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BRAINSTEM ABNORMALITIES IN NEONATES WITH NORMAL OTOACOUSTIC EMISSIONS

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There is growing awareness of a population of patients whose hearing deficit is characterized by normal or near-normal hearing sensitivity but reduced auditory perceptual or speech processing skills. First described in the late 1970s and early 1980s as paradoxical findings because of absent or abnormal auditory brainstem response (ABR) but present behavioral responses to sound, the disorder has been referred to under a variety of names: central auditory dysfunction, brainstem auditory processing syndrome, auditory neural synchrony disorder, and most recently, auditory neuropathy (Berlin, Hood, Cecola, Jackson, & Szabo, 1993; Davis & Hirsh, 1979; Kraus, McGee, Carrell, Ferre, & Hoeppner, 1993; Kraus, Ozdamar, Stein, & Reed, 1984; Sininger, Hood, Starr, Berlin, & Picton, 1995; Starr et al., 1991; Worthington & Peters, 1980).

Davis and Hirsh (1979) and Worthington and Peters (1980) were among the first to report absent ABRs in patients with measurable hearing. These patients also had disproportionately poor speech recognition or comprehension abilities relative to their behavioral pure tone thresholds. Kraus et al. (1984) described seven patients with audiometric data ranging from normal hearing to moderate impairment but either total absence of sound evoked bioelectric activity or evidence of ABR wave I or waves I or II only. Patients old enough for formal testing performed below age level on auditory as compared to visual tasks. Five of the seven patients had a medical history of either perinatal intracranial hemorrhage, asphyxia, or hyperbilirubinemia: physiological factors thought possible causes of dysfunction of the central auditory pathways. Kraus and colleagues suggested that absent ABRs or the selective loss of the later waveforms may result from disruption at the level of the brain stem of the neural synchrony necessary for ABR generation. While essential for ABR generation, neural synchrony may not be necessary for the behavioral detection of acoustic events.

More recently, Starr et al. (1991) reported findings with an 11-year-old patient who presented with only a fluctuating, mild-to-moderate hearing loss but poor word recog-

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nition ability and absent ABRs. The discrepancy between behavioral and ABR findings prompted Starr and colleagues to carry out an extensive series of electrophysiological and psychoacoustic tests which revealed that while click-evoked otoacoustic emissions and cochlear microphonics were present, acoustic reflexes were absent and performance on temporally based psychoacoustic tests was poor. Also absent were a particular set of auditory event-related potentials (ERPs) responsive to the transient features of acoustic signals. The loss of both temporally dependent auditory perceptions and neural components of ERPs sensitive to temporal cues could be accounted for, according to Starr et al., by a defect at the eighth nerve or the synapse between the inner hair cell and the eight nerve (type I fiber synapses). Kraus et al. (1993) reported on an 18-year-old with subclinical hydrocephalus who presented with normal hearing for pure tones and specific behavioral auditory processing deficits. A series of auditory event-related potentials suggested the brain stem as the site of the disorder. Electrophysiologic findings included a grossly abnormal ABR, selective impairment of the mismatch negativity (MMN), a cortical event-related potential that reflects central processing of small acoustic differences, but intact auditory middle, N1, P2, and P300 responses. Berlin et al. (1993) provided an additional dimension to physiological measures with patients who apparently lack cues regarding the temporal onset of signals by describing the absence of contralateral suppression of otoacoustic emissions in two patients with normal to near-normal pure tone sensitivity in certain frequency regions, robust evoked otoacoustic emissions, inordinately poor speech discrimination, and paradoxically absent middle ear muscle reflexes and ABRs. These authors hypothesized that absence of contralateral suppression is due to a form of central nervous system dysfunction involving the afferent-efferent feedback system, a condition they labeled as Type I afferent neuron dysfunction. In a recent review, Sininger, Hood, Starr, Berlin, and Picton (1995) summarized their current thinking on patients who present with paradoxical behavioral and physiological findings. They hypothesized that presence of normal otoacoustic emissions and cochlear microphonics but absence of auditory nerve action potentials (no ABR wave I) points to the synaptic junction between the axon terminal of the inner hair cell and dendrite of the spiral ganglion neuron, the dendrite itself, the spiral ganglion neurons themselves, or the axons of the spiral ganglion neuron with the auditory nerve in their course to the brainstem or in some combination of the above as the possible site or sites of the abnormality.

Apparent from these reviews is that many questions remain regarding this disorder. Chief among them are the exact anatomic site or sites of the disorder, the possible etiologic factors, and the viability of therapy or educational intervention.

It was the availability of ABR that provided an electrophysiological correlate to the behavioral findings of poor speech comprehension and normal hearing. The paradoxical finding of normal or near-normal behavioral thresholds but absent or abnormal ABRs provided objective electrophysiological evidence suggesting a central auditory processing disorder rather than peripheral hearing loss as an explanation for the speech comprehension difficulties shown by some children and young adults. In the past, identification depended on whether the child demonstrated speech or language delay or learning problems in school and was old enough and capable of responding to behavioral pure-tone testing. Now with the availability of evoked otoacoustic emissions (EOAE), it may be possible through objective physiological and electrophysiological measures to identify the phenomenon in infants and determine what, if any, relationship such paradoxical findings have with the disorder seen in older children and young adults. Earlier identification could also prove invaluable in identifying possible causative factors as well as bringing attention to the critical issue of earlier intervention.

