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CASE REPORT

Successful Treatment of Hyperbilirubinemia by Monitoring Serum Unbound Bilirubin in an Extremely Preterm Infant with Bacterial Infection

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SUMMARY

Background: **Bacterial infections and some antibiotics show displacer effects on bilirubin-albumin binding and increase unbound bilirubin (UB) but not total bilirubin (TB) in serum.**
Methods: **A case study was conducted to show a successful treatment of hyperbilirubinemia by monitoring UB.**
Results: **In an extremely preterm infant with bloodstream bacterial infection caused by methicillin-resistant coagulase-negative *staphylococci*, 2 days after high-dose ampicillin and regular-dose amikacin were initiated, UB markedly increased, but TB did not. After vancomycin was substituted, UB decreased immediately with phototherapy and intravenous albumin infusion.**
Conclusions: **When using antibiotics, the clinicians should be mindful regarding the displacer effect on bilirubin-albumin binding.**
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KEY WORDS

antibiotics, bacterial infection, displacer effect, total serum bilirubin, unbound bilirubin

INTRODUCTION

Unbound bilirubin (UB), which is not bound to albumin, can cross the blood brain barrier and cause neurotoxicity [1]. Increased levels of UB in the serum can predict the risk of bilirubin encephalopathy in infants [2-5]. Bilirubin encephalopathy is a rare disease in term infants in Japan, but it is seen in extremely preterm (EP) infants in Japan [4,6]. This could be attributed to the presence of a condition in EP infants that facilitates an increase in UB owing to low bilirubin capacity in the albumin, decreased albumin, and use of displacers, such as antibiotics and lipid emulsions that affect bilirubin-albumin binding [5], in addition to immaturity of the blood brain barrier. Studies have reported that EP chil-

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dren who developed bilirubin encephalopathy did not have a history of remarkable total serum bilirubin (TB) levels in the neonatal intensive care unit [4,7,8]. Therefore, we have proposed that serum UB should be monitored in EP infants in Japan using the UB-analyzer (Arrows Co, Ltd, Osaka, Japan), with covered government health insurance [6,9].

Bacterial infections and some antibiotics have a displacer effect and increase serum UB [5,10]. However, the patient reports in actual clinical practice are limited. In this report, we present the case of an EP infant who developed bloodstream bacterial infection and was administered antibiotics, including high-dose of ampicillin (ABPC). The patient was successfully treated for hyperbilirubinemia by monitoring UB levels. For publication, written informed consent was obtained from the patient's parents, and the Institutional Review Board of Nihon University Itabashi Hospital approved this case study (approval number RK-191112-5).

CASE REPORT

A female EP infant, weighing 574 g (appropriate-for-gestational age), was born at 23 weeks and 2 days of gestation to a 36-year-old mother. The mother's blood type was B with rhesus (Rh)-D positive, and no irregular blood antibodies were found. The father's blood type was also B with Rh-D positive. There was no family history of any blood disorders.

The mother was hospitalized because of vaginal bleeding at 13 weeks of gestation. At 23 weeks and 2 days of gestation, her uterine contractions increased, labor pain developed, and the infant was born through spontaneous vaginal delivery. The infant was immediately intubated owing to respiratory distress syndrome and was admitted to our neonatal intensive care unit (NICU). Routine treatment and care for her respiration, circulation, and nutrition was provided in the NICU.

Figure 1 shows her clinical course and laboratory levels of TB and UB. At 12 days of age, thrombocytopenia ($5.9 \times 10^4/\mu L$) and increased C-reactive protein (1.28 mg/dL) were observed. Severe bacterial infection was suspected, and high-dose of ABPC (400 mg/kg/day) and regular dose of amikacin (AMK, 8 mg/kg/day) were started. Because her TB and UB levels increased from 4.9 mg/dL and 0.36 µg/dL at 11 days of age to 6.4 mg/dL and 0.63 µg/dL at 12 days of age, respectively, high-intensity irradiance phototherapy (28 $\mu W/cm^2$ per nm) was initiated. At 14 days of age (on the second day from antibiotics initiation), UB levels dramatically increased to 1.58 µg/dL; however, TB levels (7.0 mg/dL) did not change, despite continuous phototherapy. No clinical symptoms of acute bilirubin encephalopathy were observed. As exchange blood transfusion could not be performed owing to unstable blood pressure, intravenous albumin infusion (1.6 g/kg by drip infusion to vein over 8 hours) with high-irradiation phototherapy was performed. Methicillin-resistant coagulase-negative *staphylococci* (MRCNS) were detected from the culture of umbilical arterial vein catheter. Bloodstream infection was diagnosed, and ABPC and AMK was changed to vancomycin (VCM, 15 mg/kg/day). UB decreased dramatically to 0.84 µg/dL after 1 day.

