A case of severe transient hyperammonemia in a newborn

Min Woo Hwang, M.D., Seung Taek Yu, M.D., and Yeon Kyun Oh, M.D.

Department of Pediatrics, Wonkwang University School of Medicine, Iksan, Korea

= Abstract =
Transient hyperammonemia in a newborn is an overwhelming disease manifested by hyperammonemic coma. The majority of affected newborns are premature and have mild respiratory syndrome. The diagnosis may be difficult to determine. This metabolic disorder is primarily characterized by severe hyperammonemia in the postnatal period, coma, absence of abnormal organic aciduria and normal activity of the enzymes of the urea cycle. Hyperammonemic coma may develop within 2-3 days of life, although its etiology is unknown. Laboratory studies reveal marked hyperammonemia (>4,000 µmol/L). The degree of neurologic impairment and developmental delay in this disorder depends on the duration of hyperammonemic coma. Moreover, the infant may succumb to the disease if treatment is not started immediately and continued vigorously. Hyperammonemic coma as a medical emergency requires dialysis therapy. Here, we report a case of severe transient hyperammonemia in a preterm infant (35 week of gestation) presented with respiratory distress, seizure, and deep coma within 48 hours and required ventilatory assistance and marked elevated plasma ammonia levels. He survived with aggressive therapy including peritoneal dialysis, and was followed 2 years later without sequelae. (Korean J Pediatr 2010;53:598-602)

Key Words: Transient hyperammonemia, Hyperammonemic coma, Newborn

Introduction

Hyperammonemia is often a sign of an underlying metabolic disorder. Excess dietary and waste nitrogen, remaining after protein synthesis, are normally converted into urea through the urea cycle. Disorders of enzymes of the urea cycle lead to accumulation of ammonia and its precursors. This can cause encephalopathy and death or devastating neurologic sequelae if not treated immediately3). So, neonatal hyperammonemia is a medical emergency requiring early diagnosis and early treatment.

But the prognosis of transient hyperammonemia in a neonate is usually better than urea cycle disorders. Very low birth weight infants may have a mild hyperammonemia (40–50 µM/L), which has lasts for about 6–8 week. These infants are usually asymptomatic, and revealed no significant neurologic deficits3).

However severe transient hyperammonemia has been rarely observed in newborn infants. The majority of affected infants are premature and have mild respiratory distress syndrome3, 5). According to available investigations, one case of severe transient hyperammonemia in the newborn infant was reported in Korea4). Hyperammonemia may occur in asphyxia and severe hepatic diseases5). The cause of the disorder is unknown, but its onset is usually in the first 24 hours after birth when the infant is undergoing mechanical ventilatory support2, 3). The diagnosis may be difficult to determine because many of these same infants are receiving sedatives and muscle relaxants3).

The mortality rate in hyperammonemia is high. However, recent advances in the diagnosis and treatment of it have greatly improved the prognosis for many infants with inborn errors in metabolism. So, early clinical diagnosis of hyperammonemia is essential and treatment of it should be initiated promptly and continued vigorously. Then, recovery without sequelae is common, and hyperammonemia does not recur even with a normal protein diet5).

In this report, we present a case of severe transient hyperammonemia associated with coma in a premature infant with respiratory distress syndrome.
Case report

A male neonate was admitted to the neonatal intensive care unit due to moaning, cyanosis and premature rupture of membrane. He was born to a 30-year-old gravida 5, para 2 mother at the 35 week of gestation. His birth weight was 2,520 g. The neonate was delivered by normal spontaneous vaginal delivery. The Apgar scores were 5 at 1 minute and 6 at 5 minutes.

On physical examination conducted 2 hours after delivery, he developed cyanosis and respiratory distress with moaning and was increased respiratory rate 75/min. So, he was intubated and inhaled oxygen 5 L/min by E-tube. Although oxygen therapy was given, his oxygen saturation level was below 85%, he was plated on a mechanical ventilator. Laboratory analysis of the blood revealed hemoglobin 13.8 g/dL, hematocrit 39.5%, white blood cell count 3,520/µL, platelet 329,000/µL, ESR 3 mm/hr, CRP 0.28 mg/L. Liver function tests were as follows: AST 68 IU/L, ALT 10 IU/L, ALP 439 IU/L, total bilirubin 3.08 mg/dL. And serum Na⁺ 148 mEq/L, K⁺ 4.6 mEq/L, total Ca 9.0 mg/dL, BUN 7.8 mg/dL, creatinine 0.69 mg/dL, and glucose screen >80 mg/dL were revealed. A sample of arterial blood showed the following results: pH 7.319, PaCO₂ 39.4 mmHg, PaO₂ 99.7 mmHg and a base excess of -5.8 mM/L (FiO₂ 0.8, RR 40/min, PIP 18 mmHg, PEEP 4 mmHg). A peripheral venous line was placed, and administration of a 10% dextrose solution was started. His heart rate ranged from 170 to 180 beats/minute and his lung sounded wet. Chest radiograph showed pulmonary opacification, obscuration of cardiac margin, and increased air bronchogram which were characteristic of hyaline membrane disease, grade III. Furthermore, mild abdominal distention was noted. Endotracheal instillation of pulmonary exogenous surfactant was performed for the treatment of hyaline membrane disease. Ampicillin and aminoglycoside antibiotics were also initiated due to maternal premature rupture on membrane and hyaline membrane disease. After then, his respiratory effort was improved and controlled by low level of oxygen (FiO₂ 0.4).

