IJN
Iranian Journal of Neonatology
http://ijn.mums.ac.ir

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Case Report

Transient Hyperammonemia of the Newborn: A Case Study

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ABSTRACT

Background: Transient hyperammonemia of the newborn (THAN) is an overwhelming condition presenting with coma within 2-3 days of life and requiring immediate treatment. The etiology of this condition remains unknown. Duration of coma determines the degree of neurologic impairment and developmental delay in hyperammonemia.

Case report: A newborn (BW=2900 g) was presented with a clear prenatal and perinatal medical history, poor sucking, refusal to feed, and deep coma within 72 hours of birth; the infant required ventilator assistance. On admission, physical examinations showed normal conditions, except for mild generalized weakness. Moreover, there was no history of consanguinity or maternal or obstetrics illnesses. However, the laboratory tests revealed marked hyperammonemia (plasma ammonia > 397 µg/dL, normal: 27-102 µg/dl) and elevated lactate (36.1 mg/dl, normal < 20 mg/dl). With aggressive therapy (no dialysis), he survived and was discharged without any complications. The follow-up examinations during the next six months showed that his development was within the normal range without any signs of delay.

Conclusion: Hyperammonemia should be considered in infants presenting with neurological deterioration as timely and appropriate intervention could result in good prognosis.

Keywords: Hyperammonemic coma, Inborn error of metabolism, Newborn, Transient hyperammonemia

Introduction

Hyperammonemia (HA) is secondary to an underlying metabolic disorder. The urea is the reminder of protein metabolism, which is normally converted through the urea cycle and from excess dietary and waste nitrogen. Defects of the urea cycle cause hyperammonemia, and then lead to encephalopathy, and if not treated, cause devastating neurologic sequelae and even death (1).

Prognosis of transient HA in the newborn (THAN) is usually more effective than that of the urea cycle disorders. Mild and asymptomatic HA (40-50 µg/dl) is common for about 6-8 weeks in very-low-birth-weight infants, which improves without significant neurologic deficits (2). In premature newborns, severe transient HA has been rarely observed because of mild respiratory distress syndrome (2, 3). THAN was first reported in 1978 (in 34-36 week old newborns), where in four out of five babies, ammonia returned to normal and lead to normal outcomes within 72 hours.

Hyperammonemia may occur in asphyxia and severe hepatic diseases (4, 5). The cause of the disorder is unknown, and it usually presents in the first 24 hours of birth (2, 3). It is revealed within the first few days of postnatal life in the form of severe hyperammonemia, comatose state, without abnormal organic aciduria, with normal activity of urea cycle enzymes, and usually ending with complete improvement (4). In neonates undergoing mechanical ventilator support, diagnosis may be difficult because of receiving sedatives and muscle relaxants (3).

The mortality rate in HA is high. However, recent advances in HA diagnosis and treatment have greatly improved prognosis for many infants with inborn metabolism errors. Early clinical diagnosis of HA is essential, and its treatment

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Please cite this paper as:
Hardani AK, Aminzadeh M. Transient Hyperammonemia of the Newborn: A Case Study. Iranian Journal of Neonatology. 2018 Mar: 9(1). DOI: 10.22038/ijn.2018.24515.1311

should be initiated promptly and continued vigorously. Here, we report a case of severe THAN experiencing coma.

Case report

A four-day-old male neonate was admitted to our neonatal intensive care unit because of progressive poor feeding since the past two days. He was born to a 29-year-old healthy mother at the 38th week of gestation with the body weight of 2800 g. The neonate was delivered through cesarean section. The Apgar score was normal and he was on breastfeeding. There was no history of consanguinity or maternal or obstetrics illnesses. The only complaints were feeding refusal and poor sucking. He was conscious and feverless and the parents did not report vomiting, abnormal odor, and/or seizure-like movements. There were no past medical histories in the family or during the pregnancy course. Physical examinations on admission revealed: pulse rate:140/min, respiratory rate: 58/min, blood pressure: 80/40 mmHg, temperature: 36.8ºc, body weight: 2920 g, length: 48 cm, and head circumference: 34 cm. All the exams were normal, except for moderately depressed neonatal reflexes and mild generalized weakness. Two hours later, he developed apnea and cyanosis and was then placed on mechanical ventilation because of recurrent apnea attacks. Administration of 10% dextrose solution was started using a peripheral venous line, and ampicillin and aminoglycoside were initiated. At that time, heart rate ranged 170-180 beats/minute and his ventilation sounded well. Also, chest radiograph showed no notable findings. However, mild abdominal distention was noted.

On the fourth day of life, seizure was developed and abruptly progressed to coma without causing any localized neurological defects. Laboratory tests showed serum creatinine of 0.7 mg/dl and normal urine output. Blood pressure was managed with more intravenous fluids and 5 µg/kg/min of dopamine.

The tests also revealed marked hyperammonemia (plasma ammonia > 397 µg/dL, normal: 27-102 ug/dl) and elevated serum lactate (36.1 mg/dl, normal < 20 mg/dl). Venous blood samples were taken and transferred on dry ice, and analyses were performed within 15 min after sampling by the enzymatic UV (monoliquid) method (BXCO376-AMMONIA). Besides intensive therapy for HA, additional investigations including serum amino acids (high performance liquid chromatography; HPLC), carnitine profile (MS/MS), and urinary concentration of organic acids were requested to rule out common inborn metabolism errors. The above test results were all negative for abnormal organic acids and urea cycle metabolites (Table 1).