Auditory brainstem response at 1 month of corrected age showed normal wave findings in both ears (Figure 2A). Magnetic resonance (MR) T2-weighted imaging of the head at 10 months of corrected age showed no abnormal high signal intensities in bilateral globi pallidi (Figure 2B). At 13 months of corrected age, she stood-up by herself, walked with support, and made auditory responses in daily life. No clinical findings of athetosis and abnormal posture were observed; further, no signs of bilirubin encephalopathy were seen.

DISCUSSION

Bilirubin encephalopathy developed in EP infants without remarkable increase in the levels of TB during their stay in the NICU [4,7,8]. Therefore, other markers are urgently required to identify infants who are at risk of development of bilirubin encephalopathy. Serum UB has been reported as a marker [2-5]. In the present case, UB was remarkably increased, and our patient was at an increased risk of developing bilirubin encephalopathy. Bilirubin encephalopathy in EP infants can be diagnosed by the following clinical features and findings: (1) athetoid cerebral palsy or delay in motor development characterized by asymmetric posture, fluctuations in muscle tone owing to emotional change, and opisthotonus, (2) abnormal signal intensities in bilateral globi pallidi on head MR T2-weighted imaging between 6 and 18 months of age, and (3) abnormal auditory brainstem responses with preserved auditory response in daily life [6-8]. In this patient, these clinical findings were not observed, and we successfully prevented the development of bilirubin encephalopathy by monitoring UB and providing continuous phototherapy and intravenous albumin infusion for treatment.

Bacterial infections and some antibacterial drugs can affect bilirubin binding to albumin and often results in higher UB levels than those at comparable TB levels at any given TB level [5,10]. When based on Japanese treatment criteria at 25 weeks of corrected gestational age [6], the TB level (7.0 mg/dL) in our present case was below the phototherapy threshold value (8.0 mg/dL), indicating no need for treatment; however, the UB level (1.58 µg/dL) greatly exceeded the exchange blood transfusion threshold value (0.8 µg/dL). In other words, if we had monitored only TB levels in our patient, intensive treatments for hyperbilirubinemia, such as high-intensity irradiance phototherapy and intravenous albumin infusion, would have been missed. Wadsworth et al. reported that the displacer effects of ABPC and VCM are classified as "moderate", while those of AMK are classified as "mild" [11]. In our present case, because UB decreased dramatically 1 day after substitute-

