Neonatal management and outcome in red cell alloimmunization

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Bacillus cereus cerebral abscesses in a term neonate with Rhesus hemolytic disease treated with exchange transfusion

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Abstract

Exchange transfusion (ET) is the most effective method for treatment of severe hyperbilirubinemia and is often required in Rhesus hemolytic disease of the newborn (RHDN). The use of ET is also associated with adverse reactions, including severe catheter-related infectious complications. We report a term neonate with RHDN treated with an ET through an umbilical venous catheter who developed brain abscesses due to a Bacillus cereus sepsis. This severe complication has not previously been reported. We discuss possible causes for this severe infection and provide suggestions on prevention.

Introduction

Exchange transfusion (ET) plays an important role in the treatment of hyperbilirubinemia of the newborn. Rhesus associated hemolytic disease of the newborn (RHDN) is one of the most common indications for ET. The main therapeutic effect of ET is removal of excess bilirubin and maternal red blood cell antibodies in order to prevent kernicterus and to reduce hemolysis. Despite improvement in neonatal intensive care, ET still remains a high-risk invasive procedure associated with a significant rate of adverse reactions. Although the mortality rate associated with ET is nowadays less then 0.3% in term infants, morbidity rates may reach 5%.[1] Morbidity includes in particular catheter-related complications such as thrombosis, sepsis and necrotizing enterocolitis.[1]

We report a term neonate with RHDN treated with an ET who developed a rare but severe cerebral infection after umbilical cord catheterization.

Case report

A 36-year-old gravida 2 para 1 with severe Rh D alloimmunization required 3 intrauterine transfusions with filtered red blood cell concentrate for fetal anemia. These procedures were uncomplicated. The last transfusion before birth was done at 34 weeks' gestation, with a post-transfusion hemoglobin level of 15.1 g/dl. The first labour had been protracted and was complicated by a complete perineal laceration after vacuum assisted delivery. For this reason the parents required a caesarean delivery, which was planned 3 weeks after the final intrauterine transfusion at a gestation of 37 weeks. A male infant was born with a birth weight of 2400 grams (25th percentile for gestational age) and Apgar scores of 10, 10 and 10 at 1, 5 and 10 min, respectively. No abnormalities were detected on physical examination, except a pale skin color. Laboratory investigations at birth showed a hemoglobin value of 9.6 g/dL, a total bilirubin concentration of 11.8 mg/dL and a conjugated bilirubin concentration of 11.3 mg/dL. Treatment with intensive phototherapy was started immediately after birth. After obtaining parental informed consent, the infant was included in a randomized placebo controlled trial to assess the short and long term effects of prophylactic use of intravenous immunoglobulin (IVIg) in neonates with RHDN (LIVIN trial: http://www.controlled-trials.com/ISRCTN14013064/). For this study a ready for use 5% IVIg solution (Nanogam® Sanquin, The Netherlands) or glucose 5% (placebo) was used. Our patient was randomized for IVIg which he received within four hours after birth. Due to persisting elevated bilirubin concentrations and possible need for an ET an umbilical venous catheterization was performed. Despite intensive phototherapy, the total serum bilirubin

level increased gradually to a maximum level of 21.2 mg/dL, exceeding the threshold for ET, which was performed on day 3 through the umbilical vein catheter.

On day 6, the infant became acutely ill, his body temperature rose to 39.0°C and he became irritable. The white blood cell count was 8,100/μL (with 10% band forms) and the C-reactive protein concentration was 59 mg/L. Cerebrospinal fluid (CSF) analysis showed pleocytosis (10,513 cells/μL) and an elevated protein content (137 mg/dL), but the volume of CSF was not sufficient for culture. A peripheral blood culture was obtained and processed according to standard protocol, using culture vials for pediatric blood specimens (BACTEC culture vials type PED PLUS™ /F, enriched soybean-casein digest broth with resins). Meningitis therapy was initiated with vancomycin and ceftazidim intravenously. Subsequently, a lumbar puncture was repeated and CSF was collected for culture. Urinalysis was normal. On day 7, the blood culture came back positive (after 24 h incubation) for a Gram-positive, rod-shaped, beta-hemolyticum bacterium, identified as Bacillus cereus. It was found susceptible to vancomycin, meropenem and clindamycin, but resistant to penicillin. Bacterial and viral CSF cultures remained negative. Cultures of the packed cells used for the intrauterine blood transfusions and for the ET were sterile.

Cranial ultrasound on day 7 revealed a lesion in the right frontal region with signs of central necrosis and a rim of hyperechogenicity around it, suspect for a cerebral abscess, whereas a cranial ultrasound performed on day 1 had shown no abnormalities.
Monotherapy with meropenem was started because of a better passage through the blood-brain barrier. Magnetic resonance imaging (MRI) on day 11 showed multiple hemorrhagic cerebral abscesses in the right frontal, temporal and occipital lobe (Figure 1) and a few small abscesses in the cerebellum.