On the 2nd hospital day, his respiratory difficulty were continued, and urine output decreased to 0.8 ml/kg/hr. Laboratory exam revealed BUN 11.04 mg/dL, creatinine 1.34 mg/dL, K⁺ 5.85 mEq/L. So, he was managed with hydration, lasix and dopamin to relieve the acute renal failure. But hyperkalemia was aggravated (serum K⁺: 9.8 mEq/L), and sine wave and PT prolongation on electrocardiogram (EKG) was revealed.

On the 3rd day of life, seizure was noted and then his mental status changed to coma abruptly. Laboratory studies revealed marked hyperammonemia (plasma ammonia as high as >715 µM/L -above data was undetectable in our laboratory), hyperkalemia (K⁺: 8.82 to 9.98 mEq/L), elevated lactate (66.1 mg/dL), and increased serum creatinine 1.5 mg/dL (Table 1). In spite of intensive therapy to re-

| Table 1. Summary of Clinical Manifestations and Laboratory Results |
|-----------------|------------|-------------|-------------|-----------------|-----------------|
| HD   | Hb (g/dL) | WBC (µL) | PLT (µL) | BUN (mg/dL) | Cr (mg/dL) | Na⁺ (mEq/L) | K⁺ (mEq/L) | Ammonia (µM/L) | Note |
| 1    | 13.7      | 3,520     | 329K      | 7.8          | 0.69      | 148       | 4.6         |               |     |
| 2    | 14.1      | 10,640    | 280K      | 11.04        | 1.34      | 146       | 5.33 to 9.98 |               |     |
| 3    | 8.4       | 16,170    | 206K      | 19.40        | 1.40      | 142.1     | 7.4 to 6.68 | >715          |     |
| 4    | 13.1      | 16,800    | 124K      | 31.06        | 1.29      | 140.6     | 5.05        | >715          |     |
| 6    | 10.0      | 17,990    | 86K       | 14.82        | 0.70      | 138.0     | 3.20        | 616 → 338     |     |
| 7–9  | 8.1       | 27,600    | 184K      | 7.6          | 0.35      | 142.1     | 3.82        | 219 → 162 → 83 |     |
| 20   |           |           |           |              |           |           |             |               |     |

Abbreviation : HD, hospital day
Transient hyperammonemia in a newborn, a condition of unknown etiology, was first described by Ballard and colleagues in 1978. The clinical picture is similar to patients with defects in the activity of the enzymes of the urea cycle that appear in the neonatal period. It may be difficult to determine the diagnosis. Very low birth weight infants may have a mild transient hyperammonemia, which lasts for about 6–8 weeks. These infants are asymptomatic and have no significant neurologic deficits. But severe transient hyperammonemia has been reported in newborn infants rarely. The majority of these infants are premature, and this disease usually develops during the course of treatment for respiratory distress syndrome. Giacoia et al reported that large premature and infant males most commonly were affected. These infants are born without any prenatal problems and are initially cared for in a regular nursery. These babies become symptomatic and can develop lethargy that rapidly progresses to somnolence and coma with intractable seizures, respiratory distress, and death. The plasma ammonia level may be enormously elevated, as high as urea cycle enzyme disorder. Hyperammonemic coma may develop within 2–3 days after birth. Laboratory studies reveal marked hyperammonemia (>4,000 \( \mu \text{M/L} \)) with moderate increases in plasma levels of glutamine and alanine. In our case, marked hyperammonemia (plasma ammonia as high as >715 \( \mu \text{M/L} \)) was continued for 5 days. After 5 days of peritoneal dialysis, the patient became mentally alert. And improvement of hyperkalemia was shown on laboratory exam and EKG. On the 9th day of life, his ammonia level returned to normal, and his brain computed tomography (CT) showed no abnormalities. On the 20th days of life, his brain magnetic resonance imaging (MRI) showed also no specific abnormalities. As a result, the diagnosis of severe transient hyperammonemia in a neonate was made. And he was discharged on 21th day of life. At the follow-up examinations for 2 years, his development is in the normal range without any sign of delay.

