Abstract: Hypotonia is a serious physical finding in a newborn infant. Nonketotic hyperglycinemia (NKH) is a rare cause of neonatal hypotonia. It is a defect of the glycine metabolism and has poor prognosis. We report a case of a newborn infant with NKH, presented with mild hypotonia and high creatine kinase values. NKH should be considered in a hypotonic newborn, especially if associated with acute deterioration, lethargy and seizures.

Key Words: Nonketotic hyperglycinemia, hypotonia.

Introduction

Hypotonia, central or peripheral, is a serious physical finding in a newborn infant. There are many disorders that cause hypotonia. It may arise from disorders of the brain, spinal cord, peripheral nervous system and motor unit. Inborn errors of the metabolism may also cause hypotonia. Nonketotic hyperglycinemia (NKH) is an inborn error of glycine degradation, which causes hypotonia, lethargy, apnea, seizures, and hiccups (1, 2). Its frequency is lower than 1 in 200,000 and most of the patients die during the neonatal period. Özalp et al. reported that the prevalence of NKH was 0.04% in 6050 high-risk infants for metabolic disease in Turkey (3). We report a newborn infant with NKH as a rare cause of neonatal hypotonia.

Patient Report

A 24-hour-old female infant was admitted to our unit with mild hypotonia. She had a history of sibling death. The infant was born at term to a 25-year-old woman, following an uncomplicated pregnancy. The parents noted her to be hypotonic with poor feeding and crying immediately after delivery similar to the sibling that died at 20 days of age two years previously. There was no parental consanguinity.

Her weight, length and head circumference were 3300 g, 51 cm and 35 cm, respectively. No abnormal physical findings were determined except hypotonia and poor sucking. A sepsis work-up was performed and antibiotics were administered. On the 2nd hospital day, the patient deteriorated acutely, and she was intubated and placed on mechanical ventilation because of impending respiratory failure. Respiratory alkalosis improved after ventilatory support. Within five days, two serial blood cultures showed Candida lipolytica, and amphotericin B was administered.

Blood urea nitrogen, creatinine, aspartate transaminase, alanin transaminase, serum glucose and electrolytes were normal. Serum thyroid hormone levels were also normal. The serum creatine kinase (CK) level was 1883 U/L (normal serum level is 87-725 U/L at 72-100 h of life). The plasma ammonium level was 203 µg/L (normal serum level is 15-90 µg/L), but this subsided within 72 hours. The blood lactate level was normal. Cranial ultrasonography and echocardiography did not show any abnormality. Computed tomography (CT) revealed an arachnoid cyst in the occipital area.

In the following days, the infant developed generalized seizures and hiccups, and hypotonia became severe and was thought to be permanent. The frequency and duration of the convulsions decreased with phenobarbital treatment. High CK values (1883-923-387 U/L, respectively) decreased to normal within 2 weeks. Electromyography (EMG) and muscle biopsy were evaluated as normal. Electroencephalography (EEG) showed a burst suppression pattern. Serum and CSF glycine were 1449 and 224 mumol/L, respectively. (Normal serum level is 104-
254 mumol/L and CSF level is 5 +/- 2 mumol/L. The CSF/serum ratio of glycine was 0.15 (a value of greater than 0.08 is diagnostic).

The patient was diagnosed as having NKH, and sodium benzoate (500 mg/kg/day) and folic acid treatment was started with protein restriction. This treatment regimen resulted in cessation of seizure activity, so phenobarbital medication was stopped. But lethargy and hypotonia continued. The patient was weaned off the ventilator at 47 days of age, but did not tolerate gavage feeding well. Different antibiotics were administered such as vancomycin, meropenem and amikacin, due to bronchopneumonia and sepsis.

The patient died at the end of 4 months of age because of bronchopneumonia caused by Pseudomonas aeruginosa that was resistant to multiple drugs.