In this article we describe findings with a series of four infants who on screening in

an infant special care nursery (ISCN) passed evoked otoacoustic emissions but failed ABR, the hallmark signs in older children and young adults of some form of auditory nerve pathology, brainstem neuronopathy, or brainstem conduction defect. These paradoxical findings were confirmed through serial follow-up audiological testing after discharge home. Follow-up testing, including pediatric neurological evaluations, continues and, although some degree of normalization or reversal of initial ABR abnormality appears to have occurred in two of the infants, ABR waveform morphology continues to be abnormal in the remaining two infants, thereby increasing the possibility of a long-term rather than transient condition.

METHOD

Data on the four infants with paradoxical EOAE/ABR findings we report on derive from a limited study contracted to provide data on the feasibility of using EOAE to screen infants admitted to an ISCN. Largely as a result of the recommendations put forth in the NIH Consensus Statement on Early Identification of Hearing Impairment in Infants and Young Children (1993), the Clinical Neurophysiology Laboratory and the Division of Neonatology, Department of Pediatrics of the Evanston Hospital, a Northwestern University Medical School affiliated hospital, requested one of the present authors (L.K.S.) to develop data comparing EOAE screening with the ABR test protocol in use at the time in the ISCN. It was during the course of this joint Evanston Hospital/Northwestern University ISCN hearing screening feasibility study that we first identified and were subsequently able to follow the four infants who showed paradoxical TEOAE/ABR screening results.

ISCN Screening and Testing Protocol

TEOAE screening was carried out using the ILO88 system from Otodynamics Ltd. A detailed description of this system can be found elsewhere (Bray & Kemp, 1987; Kemp & Ryan, 1993; Kemp, Ryan, & Bray, 1990; Vohr, White, Maxon, & Johnson, 1993. Only a brief description of parameters specific to our application will be given here. TEOAE stimuli consisted of 80 μsec clicks delivered through the specially designed infant probe and associated coupling cuffs supplied with the ILO88 system. The ILO88 QuickScreen mode was used with all infants. The QuickScreen mode (Kemp & Ryan, 1993) was introduced specifically for infant screening as an attempt to limit collection of TEOAE data below 1 kHz by reducing the ILO88 adult default setting from a 20 msec sweep time to 12.5 msec (the latency of 500 Hz is 15 to 20 msec whereas most high frequency TEOAE energy is emitted within the first 5 msec after stimulation). TEOAE measures below 1 kHz are often obscured by low-frequency infant physiological noise (breathing, sucking, and movement) and since the intent of most infant screening is to identify sensorineural loss, invariably a high-frequency loss, limiting collection of EOAEs to the higher frequencies where EOAEs are most robust, is clinically sound as well as more efficient.

Hospital staff for medical-legal reasons preferred for the feasibility study adoption of a TEOAE screening protocol based on published data. Their specific concern centered on the question of what constituted a pass or a fail. Since the Rhode Island Hearing Assessment Project (RIHAP) (White & Behrens, 1993) is by far the most extensive published study on the use of otoacoustic emissions in infant screening, we adopted the pass, partial pass, fail criteria outlined by Vohr et al. (1993) for the RIHAP. Briefly, the RIHAP scoring of TEOAE results are defined as: Pass, a 3 dB signal to noise ratio (SNR) present at least halfway across each of the test frequency bands of 1 to 2, 2 to 3, and 3 to 4 kHz; Partial Pass, only one or two of the frequency bands shows a 3 dB SNR halfway across the frequency band; and Fail, no response in any of the frequency bands. Applying the RIHAP criteria yielded pass/partial pass/fail results with the 100 ISCN infants in our series virtually identical to the

pass/partial pass/fail results originally published by the RIHAP (White & Behrens, 1993).*

The Evanston Hospital ISCN is a Level III regional facility with approximately 300 to 350 admissions annually. TEOAE screening was conducted in one of a suite of three special procedures/isolation rooms of the ISCN complex where ambient noise levels were below those that interfered with recording TEOAEs. All TEOAE screening was conducted by licensed audiologists experienced in EOAE or ABR infant hearing screening. ABR testing of the ISCN infants was conducted by EEG technicians under the direction of the Clinical Neurophysiology Laboratory of the Evanston Hospital. The ABR protocol employed required obtaining recordings for each ear at 40, 60, and 75 dB HL using a stimulus rate of 11/sec. Infants were sedated and transported to the EEG Laboratory where testing was conducted using a Biologic Navigator unit equipped with TDH-39 earphones. The ABR results were read on a rotating basis by one of three neurologists. TEOAE and ABR results not in agreement were referred for a repeat EOAE in conjunction with diagnostic auditory evoked response testing.

