

# Perinatal/Neonatal Case Presentation

## Auditory Brainstem Response Detects Early Bilirubin Neurotoxicity at Low Indirect Bilirubin Values

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When sedation, prematurity or other disease processes mask symptoms in the clinically ill newborn, serum bilirubin concentration is monitored as the sole indicator of kernicterus risk. This case emphasizes the value of auditory brainstem responses for the management of indirect hyperbilirubinemia complicated by prematurity, hemolytic anemia, asphyxia, and direct hyperbilirubinemia.

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### INTRODUCTION

The debate about the serum bilirubin concentration that becomes neurotoxic to neonates continues. Vigintiphobia is criticized as archaic, nonspecific and insensitive. In the presence of hyperbilirubinemia, lethargy, poor feeding and hypotonia are early signs of kernicterus that are potentially reversible with treatment by phototherapy or exchange transfusion.<sup>1</sup> However, in the clinically ill newborn, when sedation, prematurity or other disease processes mask these symptoms, serum bilirubin concentration is monitored as the sole indicator of kernicterus risk. Auditory brainstem response (ABR) testing provides a supplementary indicator of early bilirubin neurotoxicity. We report the present case as a reminder that the ABR provides objective evidence of bilirubin-induced neurotoxicity in newborns with masked clinical symptoms and indirect bilirubin values substantially less than 20 mg/dl.

### CASE REPORT

This 2200 g premature infant was delivered at 33 weeks gestation to a G3P1304 mother of O Rh<sup>-</sup> blood type. Past obstetrical history

was complicated by Rh isoimmunization and failure to receive RhoGAM during her second pregnancy. Prenatal care for the current pregnancy began at 17 weeks gestation and was complicated by fetal anemia secondary to Rh isoimmunization. Maternal blood was positive for anti-Kidd and anti-D antibodies. Amniocentesis at 28 weeks gestation confirmed Rh<sup>+</sup> fetal blood type. Serial ultrasounds confirmed normal middle cerebral artery (MCA) velocities until approximately 30 weeks gestation. Three fetal transfusions were performed. The final transfusion was performed at 33 weeks after the mother noted decreased fetal movements, and fetal heart rhythm became sinusoidal. Fetal hematocrit rose from 17 to 35%, and the abnormal fetal rhythm resolved. After 6 days, MCA velocities diminished, and the fetus was delivered via Cesarean section. Apgar scores were 4, 7 and 8 at 1, 5 and 10 minutes, respectively. A tight knot in the umbilical cord also complicated delivery.

The neonate was intubated while in the delivery suite and administered one dose of endotracheal surfactant for suspected respiratory distress syndrome. He remained hypotensive despite aggressive volume resuscitation in the NICU, and dopamine, dobutamine and hydrocortisone were required to maintain adequate perfusion. Severe hemolytic anemia (initial hematocrit 22%) accompanied by generalized edema confirmed the diagnosis of hydrops fetalis secondary to Rh isoimmunization. Initial total and direct bilirubin values were 4.8 and 0.5 mg/dl, respectively. Phototherapy was initiated, and three transfusions with O Rh<sup>-</sup>, irradiated packed red blood cells (15 cm<sup>3</sup>/kg) raised the hematocrit to 33% within 24 hours. At birth, neurologic exam revealed appropriate reactivity and tone for gestational age. However, by day of life (DOL) 2, tone and reactivity had severely diminished despite withdrawal of sedating drugs. By DOL 3, indirect bilirubin had risen to only 13.3 mg/dl. However, direct bilirubin had risen to 6.6 mg/dl, and phototherapy was intermittently discontinued because of early skin bronzing.

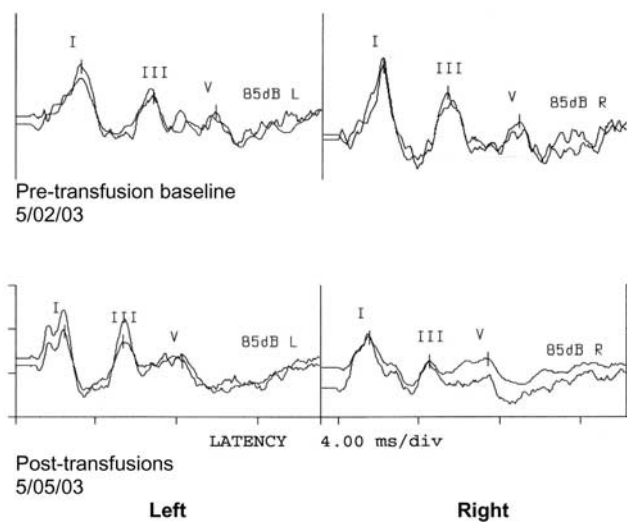
Although the indirect bilirubin value appeared insufficiently low to warrant a double volume exchange transfusion on DOL 3, the abnormally nonresponsive neurologic exam suggested early kernicterus. We reasoned that hydrops fetalis, anemia, hypoalbuminemia (1.5 g/dl) and secondary asphyxia compounded by a knotted umbilical cord may render the CNS more susceptible to bilirubin toxicity at indirect values as low as 10 to 13 mg/dl. To test for other evidence of bilirubin toxicity, an ABR was performed.

