ARTICLE

Unbound Bilirubin Concentration is Associated With Abnormal Automated Auditory Brainstem Response for Jaundiced Newborns

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What's Known on This Subject

It is known that bilirubin alters the auditory brainstem response, testing of which has been automated to screen newborn hearing. However, there have been no studies evaluating the impact of jaundice on hearing screening results.

What This Study Adds

This study alerts clinicians to the possibility that a refer (abnormal) automated auditory brainstem response result for a jaundiced newborn may indicate a high unbound bilirubin level and possibly increased risk of bilirubin toxicity, in addition to congenital deafness.

ABSTRACT

OBJECTIVE. This study was conducted to determine whether incidental jaundice affects automated auditory brainstem response results.

METHODS. We reviewed the medical charts of jaundiced newborns of ≥34 weeks of gestation who underwent automated auditory brainstem response testing within 4 hours of plasma total bilirubin concentration and unbound bilirubin concentration measurements. We tested the hypothesis that the likelihood of abnormal automated auditory brainstem response results would increase as total bilirubin and unbound bilirubin concentrations increased.

RESULTS. Forty-four infants with proximate total bilirubin concentration, unbound bilirubin concentration, and automated auditory brainstem response measurements were identified, and 4 (9%) had bilateral refer automated auditory brainstem response results. The mean total bilirubin concentration of 21.4 mg/dL (SD: 4.0 mg/dL; range: 14.4–29.5 mg/dL) for the 40 infants with bilateral pass automated auditory brainstem response results was not significantly different from that of 23.0 mg/dL (range: 14.9–33.1 mg/dL) for the 4 infants with bilateral refer automated auditory brainstem response results. However, the mean unbound bilirubin concentration of 1.32 μg/dL (range: 0.22–2.99 μg/dL) for the 40 infants with bilateral pass results was significantly lower than the mean of 2.62 μg/dL (range: 0.88–4.41 μg/dL) for the 4 infants with bilateral refer results. Logistic regression showed that increasing unbound bilirubin concentrations but not increasing total bilirubin concentrations were associated with of bilateral refer automated auditory brainstem response results.

CONCLUSIONS. The probability of bilateral refer automated auditory brainstem response results increases significantly with increasing unbound bilirubin concentrations but not with increasing total bilirubin concentrations. Because unbound bilirubin concentrations are also more closely correlated with bilirubin neurotoxicity than are total bilirubin concentrations, bilateral refer automated auditory brainstem response results for jaundiced newborns may indicate increased risk of bilirubin neurotoxicity, in addition to the possibility of congenital deafness.

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Key Words
newborn jaundice, hyperbilirubinemia, unbound bilirubin, peroxidase test, free bilirubin, automated auditory brainstem response, hearing screening

Abbreviations
AABR—automated auditory brainstem response
TBC—total bilirubin concentration

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AUTOMATED AUDITORY BRAINSTEM response (AABR) testing is widely used to screen newborn hearing during the first few days of life. Transient newborn jaundice (hyperbilirubinemia) also occurs during this period, and hyperbilirubinemia has been shown to alter the auditory brainstem response.[1–3] Subtle changes in the auditory brainstem response have been demonstrated at plasma total bilirubin concentrations (TBCs) as low as 10 mg/dL,[2,3] but bilirubin-induced changes in the auditory brainstem response correlate better with plasma unbound or "free" bilirubin concentrations.[4] Because in our practice we often measure both TBCs and unbound bilirubin concentrations when evaluating newborn jaundice, we undertook this study of our clinical data to determine the impact of newborn jaundice on AABR hearing screening results.

METHODS

We reviewed the medical charts of jaundiced newborns who underwent AABR hearing screening as well as TBC and unbound bilirubin concentration measurements. Included for study were newborns at ≥34 weeks of gestation who

had no problems other than jaundice and who underwent AABR measurements within 4 hours of the TBC and unbound bilirubin concentration measurements. The review of medical charts for this purpose was approved by the California Pacific Medical Center institutional review board.

TBCs and unbound bilirubin concentrations were measured with the peroxidase method in a Clinical Laboratory Improvement Amendments-certified laboratory, by using a Food and Drug Administration-approved Arrows UB analyzer (Arrows Co, Osaka, Japan).[5] Unbound bilirubin concentrations were also measured at one half the recommended peroxidase concentration to obtain the equilibrium unbound bilirubin concentrations, as described elsewhere.[6]

AABR testing was performed by using the ALGO hearing screening system (Natus Medical, San Carlos, CA). The instrument's algorithm assumes that an infant is deaf until the acquired data fit, with 99.96% likelihood, a template composed of auditory brainstem responses obtained at 35 dB from normal hearing newborns. Failure of an ear to attain this likelihood is reported as a refer result (versus a pass result), which indicates that the infant needs follow-up hearing testing. For this study, we considered bilateral refer results as abnormal and bilateral pass results as normal.

We tested the hypothesis that bilateral refer results would be more likely as the TBC and unbound bilirubin concentration increased by using logistic regression analysis. The likelihood ratio test was used to determine the impact of the independent variables of TBC and unbound bilirubin concentration on the dependent variable of bilateral refer results.[7] Continuous data (expressed as mean, SD, and range) were evaluated by using standard statistical methods.