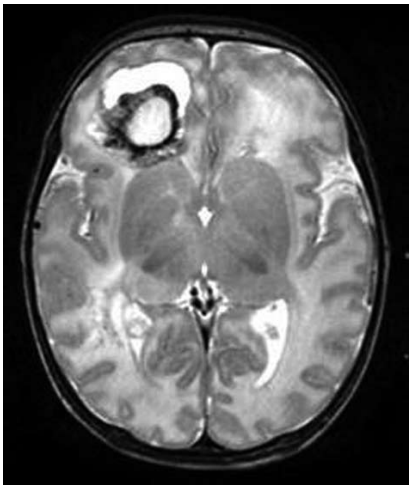

Figure 1 T2-weighted MRI showing a large hemorrhagic abscess in the right frontal lobe

On day 21 the child again became irritable and developed a seizure (stretching of both arms and legs). Because of the short duration of the seizure (less than 1 min) and a normal electroencephalogram (EEG), anticonvulsant medication was not required. On day 29 the infant had a recurrent generalized convulsion and anticonvulsant treatment (phenobarbital) was initiated. Again, the EEG showed no epileptic activity. A MRI performed a few days after the seizures showed no changes in the cerebral lesions.

After 6 weeks of intravenous meropenem administration, antibiotic treatment was discontinued. The infant was discharged home on day 61 with anticonvulsant therapy. At 2 years of age, the infant had no neurologic sequelae on physical examination. Mental and psychomotor development indexes, assessed at 2 years of age with the Bayley Scales of Infant Development, were within normal ranges.

Discussion

ET has been used in neonatal intensive care units for more than 50 years and is still the most effective method for treatment of severe hyperbilirubinemia. However, ET is also associated with severe adverse reactions, including catheter-related infectious complications.[2] We report a term infant with cerebral abscesses due to a Bacillus cereus sepsis, a severe complication which has not previously been reported.

Bacillus cereus is a probably ubiquitous soil bacterium and an opportunistic pathogen that is a common cause of food poisoning. In (premature) neonates, toxins produced by Bacillus cereus can cause necrosis of infected tissue. Bacillus cereus infections in neonates include meningoencephalitis and brain abscesses, characterized by liquefactive necrosis. A few sporadic cases have been reported in the literature and usually involved premature infants, suggesting an association with decreased immune response. Most cases of neonatal meningoencephalitis and cerebral abscesses with Bacillus cereus described in the literature resulted in neonatal death.[3-7]

Several potential risk factors may have led to the Bacillus cereus infection in this infant. Because of severe RHDN, three intrauterine blood transfusions and one ET were required. Multiple blood transfusions are associated with an increased risk of infection. However, cultures of all donor blood used for the transfusions were sterile. Intrauterine transfusions have also been associated with several procedure-related complications, including, although rarely, intrauterine infections. In the largest published series on complications of intrauterine transfusions, only two infections with E. Coli, both resulting in fetal distress within 48 h

after the procedure, were found in 740 procedures.[8] In the current case, no signs of infection were present prenatally, and there was no premature rupture of membranes prior to the elective caesarean section. It seems therefore highly unlikely that the Bacillus cereus infection had a prenatal origin. Moreover, cranial ultrasound on day 1 showed no abnormalities, excluding a link between the cerebral abscesses and antenatal invasive procedures.

Although very unlikely, another potential cause for infection in this case could be the IVIg solution. All IVIg preparations are routinely tested for sterility. The production of IVIg is an aseptical process. Up till now more than 80 batches resulting in approximately 100.000 vials of Nanogam® have been produced. Sterility tests on all these batches were negative.

Lastly, the most probable cause for infection in this case was the umbilical venous catheterization. Although umbilical venous catheterization is a common procedure in the management of sick neonates, it can lead to serious complications. Sequelae include thrombosis, embolization, hemorrhage, arrhythmias, (pericardial) effusions, portal hypertension and infection.[9] In the literature the incidence of sepsis related to umbilical venous catheterization is reported between 6% and 24%.[2]

Umbilical venous catheterization was required in this case because an ET was deemed necessary to reduce the elevated bilirubin levels and the risk of bilirubin encephalopathy. However, whether catheterization and ET was strictly unavoidable is questionable.

First, hyperbilirubinemia was mainly due to elevated levels of the conjugated bilirubin fraction. Elevated levels of conjugated bilirubin are not a rare phenomenon in neonates with RHDN, although the etiology is not clear. The current AAP guidelines state that thresholds for treatment in hyperbilirubinemia should be based on the total bilirubin levels, without subtracting the conjugated bilirubin fraction.[1] Nevertheless, when conjugated bilirubin is significantly elevated (i.e. > 50%) there is no bilirubin threshold at which intervention is recommended. Bilirubin encephalopathy is due to unbound, unconjugated bilirubin. Whether neonates with increased conjugated bilirubin are at increased risk for kernicterus is not known and management remains controversial. Management should ideally be based on the measurement of unbound, unconjugated bilirubin, but these measurements have not yet been adapted to clinical use.

Second, the AAP guidelines recommend the use of IVIg in case of failure of intensive phototherapy in order to reduce the need for ET.[1] The evidence to recommend routine prophylactic treatment with IVIg is considered insufficient.[10,11] A recent Cochrane review suggests that the results of further trials of higher quality should be awaited.[10] Although the risk for

adverse effects of umbilical venous catheterization and ET may decrease in the future, it will never completely disappear. The best way to prevent procedure-related complications in RHDN is to reduce the need for ET.

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