Is neonatal antiretroviral therapy a risk factor for NEC occurrence?

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An association between maternal human immunodeficiency virus (HIV) infection and increased necrotizing enterocolitis (NEC) risk has been reported. Viral exposure and maternal antiretroviral therapy have been described as mediators of this risk.

We report a preterm patient with delayed meconium passage and subsequent NEC, in which both the above-mentioned mechanisms were excluded, suggesting that neonatal antiretroviral therapy could be the most relevant risk factor for NEC in a susceptible preterm gut.

Key words: antiretroviral therapy, newborn, necrotizing enterocolitis, human immunodeficiency virus.

An association between maternal human immunodeficiency virus (HIV) infection and necrotizing enterocolitis (NEC) in preterm infants has been reported recently[1]. Schmitz et al.[2] also highlighted this association in a term neonate.

Two mechanisms have been proposed to explain the increased risk of NEC: the exposure to HIV during fetal life and the maternal treatment with antiretroviral drugs.

We report a preterm infant in whom both mechanisms could be excluded and provide new findings about the NEC pathogenesis in preterm infants born to HIV-positive mothers.

Case Report

An 800 g male preterm infant was born at 28 weeks of gestation by vaginal delivery because of premature rupture of membranes and chorioamnionitis. A week before delivery, vaginal cultures were positive for *Klebsiella pneumoniae* and *Ureaplasma urealyticum*, and specific antibiotics (gentamicin and clarithromycin) were administered. A complete course of prenatal steroids was also provided.

The mother was affected by hepatitis C virus (HCV) and HIV infection. During the pregnancy, she received a multiple antiretroviral therapy (stavudine, tenofovir, ritonavir, tipranavir and enfuvirtide) because of viral multiresistance. This therapy was interrupted at the 23rd week, when liver failure and severe coagulopathy occurred. At delivery, maternal CD4 cell count was 164 cells/μl and HIV viral load was <50/ml.

At birth, the infant needed intubation and ventilation (Apgar scores were 2 and 5 at 1 and 5 minutes, respectively), and surfactant (Curosurf, 200 mg/kg) was administered because of respiratory distress syndrome. Venous umbilical catheter was positioned, and the tip was radiographically localized in the inferior vena cava. Arteriosus umbilical catheter was also positioned for monitoring blood gases and blood pressure in the first 24 hours from birth; X-ray showed the tip correctly positioned at the D9 level. Because of maternal chorioamnionitis, antibiotic therapy (ampicillin/sulbactam, clarithromycin and amikacin) was administered.

Antiretroviral therapy was started from the 6th hour of life with zidovudine (ZDV, 1.5 mg/kg intravenously, twice a day), and because of both viral multiresistance and interruption of maternal therapy, oral lamivudine (2 mg/kg, twice a day) was also added on the 3rd day of life.

Total parenteral nutrition was started in the first 12 hours of life. No oral feeding was ever allowed.

Serial Doppler echocardiographies excluded patent ductus arteriosus. Blood and bronchoalveolar lavage fluid cultures were negative. Arterial and venous umbilical catheters were removed on the 2nd and 3rd days of life, respectively; both tip cultures were also negative.

Clinical conditions progressively improved, so he was successfully extubated to nasal continuous positive airway pressure on the 6th day of life. Since there was still no meconium passage at this time, blood trypsin level was determined.

On day 7 of life, clinical conditions suddenly worsened. The neonate showed hyperglycemia, recurrent episodes of apnea, metabolic acidosis, abdominal distention and bilious stagnation, and needed to be intubated and ventilated. Antibiotic therapy with vancomycin and gentamicin was started. Abdominal X-ray revealed pneumoperitoneum, and iliac resection and ileostomy were performed. A diffuse iliac involvement was shown with an iliac perforation on the antimesenteric side. The baby died six hours after the surgery, despite intensive care. Blood, cerebrospinal fluid and urine cultures were negative, and trypsin level was normal. HIV-DNA polymerase chain reaction tests performed at birth showed negative results.

Discussion

The current multifactorial theory about NEC pathogenesis suggests that the most important risk factors are prematurity, hypoxia/ischemia, bacterial infection, and feeding[3]. All these factors imply the endogenous production of inflammatory mediators that precipitate the development of gut injury.

Some of these factors were present in our patient: prematurity, neonatal asphyxia, and arterial umbilical catheterization. Nevertheless, most of them were no longer present at the time of NEC occurrence: umbilical arterial catheter was removed after 24 hours of life, and the baby had neither hypotension nor any sign of hypoxic systemic damage. Finally, no infections were demonstrated and no oral feeding was ever allowed.

At the time of NEC occurrence, the patient was clinically stable, with the only problem being the absence of meconium passage, and trypsin level was normal.

To date, the pathogenesis of NEC in neonates born from HIV-positive mothers has not been clearly defined. It has been supposed that exposure to HIV determines an alteration of interleukin (IL)-12 expression in the gut mucosa and a decreased T-cell function[4]. Furthermore, maternal antiretroviral drugs may induce a mitochondrial dysfunction interfering with intestinal mitochondrial DNA polymerases and therefore playing an important role in the NEC pathogenesis. Nevertheless, in this case, the exposure to HIV and to the maternal antiretroviral therapy can be excluded: maternal viral load was very low, maternal treatment was interrupted five weeks before delivery, and the patient's viral state at birth was negative.

How could NEC risk, in this patient, have been increased by the presence of maternal HIV infection?

We speculate that, rather than the maternal therapy, it is the neonatal therapy that played the main role in increasing the risk of NEC. It has been reported that in term neonates, ZDV, causing mitochondrial toxicity, determines the occurrence of hypoperistalsis and intestinal pseudo-obstruction[5,6]. Our baby showed no passage of meconium up to the 7th day of life and, although preterm babies sometimes do not show meconium passage within 24 hours from birth, our infant showed an extreme delay. Hypoperistalsis and consequent delayed transit represented, in this patient, the most important risk factor for NEC. In fact, hypoperistalsis permitted bacterial overgrowth that, in a susceptible preterm gut, initiated the cascade of events leading to NEC[7,8].

Since most of the risk factors for NEC had already resolved, ZDV therapy was the only concurrent factor still present at the moment of NEC occurrence. Moreover, oral lamivudine had been started from the 3rd day of life in a baby with signs of hypoperistalsis and without oral feeding: the administration of such high osmolarity syrup (610 mosmol/L) may have directly injured the mucosa, especially in the presence of reduced gut motility.

In conclusion, in our patient, neonatal antiretroviral therapy may have been the main and most relevant factor for the increased NEC risk. We should keep in mind that ZDV administration in preterm babies with delayed meconium passage or even in the presence of other NEC risk factors may accelerate the cascade of events leading to NEC. Moreover, orally administered drugs for this purpose should be used with caution, especially in babies with reduced gut motility or in the presence of other NEC risk factors. Of course, we know that this is only a potential adverse effect in comparison with the enormous benefits resulting from the use of ZDV in newborn infants. Our aim is to alert neonatologists about the possible association between postnatal antiretroviral therapy and increased risk of NEC, in order to improve the management of these infants.

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