**Discussion**

Nonketotic hyperglycinemia, classified as neonatal, infantile, late onset and transient based on its clinical course, is a very rare autosomal recessively inherited disease. The metabolic defect of NKH is in the glycine cleavage system (GCS), a complex enzyme system with four components: the P, the H, the T, and the L protein (4). Most patients with the neonatal type have a defect in the P protein. Later-onset cases have been thought to have defects in the H or T protein. Due to deficient activity of the GCS, the major pathway for the catabolism of glycine, large quantities of glycine accumulate in all body tissues. High concentrations of glycine in the central nervous system produce excitoneurotoxicity, seizure and brain damage, through the overstimulation of the N-methyl-D-aspartic acid (NMDA) receptor, via an action at the associated glycine modulatory site (4). Otherwise, glycine is inhibitory in the spinal cord and brain stem and this may be responsible for the apnea seen in the disease.

Most patients have the neonatal type characterized by lethargy, hypotonia and poor sucking in the first few days of life, while the infants are usually well at birth. Encephalopathy progresses to coma and most patients require assisted ventilation and die in the neonatal period. The patients who survive develop intractable seizures and mental retardation. Hiccups may be seen because of diaphragmatic spasms. The presenting features of our patient suggested spinal muscular atrophy (SMA) or an inborn error of metabolism. As the patient was not alert, tongue fasciculation was absent and specific EMG findings related to Werdnig-Hoffman were not recorded, SMA was ruled out.

The main laboratory finding in NKH is elevation of glycine in serum, urine and CSF. A value of greater than 0.08 in the CSF/serum glycine concentration ratio is diagnostic. The serum and CSF glycine levels in our patient were diagnostic for NKH. Liver GCS activity is indicated to determine the severity of the disease and for prenatal diagnosis. We were unable to measure GCS activity in our patient due to technical limitations. Carnitine deficiency (5) and transient hyperammoniemia (6) have been reported in some cases. We detected high CK values in our patient, which have never been reported previously. We suggested that the elevated level of serum CK was due to undocumented perinatal asphyxia in this patient. Even though hypotonia persisted, the CK level decreased to normal after the second week of life.

Agenesis or hypoplasia of the corpus callosum is a characteristic finding of the disease but not diagnostic. Delayed myelination of the cerebral white matter has been reported in most cases of NKH. Gyral malformation, ventricular enlargement, cerebellar hypoplasia (7) and intracranial hemorrhage (6) and hydrocephalus (8) have been described in some cases. There was no abnormality on CT except the arachnoid cyst in our patient. Magnetic resonance (MR) examination is the imaging modality of choice for NKH because it can demonstrate the degree of myelination.

A burst-suppression pattern seen on our patient’s EEG is not diagnostic of NKH but is highly suggestive, since its most common cause is NKH.

There is no effective treatment. Therapy strategies are directed to decrease the glycine concentration (sodium benzoate) and NMDA receptor antagonization (dextromethorphan and ketamine). While some investigators reported improvement (5,6), others saw no clinical response (9). Seizures in NKH may be controlled with only sodium benzoate and/or dextromethorphan (10,11). But for some patients, it is required to use additional anticonvulsant therapy such as phenobarbital, diazepam-a competitor for glycine receptors, or felbamate (10). In our patient, seizures disappeared with sodium benzoate therapy and did not recur after the discontinuation of phenobarbital medication.
In conclusion, NKH is a rare cause of neonatal hypotonia without consistently effective treatment and should be considered in a hypotonic newborn, especially if associated with lethargy and seizure, and acute deterioration of an infant that seems relatively well after delivery. The recognition of this metabolic disorder as the cause has important implications not only for the immediate care of the patient, but also for genetic counseling in order to prevent recurrences in future pregnancies. Also we would like to draw attention to the fact that neonatal central hypotonia associated with elevated serum CK activity should be followed up before the final diagnosis has been established.

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Correspondence author:
Rahmi ORS
Atatürk Üniversitesi, Tip Fakültesi,
Yakutiye Araştırma Hastanesi,
25240, Erzurum-TURKEY

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