All the investigations for sepsis, urinary infection, and meningitis along with their culture results were negative. Dialysis was suggested, but it was rejected by the parents. Consequently, treatment with sodium benzoate (500 mg/kg/day) and carnitine was started. All the laboratory exam results revealed normal range. The neonate was extubated, and therefore, gavage feeding was started and tolerated. The infant was successfully extubated after two days, while receiving nasogastric feeding along with the rising of consciousness level. Serum ammonia level regularly decreased to the normal range on the 8th day of life, during the four days of treatment, his ammonia decreased on a daily basis from 397 µg/dL to 240 µg/dL, 180 µg/dL, 97 µg/dL, and 57 µg/dL on the fourth day, respectively. His general condition improved rapidly to commence breastfeeding and regular care. Brain magnetic resonance imaging (MRI) showed no specific abnormalities.

Finally, the diagnosis of THAN was made, and he was discharged on the 12th day of life. The patient was regularly followed up every two weeks for two months (with oral sodium benzoate 250 mg/kg/day then discontinued) and then every month up to 6 months of age. The follow-up examinations during the next six months indicated that his development was within the normal range without any signs of delay.

Table 1. Laboratory findings of a neonate with transient severe hyperammonemia

HB	10.8 g/dl	Na	136 mEq/L	Alk.P	439 IU/L
WBC	9.520 /µl	K	3.6 mEq/L	Bili/T	11.8 mg/dL
Plt	329,000 /µl	BUN	64 mg/dL	Ca	7.5 mg/dL
ESR	3 mm/hr	Cr	1.1 mg/dL	pH	pH= 7.21
CRP	1+	AST	68 IU/L	HCO_3	13 mEq/L
BS	127 mg/dL	ALT	10 IU/L	$PaCO_2$	29.4 mmHg
Ammonia	397 µg/dL	Lactate	36.1 mg/dl	PaO_2	126.4 mmHg

HB: Hemoglobin, WBC: white blood cell, Plt: platelet, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, BS: blood sugar, BUN: blood urea nitrogen, AST: aspartate aminotransferase, ALT: alanine aminotransferase

Discussion

In the current paper, a case of severe THAN with complete improvement and unknown etiology was presented. Although very-low-birth-weight infants may experience mild transient hyperammonemia that lasts for about 6-8 weeks, severe transient neonatal hyperammonemia has been rarely reported (6-10). The majority of such infants are premature, and this disease usually develops during the course of treatment for respiratory distress syndrome (2).

Giacoia et al. reported that large, premature, and male infants were most commonly affected (8). These infants are cared for in regular nurseries without any prenatal problems and become symptomatic with lethargy that rapidly progresses to somnolence, coma, and intractable seizure, respiratory distress, and death. Moreover, the plasma ammonia level may be as high as that in the urea cycle enzyme disorder (2, 3). Hyperammonemic coma may develop within 2-3 days after birth.

Laboratory studies reveal marked hyperammonemia (> 150 µg/dL) with moderate increases in plasma levels of glutamine and alanine. In our case, marked hyperammonemia was also discovered, but plasma the levels of glutamine and alanine did not elevate. Several researchers have sought to implicate hypoxia as a prerequisite to the development of hyperammonemia (11, 12). Beddis et al. noted a significant number of nursery admissions with birth asphyxia or hyaline membrane disease and significant hypoxia suffered from hyperammonemia (13).

Hyperammonemia is the most significant laboratory finding in acute encephalopathy associated with inborn metabolism errors (7). Symptomatic neonatal hyperammonemia can be THAN only after exclusion of inborn metabolism errors of the urea cycle and organic academia. This differentiation has to be made by measuring plasma and urine amino acids, urine ketones, organic acids, and enzyme activities (14). These laboratory findings were normal in our case and suggested no urea cycle enzyme disorder. Hyperammonemic coma is a medical emergency, and favorable outcome is accessible by rapid resolution of hyperammonemia (2, 3, 15, 16) because rapid detoxification plays a critical role in minimizing the damage to the brain and other organs (18) and stabilizes the affected metabolic pathways. If high ammonia level is the cause of alteration in the central nervous system status, ammonia-scavenging therapy should be initiated while hemodialysis or extracorporeal membrane oxygenation is prepared (7).

Duration of coma is related to the prognosis of recovery. Irreversible neurological damage due to severe hyperammonemia (> 800 µM/l # >560 µg/dl) for more than 24 hours proved that the duration of hyperammonemia is a more important risk factor than the peak level. As with hyperammonemic coma in the urea cycle enzyme disorder, this medical emergency requires dialysis therapy (16). Khalessi et al. reported that in all their patients with hyperammonemia, treatment with sodium benzoate was continued for 3-7 days until the normalization of plasma ammonia levels, as we did in our case (17).

The mortality rate in hyperammonemia is high. However, recovery without sequelae can be possible if the patient is treated early and aggressively (2, 3, 16). If not treated early, neurologic sequelae, including mental retardation, seizure, cortical atrophy, and spastic quadric paresis, may occur depending on the duration of hyperammonemia. Persisting coma for more than two days usually leads to neurologic deficits (19).

Conclusion

In newborns with signs of change in the mental status, emesis, seizure, and/or poor feeding, plasma ammonia level should be examined as a routine diagnostic test. Hyperammonemia in neonates has a good prognosis if prompt diagnosis and aggressive therapy are performed.

Acknowledgments

The authors would like to thank all the medical staff providing medical care for the patients during the hospital stay.

Conflicts of interests

None declared.

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