polymorphs. CSF and blood cultures showed no bacterial growth. On the fifth day, an eye examination was conducted for metabolic disorders, which was normal.

Magnetic resonance imaging was performed and interpreted as a limitation on diffusion-weighted images. Then MR spectroscopy was performed because of we suspected from metabolic disease. Cranial magnetic resonance spectroscopy revealed an elevated glycine peak at 3.56 ppm (Figure 1a). Amino acids analysis of CSF and plasma samples showed increased glycine levels in CSF (511 µmol/L) and plasma (1292 µmol/ L). CSF/plasma ratio was 0.39. With these findings, we suspected from a neonatal form of NKH. EEG was recorded on eleventh day which showed burst-suppression pattern.

The patient was diagnosed with a neonatal type of NKH, which has a very poor prognosis. Gene analysis was performed for the definitive diagnosis. The patient was started on a protein-restricted diet. Phenobarbital and sodium benzoate treatments were continued.

The patient's spontaneous breathing started. Although his convulsions disappeared, not observed a significant improvement his hypotonia. The feeding was provided through a nasogastric tube. On the fourteenth day, the patient was discharged together with phenobarbital, sodium benzoate and Vitamin B complex were prescribed. It was learned that the patient, for whom outpatient follow-up was recommended, continued follow-up at the neurology and metabolism clinics at the age of eight months, and received physiotherapy due to neuromotor retardation.

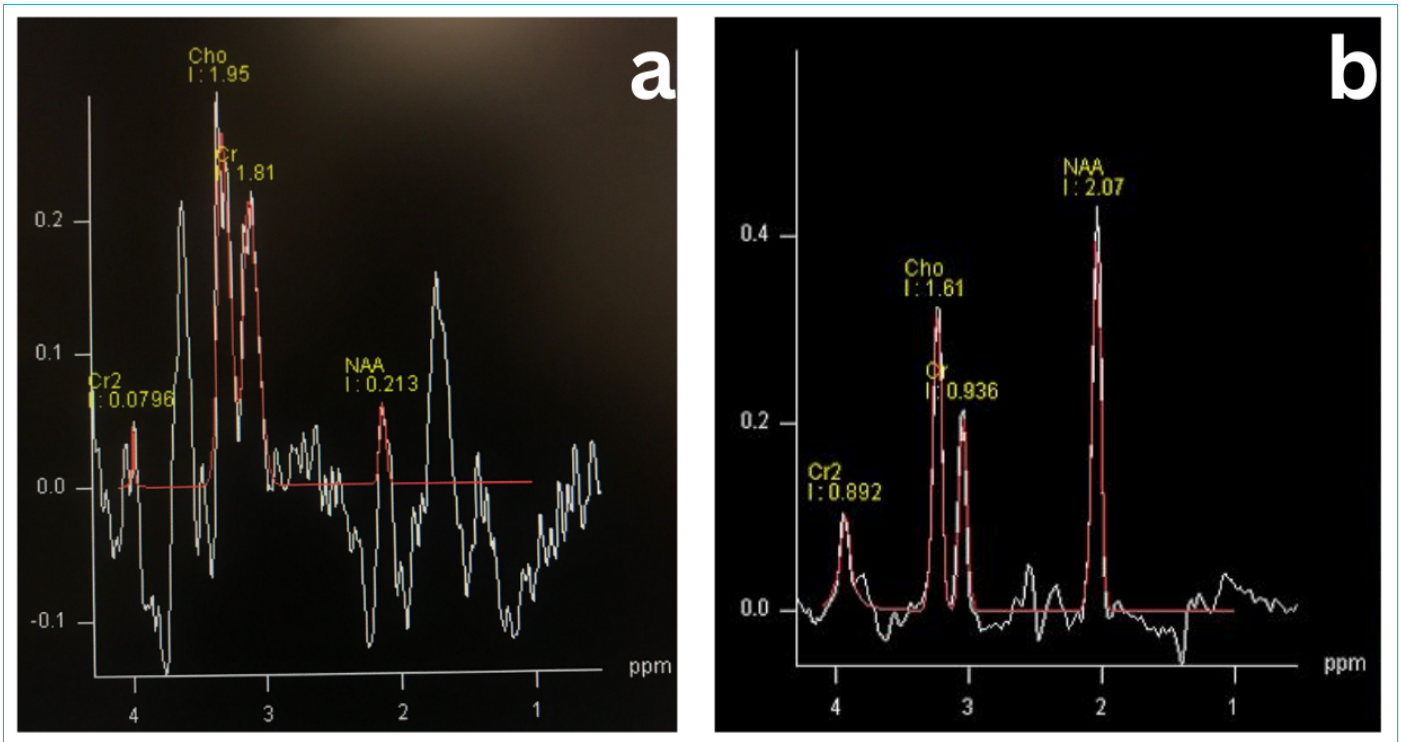

Figure 1. a. Cranial magnetic resonance spectroscopy with an elevated glycine peak at 3.56 ppm; **b.** A normal cranial magnetic resonance spectroscopy

DISCUSSION

In neonatal lethargy, hypotonia and weak reflexes are considered metabolic disorders, especially in our country where consanguineous marriage rates are high. It is vital to recognize such diseases early in terms of starting treatment. The clinical course becomes worse rapidly in these patients and it progresses to encephalopathy as in our case. This situation due to accumulation of intermediate metabolites in central nervous system and other parts of body. In NKH, this metabolite is glycine that accumulates in different parts of the brain that have glycine receptors. NKH is an autosomal recessive disorder caused by a defect in the glycine cleavage enzyme (GCE). The estimated incidence of 1 per 250,000 (2).

