A Diagnostic Dilemma: Nonketotic Hyperglycinemia in a Newborn with Neonatal Abstinence Syndrome—A Case Report

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Abstract

This case report highlights the difficulties in diagnosing non-ketotic hyperglycinemia in a neonate with maternal substance abuse and neonatal abstinence syndrome. Despite initial treatment for neonatal abstinence syndrome, the neonate suffered sudden cardiopulmonary arrest and had elevated glycine levels in the serum, cerebrospinal fluid, and urine, suggestive of non-ketotic hyperglycinemia. However, immediate treatment failed to improve the newborn’s condition, and the infant died of ventilator-associated pneumonia. The report underscores the importance of considering other differential diagnoses in infants with neonatal abstinence syndrome and highlights the challenges of diagnosing and treating rare genetic disorders, such as non-ketotic hyperglycinemia, in the neonatal period.

Keywords: Drug misuse, hyperglycinemia, neonatal abstinence syndrome, nonketotic

Introduction

Neonatal abstinence syndrome (NAS) is a condition in which a newborn exhibits withdrawal symptoms after being exposed to drugs in utero. Neonatal abstinence syndrome has become an increasingly important issue in recent years due to the increase in substance abuse among pregnant women (Patrick et al., 2015). This increase is largely attributed to the opioid epidemic, as opioids are the most commonly used drugs during pregnancy that can cause NAS (Winkelman et al., 2018). The NAS can have significant short- and long-term consequences in affected infants. Infants with NAS are more likely to experience respiratory distress, feeding difficulties, and seizures. These symptoms are also commonly observed in two serious neonatal differential diagnoses: early-onset neonatal sepsis and inborn errors of metabolism (IEM). Both conditions require distinct and important therapies that must be promptly addressed (Kocherlakota, 2014).

Hyperglycinemia is a rare IEM caused by a deficiency in the glycine cleavage enzyme and typically occurs in the neonatal period. The clinical presentation of hyperglycinemia can vary but typically includes lethargy, hypotension, seizures, and respiratory distress. These symptoms can be severe and can lead to significant neurological sequelae. Hyperglycinemia is usually diagnosed by simultaneous measurement of glycine levels in the blood and cerebrospinal fluid (CSF). Early diagnosis is critical because prompt treatment can improve the outcomes in affected infants (Nowak et al., 2022).

Case Presentation

A male newborn was delivered vaginally at 36 weeks gestation with a birth weight of 2855 g. The mother, who was 30 years old, had a history of substance abuse, including heroin and methamphetamine. She had engaged in the misuse of heroin through intravenous administration and methamphetamine through smoking. She used these drugs throughout her pregnancy. She had consumed the last dose of heroin 1 hour prior to being admitted for labor (3 hours before delivery), and the last dose of methamphetamine was administered the day before admission. The exact dosage of these drugs was not specified.
The Apgar score at minute 1 was 6, which improved to 8 by minute 5. However, shortly after birth, the infant was admitted to the neonatal intensive care unit (NICU) because of respiratory distress and was treated with ampicillin and amikacin. In addition, the baby received oral morphine, intravenous, and then oral phenobarbital for NAS symptoms.

On the sixth day after birth, the newborn suffered a sudden cardiopulmonary arrest that required prolonged resuscitation efforts. The medical team noted that the baby’s serum phenobarbital level was high at 53 µg/mL, which, along with the concomitant effects of morphine administration, may have contributed to the respiratory depression that led to cardiopulmonary arrest. Following this event, brain ultrasonography was performed, which revealed bilateral symmetric echogenic regions in the lentiform nuclei and thalamus. These findings were suggestive of hemorrhage, hypoxic-ischemic encephalopathy, or inborn errors of metabolism. Persistent loss of consciousness was attributed to hypoxic ischemic encephalopathy (HIE) after prolonged resuscitation.