RESULTS

Of 156 newborns of ≥34 weeks of gestation who had AABR, TBC, and unbound bilirubin concentration measurements, 44 (28%) met the study requirements. There were 28 male infants and 16 female infants, most infants were white or Asian, and the mean birth weight and gestational age were 3197 g (SD: 602 g; range: 1840–4727 g; $n = 44$) and 38 weeks (SD: 2 weeks; range: 34–41 weeks; $n = 44$), respectively. Twenty-seven infants (61%) were readmitted because of jaundice and 16 (36%) had positive direct antiglobulin test results, but only 1 had evidence of hemolysis and required an exchange transfusion. The mean TBC was 21.6 mg/dL (SD: 4.5 mg/dL; range: 14.4–33.1 mg/dL; $n = 44$), and the mean unbound bilirubin concentration was 1.44 μg/dL (SD: 0.85 μg/dL; range: 0.39–4.41 μg/dL; $n = 44$). The AABR results were obtained within a mean of 1.5 hours (median: 1 hour; maximum: 4 hours) of the TBC and unbound bilirubin concentration measurements. Bilateral pass results were obtained for 40 infants (91%) and bilateral refer results for 4 (9%), and there were no significant differences in mean birth weight or gestational age between the 2 groups.

The mean TBC of 21.5 mg/dL (SD: 4.0 mg/dL; range: 14.4–29.4 mg/dL; $n = 40$) for the infants with bilateral pass AABR results was not significantly different from the mean TBC of 23.0 mg/dL (SD: 8.8 mg/dL; range: 14.9–33.1 mg/dL; $n = 4$) for the infants with bilateral refer results ($P = .951$, Mann-Whitney U test). However, the mean unbound bilirubin concentration of 2.63 μg/dL (SD: 1.44 μg/dL; range: 0.88–4.41 μg/dL; $n = 4$) for the infants with bilateral refer results was significantly greater than the mean of 1.32 μg/dL (SD: 0.69 μg/dL; range: 0.39–2.99 μg/dL; $n = 40$) for the infants with bilateral pass results ($P = .048$, Mann-Whitney U test).

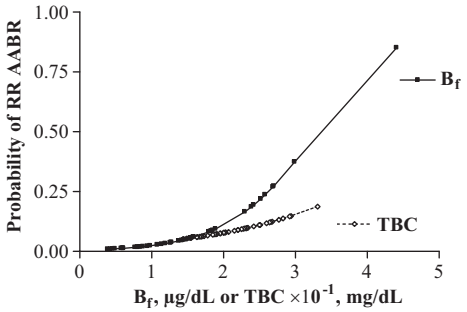

FIGURE 1
Probability of bilateral refer AABR results (RR AABR) as a function of the observed unbound bilirubin concentration (B_f) (solid line) or TBC (dashed line). TBC values were multiplied by 0.1 to allow both variables to be plotted on the abscissa. The probability of bilateral refer AABR results even at the highest TBC observed (33.1 mg/dL) was still <0.25.

Increasing unbound bilirubin concentrations were significantly associated with refer results in logistic regression analysis ($\chi^2 = 7.7228$; $P = .0072$). The logit coefficient (β) for the unbound bilirubin concentration was 1.59 (SE: 0.72; $P = .0277$), with an intercept of −5.2850 and an odds ratio of 4.92 (95% confidence interval: 1.19–20.37). Increasing TBCs, however, did not significantly predict bilateral refer results ($\chi^2 = 0.4404$; $P = .5070$; logit coefficient: 0.077; SE: 0.115; $P = .504$; intercept: −4.0106; odds ratio: 1.07; 95% confidence interval: 0.86–1.35). Adding TBCs to the unbound bilirubin concentration model did not improve the regression significantly, and the area under the receiver operating characteristic curve for unbound bilirubin concentrations was 0.82 (SE: 0.097). Figure 1 shows the probability of bilateral refer results as a function of the observed unbound bilirubin concentration or TBC.

DISCUSSION

A refer AABR result for 1 or both ears occurs in ~4% of newborn hearing screening tests, whereas congenital deafness occurs in just 1 or 2 infants per 1000.[8] Therefore, nearly all screening refer results are not attributable to congenital deafness. The false-positive results are usually attributed to technical (movement) or anatomic (ear canal obstruction) difficulties. Our data suggest that newborn jaundice, particularly jaundice associated with higher unbound bilirubin concentrations, may be an unrecognized cause of a refer AABR result. Although this is most likely transient, because the auditory brainstem response usually improves with the resolution of jaundice,[1–3] the association between bilateral refer AABR

results and elevated unbound bilirubin concentrations should not be dismissed as inconsequential.

Unbound bilirubin concentrations have been shown to correlate better than TBCs not only with abnormalities in the auditory brainstem response[4] but also with bilirubin neurotoxicity.[9] Although the auditory brainstem response may be absent in infants after overt kernicterus in the neonatal period,[10] recovery of the auditory brainstem response after an acute central nervous system injury does not guarantee normal hearing.[11]

Although the TBC has long been ingrained in clinical thinking and practice as the principle metric for determining the likelihood of bilirubin-induced neurotoxicity, it is evident from our data that bilirubin may at times be inappropriately acquitted as the culprit in hearing deficits because the TBC is "unremarkable." Additional studies of the relationship between unbound bilirubin concentrations, AABR results, and sensorineural deafness or auditory neuropathy/auditory dyssynchrony[12] may provide valuable insight into the actual prevalence and role of bilirubin in these disorders. The AABR may also provide important information about the magnitude of unbound bilirubin concentrations when only TBC data are available to monitor advancing jaundice.

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