ABR testing was conducted using a Biologic Navigator unit equipped with insert EAR earphones. The patient was not sedated

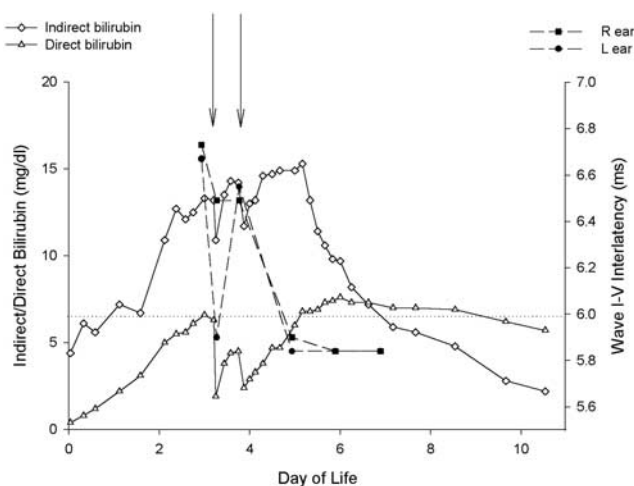
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during testing. Axillary temperatures during ABR testing were consistently  $36.9 \pm 0.1^\circ\text{C}$ . Silver-chloride clip electrodes were placed on the right and left earlobes, and a cup electrode was attached to the forehead. The protocol employed recordings for each ear at 85 dBHL using a rapid onset, transient click stimulus rate of 21.1 clicks/second. Filter settings were 100 to 1500 with a gain of 100,000. Recordings were accepted with minimum replications of 1500. In the initial study (Figure 1), baseline ABR demonstrated prolonged interlatencies of waves I to V (6.73 ms on the right (R) and 6.67 ms on the left (L) – normal value for 33 to 34 weeks  $5.27 \pm 0.36$  ms) without history of exposure to ototoxic drugs



**Figure 1.** Serial ABR waveforms are presented that were performed shortly prior to the first exchange transfusion and 70 hours later (following the second exchange transfusion).



**Figure 2.** Serum bilirubin values and ABR interlatencies respond to treatment by 2 double volume exchange transfusions (indicated by arrows). The horizontal dotted line indicates the upper limits of normal (mean + 2 SD) for wave I to V interlatency at 34 weeks gestational age.

(Figure 2). Cranial sector scan was normal. In an attempt to rapidly decrease indirect bilirubin values and minimize further bronzing from phototherapy, a double volume exchange transfusion was performed at 75 hours of life. Indirect and direct bilirubins decreased modestly, but repeat ABR demonstrated normalizing wave interlatencies (Figure 2). A second exchange transfusion was performed for rising bilirubin values and continued depression of neurologic responsiveness. Bilirubin values responded, wave V latencies improved to the upper limits of normal (Figure 1), and neurologic exam normalized over the next 2 days. Phototherapy was withheld to minimize further bronzing. He was weaned off mechanical ventilation and vasopressors by DOL 6, and the subsequent neonatal course remained uneventful.

During follow-up, cholestasis resolved by 2 months (adjusted gestational age), neurologic exam and neurodevelopment (Capute scales) normalized by 3 months, and ABR/otoacoustic emissions remained normal.

## DISCUSSION

Current knowledge regarding bilirubin encephalopathy derives primarily from term neonates lacking other complications.<sup>2–8</sup> The present case describes a premature infant who presented with prolonged fetal anemia and complicating hypoalbuminemia, hypotension, and knotted umbilical cord. Although serum indirect bilirubin values remained within a range considered nontoxic, clinical features and ABR results suggested bilirubin toxicity. In differentiating hypoxic–ischemic encephalopathy from bilirubin encephalopathy as a cause for this newborn's depressed neurological status, the ABR provided an excellent tool for distinguishing early bilirubin toxicity.

The term “ABR” refers to observed auditory evoked responses that arise from the eighth cranial nerve, superior olive and inferior colliculus within the first 10–15 ms of auditory stimulation. Wave components labeled I to V comprise the typical ABR. Applying this methodology, Chisin et al. were among the first to recognize changes in the neonatal ABR following hyperbilirubinemia.<sup>9</sup> They reported that hearing loss after neonatal hyperbilirubinemia correlated well with the absence of Wave I during ABR testing.

To prevent the neurotoxicity that may follow hyperbilirubinemia, more recent investigators have studied coincidental ABR abnormalities that occur during hyperbilirubinemia.<sup>4,10</sup> They report that diminished responses of waves I to V or delayed latencies sometimes occur at serum indirect bilirubin values even less than 20 mg/dl.<sup>6,8,10–12</sup> As reported by the present case and others, normalization of suppressed or delayed ABR results through treatment of marginally elevated bilirubin values demonstrate the clinical validity of ABR as an indicator of bilirubin toxicity.<sup>1,4,6,8,13,14</sup> In contrast to ABR, serum bilirubin values do not consistently predict toxic brain levels because the

blood–brain barrier threshold differs among newborns.<sup>7,15</sup> Particularly in hyperbilirubinemic premature infants, abnormal ABR provides a better indicator of bilirubin toxicity than serum bilirubin alone. In neonates unable to exhibit additional lethargy, poor feeding or hypotonia because of preceding medical conditions or therapies, ABR provides an objective tool for determining early phases of toxicity. In addition, the present case emphasizes that in newborns at risk of developing bronzing by phototherapy during combined indirect and direct hyperbilirubinemia, the risk of exchange transfusion is validly justified by abnormal ABR results when phototherapy is contraindicated.

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