Upon conducting a comprehensive history assessment, it was discovered that the newborn had an older male sibling who was born three years earlier. The older sibling was born vaginally under non-sterile conditions, with an unknown gestational age and birth weight of 2600 g. The mother was addicted to heroin at the time. Laboratory findings showed an elevated white blood cell count of 26,000/mm³, a low platelet count of 81,000/mm³, and a low hemoglobin level of 8.4 mg/dL. In addition, the C-reactive protein level was significantly elevated at 39 mg/L, indicating inflammation or infection. Echocardiography revealed an atrial septal defect, patent ductus arteriosus, and mild peripheral pulmonary stenosis. The medical team prescribed packed cells and ampicillin, amikacin, meropenem, vancomycin, and phenobarbital for NAS. Ultrasonography of the brain revealed no abnormalities. However, on the fourth day after birth, the baby had suffered sudden cardiopulmonary arrest and died, which had been attributed to early-onset neonatal sepsis at that time.

Because of the worrisome medical history of the neonate’s older sibling, we decided to investigate the possibility of IEM in this case. Although initial laboratory findings, including serum ammonia, glucose, and venous blood gas levels, were within normal limits, further testing was performed. Simultaneous analysis of the serum and CSF amino acid profiles by high-performance liquid chromatography revealed that the newborn had elevated levels of glycine in serum (603 µmol/L), CSF (55 µmol/L), and urine (1852 µmol/L), such that the ratio of glycine in CSF to plasma exceeded 0.08. These findings were consistent with the diagnosis of nonketotic hyperglycinemia (NKH).

Once the diagnosis of NKH was confirmed, the neonate was treated promptly. Adequate intravenous fluids, sodium benzoate, and dextromethorphan were administered. Antibiotics were changed to cefotaxime and vancomycin. Despite these efforts, the neonate’s condition continued to deteriorate, and on the twenty-first day of life, the baby died of ventilator-associated pneumonia. The medical team provided supportive care and comfort measures until the very end. Written informed consent was obtained from the patient’s parents for the publication of a scientific article.

Discussion

Neonatal sepsis and IEMs are the main differential diagnoses of NAS, which has been a growing health problem in recent years (Patrick et al., 2015).

The diagnosis of NKH in the neonatal period can be challenging due to several factors. Nonketotic hyperglycinemia is a rare genetic disorder that impairs the breakdown of the amino acid glycine, resulting in an accumulation of glycine in the body and causing severe neurological symptoms. Some of the difficulties in diagnosing NKH in the neonatal period are described below:

1. Nonspecific symptoms: Symptoms of NKH in the neonatal period may be nonspecific and overlap with other conditions, including NAS, sepsis, metabolic disorders, and HIE. These symptoms may include lethargy, poor feeding, hypotension, seizures, respiratory distress, and apnea (Almannai & El-Hattab, 2018).

2. Variable presentation: the severity and expression of NKH can vary widely, even among individuals with the same genetic mutation. Some infants may have a mild course that may not be recognized until later in life, while others may have severe symptoms at birth (Swanson et al., 2015).

3. Limited awareness: NKH is a rare disorder, and many health care providers may not be familiar with the condition or consider it as a possible diagnosis. As a result, diagnosis may be delayed or missed altogether (Bhumika et al., 2022).

4. Challenges with diagnostic testing: diagnosis of NKH typically requires specialized testing, including measurement of glycine levels in blood, urine, and CSF, as well as genetic testing. These tests may not be readily available, or results may take several days to become available, which can delay diagnosis and treatment (Farris et al., 2020).

5. Treatment challenges: NKH is a life-threatening disease, and early diagnosis and treatment are critical to improving treatment outcomes. However, limited treatment options are available, and treatment of the disease often consists of supportive care and symptom control (Nowak M et al., 2022).

As a take-home message, a detailed history and thorough physical examination are critical to investigate other differential diagnoses in infants with NAS. If all symptoms and problems are attributed to NAS, it can severely compromise the health of these infants.

Informed Consent: Written informed consent was obtained from the parents of the patients.

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