**Discussion**

Transient hyperammonemia in a newborn, a condition of unknown etiology, was first described by Ballard and colleagues in 1978. The clinical picture is similar to patients with defects in the activity of the enzymes of the urea cycle that appear in the neonatal period. It may be difficult to determine the diagnosis. Very low birth weight infants may have a mild transient hyperammonemia, which lasts for about 6–8 weeks. These infants are asymptomatic and have no significant neurologic deficits. But severe transient hyperammonemia has been reported in newborn infants rarely. The majority of these infants are premature, and this disease usually develops during the course of treatment for respiratory distress syndrome. Giacoia et al reported that large premature and infant males most commonly were affected. These infants are born without any prenatal problems and are initially cared for in a regular nursery. These babies become symptomatic and can develop lethargy that rapidly progresses to somnolence and coma with intractable seizures, respiratory distress, and death. The plasma ammonia level may be enormously elevated, as high as urea cycle enzyme disorder. Hyperammonemic coma may develop within 2–3 days after birth. Laboratory studies reveal marked hyperammonemia (>4,000 \( \mu \text{M/L} \)) with moderate increases in plasma levels of glutamine and alanine. In our case, marked hyperammonemia (plasma ammonia as high as >715 \( \mu \text{M/L} \)) was continued for 5 days. After 5 days of peritoneal dialysis, the patient became mentally alert. And improvement of hyperkalemia was shown on laboratory exam and EKG. On the 9th day of life, his ammonia level returned to normal, and his brain computed tomography (CT) showed no abnormalities. On the 20th days of life, his brain magnetic resonance imaging (MRI) showed also no specific abnormalities. As a result, the diagnosis of severe transient hyperammonemia in a neonate was made. And he was discharged on 21th day of life. At the follow-up examinations for 2 years, his development is in the normal range without any sign of delay.
to remove ammonia rapidly from the body\textsuperscript{16, 17}. Rapid detoxification plays a critical role in preventing or minimizing the damage to the brain and other organs\textsuperscript{18}. This approach not only prevents further damage due to direct effects of a metabolite, such as ammonia, but also stabilizes the metabolic pathways that may be affected subsequently. While preparing for hemodialysis or extracorporeal membrane oxygenation, ammonia scavenging therapy should be initiated, even prior to the diagnosis of a specific metabolic etiology, if it is felt that alteration in the central nervous system status is a result of the high ammonia level\textsuperscript{16}. Current literature suggests that patients with very high ammonia level should receive hemodialysis prior to extracorporeal membrane oxygenation\textsuperscript{16}. We think that, even if the ammonia was slowly relieved, peritoneal dialysis in this patient may be served to improve the clinical and laboratory findings, especially hyperammonemia.

The mortality rate in hyperammonemia is high. However, if a patient who can be treated early and aggressively, recovery without sequelae is common\textsuperscript{2, 3, 16}. If, not be treated early, many survivors may suffer from neurologic sequelae, e.g., mental retardation, seizures, cortical atrophy, and spastic quadriparesis. Neurologic sequelae and survival depend on the duration of hyperammonemic coma. Neurologic deficits usually occur if the coma persists for more than 2 days\textsuperscript{19}.

In conclusion, although hyperammonemia in neonate has a good prognosis as a prompt diagnosis and aggressive therapy, a plasma ammonia levels should be considered as a routine diagnostic test in cases of newborn infants with signs of changes in the mental status, emesis, seizures and/or poor feeding.

한 글 요약

신생아의 심한 일과성 고암모니아혈증

황민우, 유효택, 오연균

신생아 일과성 고암모니아혈증은 고암모니아혈증을 특징으로 하며 대부분 호흡곤란 처방을 받는 미숙아에서 발생한다. 발생 원인은 정확히 알리지 않으나 생후 2-3일에 호흡곤란, 기 면, 혼수 등의 임상 증상을 보이고, 생화학적 검사 상 혈증 암모니아 농도가 현저히 증가하며 요소수로 요소 치는 정상을 보 인다. 치료가 늦으면 사망에 이르는 응급을 요하는 질환이나 즉 각적이고 적절한 치료 시 신경학적 손상을 남기지 않고 호전 가 능하다.

저자들은 호흡곤란을 보여 호흡기 치료를 받던 35주 미숙아에 서 48시간 내에 경련과 함께 혼수상태에 빠지고 검사상 고암모니 아혈증을 보여 신속한 치료 후 회복되었으며 2년 추적관찰 에서 정상을 보인 환자를 보고하는 바이다.

References