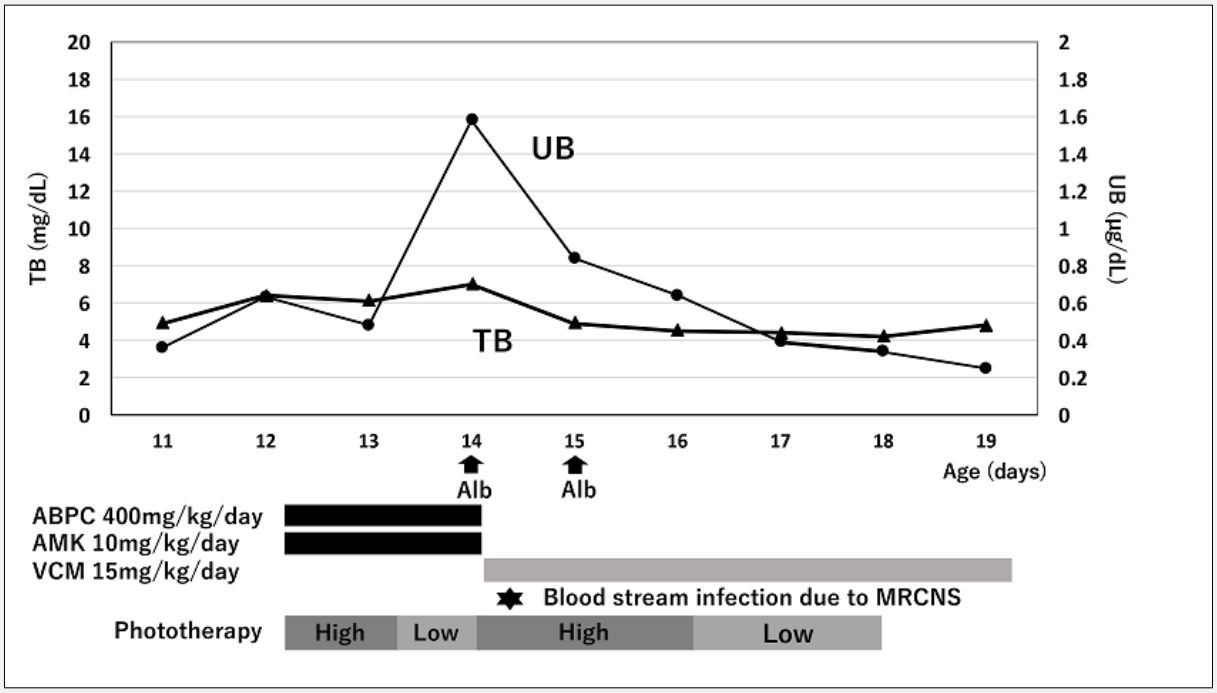

Figure 1. Clinical course and laboratory data of total serum bilirubin and unbound bilirubin.

"High" and "Low" phototherapies mean high-intensity irradiance phototherapy (28 μW/cm^2 per nm) and low-intensity irradiance phototherapy (12 μW/cm^2 per nm), respectively.
ABPC - ampicillin, Alb - intravenous albumin infusion, AMK - amikacin, MRCNS - methicillin-resistant coagulase-negative *staphylococci*, TB - total serum bilirubin, UB - unbound bilirubin, VCM - vancomycin.

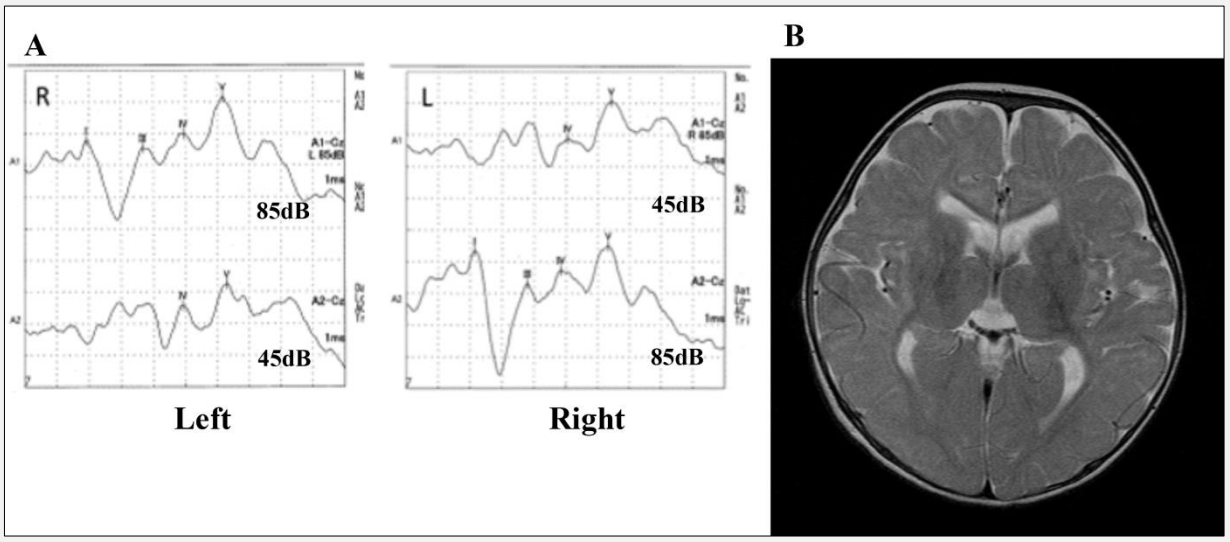

Figure 2. (A) Auditory brainstem response at 1 month of corrected age and (B) magnetic resonance T2-weighted imaging of the head at 10 months of corrected age.

ing high-dose of ABPC and regular dose of AMK to regular dose of VCM, we speculated that treatment with the high-dose of ABPC or a combination of ABPC and AMK cause the discrepancy between TB and UB, in addition to bloodstream infection caused by MRCNS.

CONCLUSION

We reported the case of an EP infant who developed bloodstream bacterial infection and was treated with antibiotics having displacer effects. We successfully treated hyperbilirubinemia by monitoring UB. When using antibiotics for any bacterial infections, clinicians must be mindful about their displacer effects on bilirubin-albumin binding and should be monitor UB levels.

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Declaration of Interest:
All authors declare no conflicts of interest related to this work.

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