In the presence of suspicious clinical findings (feeding difficulties, coma, lethargy, severe hypotonia, apnea, irritability, and myoclonic seizures), high plasma and CSF glycine levels in metabolic tests make the diagnosis of hyperglycinemia. NKH is a rare clinical presentation in which hyperglycinemia is not accompanied by ketones and acidosis. The cerebrospinal fluid glycine/serum glycine ratio is above 0.08. A burst-suppression pattern on the EEG is diagnostic in a neonate has hiccups, apnea and/or myoclonic seizures. Cortical atrophy and hypoplasia of vermis along with delayed or deficient myelination is seen on CT/MRI (4). The gold standard for diagnosing NKH is glycine cleavage enzyme assays on liver biopsy, which is not applicable in most cases. Perinatal diagnosis is feasible by measuring enzyme activity in chorionic villi.

NKH has four types according to the onset of symptoms: Neonatal, infantile, late onset and transient type. The neonatal type is the most common and severe type. In our newborn, the presence of hiccups and severe hypotonia that led to respiratory depression was important. The ketone was negative, and in addition to the burst-suppression pattern on the EEG, the CSF glycine/plasma glycine ratio increased.

Iqbal et al., in 2015, reported three cases that had a typical presentation with a CSF/plasma glycine ratio above the diagnostic value of >0.08 (6). All three cases had abnormal EEG and had a history of hiccups, which is an important clinical finding in NKH (6). It has been reported that two patients died after withdrawal of care, and the third patient was discharged home on oral dextromethorphan and ketogenic diet (6). The clinical and laboratory findings of our case were consistent with other NKH cases reported in the literature.

No effective treatment exists for NKH. The purpose of supportive care is to reduce the plasma concentration of glycine and seizure frequency. Thus, the standard treatment strategies for NKH include sodium benzoate and N-methyl D-aspartate receptor antagonists (dextromethorphan, ketamine) (7). Sodium benzoate can be effective in reducing plasma glycine levels and controlling convulsions, however its effect on CSF glycine levels is weak (8,9). The other target in NKH is seizure control with the use of antiepileptic medications. Ketogenic diet, peritoneal dialysis, exchange transfusion are other supportive treatments.

CONCLUSION

In newborns with a history of consanguineous marriage, who often appear healthy at birth, but whose general condition is impaired, such as decreased activity and sucking due to unexplained reasons, metabolic diseases, such as NKH, should be considered in the foreground.

Patient Consent Form / Hasta Onam Formu

The parents' of this patient consent was obtained for this study.

Conflict of Interest / Çıkar Çatışması

The authors declared no conflicts of interest with respect to authorship and/or publication of the article.

Financial Disclosure / Finansal Destek

The authors received no financial support for the research and/or publication of this article.

REFERENCES

1. Hennermann JB. Clinical variability in glycine encephalopathy. Future Neurol 2006, 1: 621-30.
2. Tada K, Kure S. Nonketotic hyperglycinemia: pathophysiological studies. Proc Jpn Acad Ser B Phys Biol Sci 2005, 81: 411-17.
3. Hoover-Fong JE, Shah S, Van Hove JL, et al. Natural history of nonketotic hyperglycinemia in 65 patients. Neurology 2004, 63:1847-53.
4. Dobyns WB. Agenesis of the corpus callosum and gyral malformations are frequent manifestations of nonketotic hyperglycinemia. *Neurology* 1989; 39: 817-20.
5. Volpe J. Neurology of the Newborn. 5th ed. Philadelphia: WB Saunders; 2008. pp. 659–67.
6. Iqbal M, Prasad M, Mordekar SR. Nonketotic hyperglycinemia case series. J Pediatr Neurosci 2015; 10: 355-8.
7. Van Hove JL, Vande Kerckhove K, Hennermann JB, et al. Benzoate treatment and the glycine index in nonketotic hyperglycinaemia. J Inherit Metab Dis 2005; 28: 651–63.
8. Rezvani I. Defects in metabolism of aminoacids. In: Kliegman RM, Behrman RE, Jenson HB, Stanton BF editors. Nelson textbook of pediatrics. Philadelphia: Saunders; 2007; 549-50.
9. Chung BHY, Wong KY, Lee JSK, et al. Non-ketotic Hyperglycinaemia: A Case Report and Review on Treatment. HK J Paediatr 2002; 7: 152-6.