Follow-up Testing

Follow-up diagnostic EOAE and auditory evoked response testing was carried out at the Otoacoustic Emissions Laboratory and Auditory Neuroscience Laboratory Northwestern University Evanston. Transient and distortion product otoacoustic emission (DPOAE) testing utilized the ILO 88/92 system from Otodynamics, Ltd. DPOAE measures were also obtained using the Bio-Logic Scout DPOAE system. Auditory brainstem and middle latency response (MLR) measures were conducted using the Biologic Navigator. Sleep stages during MLR testing were monitored using an on-line method described by McGee, Killion, Rosenberg, and King (1993).

RESULTS

The four confirmed cases of paradoxical TEOAE/ABRs were identified from a consecutive series of 100 infants admitted to the ISCN during a 3-month period following an initial series of pilot studies. Recommendations to the hospital medical staff regarding a hearing screening program for the ISCN were based on data obtained with this sample.

Table 1 summarizes identifying information, screening results, and follow-up test findings with the four admissions that demonstrated paradoxical EOAE/ABR results. All four of the infants were male and preterm (G.A. < 37 wk). One was termed a very low birthweight (VLBW) infant (< 1500 g) and two as low birthweight (LBW) infants (< 2500 g). The prominent medical condition in three of the four infants was hyperbilirubinemia (detailed birth history is summarized in Table 3 and will be discussed later).

*Maxon, White, Vohr, & Behrens (1993) reported on a sample of 1850 infants (16.4% NICU infants), a 15% fail and a 12% partial pass rate on initial screen (27% had to be screened or tested a second time). Our data on 100 ISCN infants were 17% fail, 11% partial pass for a total of 28% that required a second screening. Later we reexamined our data in terms of the partial pass category, which in fact meant a near 30% fail rate since all partial pass infants had to be rescreened or referred for follow-up testing, and found that all of the TEOAE measures that were classed as partial pass were due to failure to meet the requisite SNR in the 1-2 kHz frequency band but that robust TEOAEs were present in the 2-3 and 3-4 kHz high frequency bands. By reclassifying partial pass to pass, our fail rate dropped to 17%. Limiting the collection of EOAEs to a narrow-band from 2-4 kHz has been recently proposed by Brass, Watkins, & Kemp (1994) and Whitehead et al. (1995). In a recent article, Maxon, White, Behrens, & Vohr (1995) reported a fail rate of 9% in the NICU and a fail rate of 6% in the regular nursery, a significant improvement from the earlier results reported from the RIHAP. The improvement is attributed to the use of a two-stage screening protocol, modifications in ILO88 hardware and software, modifications in probe fit techniques, and the experience of the screeners. It is our understanding that the RIHAP recently did away with the partial pass category and a pass is now defined as a SNR of +6 dB over half of the two frequency bands 2–3 and 3–4 kHz (White, 1995).

TABLE 1. Summary of Infant Data and Audiologic Test Results

Name	*Infant Data*				*Screening Results*		*Follow-Up Testing*		
	Sex	*GA (Wks)*	*Birth Weight (Gs)*	*History*	*EOAE*	*ABR*	*EOAE*	*ABR*	*MLR*
S.G.	M	25	886	RDS[1] VLBW[3] Phototherapy	Pass bilaterally	Fail: abnormal	Present bilaterally	Wave V 40 dBnHL; delayed III-V	Present: 10 dBnHL
G.P.	M	35	2615	RDS Hyperbilirubinemia	Pass bilaterally	Fail: abnormal	Present LE; absent RE	Delayed, decreased	Present: 40 dBnHL
C.W.	M	33	2370	Rh Hyperbilirubinemia LBW[2]	—	Fail: abnormal	Present bilaterally	Delayed, decreased	Present: 40 dBnHl
C.P.	M	34	2005	Rh Hyperbilirubinemia PVL[4]	Pass bilaterally	Fail: abnormal	Present bilaterally	Wave V 50 dBnHL; delayed, decreased	Present: 70 dBnHL

[1]RDS: respiratory distress syndrome.
[2]LBW: low birth weight.
[3]VLBW: very low birth weight.
[4]PVL: left frontal cystic periventricular leukomalacia.

ISCN Screening and Test Results

TEOAE screening was completed before discharge on three of the four infants listed in Table 1 and, although TEOAE screening was not done before discharge on the fourth infant listed (C.W.), TEOAEs were found to be present on follow-up at a corrected age of less than 1 month, and, therefore, we might assume EOAEs would have been present at the time the screening TEOAE would have been done. All of the TEOAE screening responses met the original RIHAP criteria for pass (3 dB SNR at three frequency bands). ABR employing the protocol described earlier was done before discharge on all four infants. All of the ABR records were judged fails by the reviewing neurologists. All were labeled "markedly abnormal" and characterized as: absent wave V at levels as high as 95 dB HL; possible wave I at 95 dB HL; possible wave I, III, and V at 85 dB HL but poor replicability; or questionable wave V at 85 dB HL.

Follow-up Test Results

Table 2 provides a summary description of the ABR and MLR threshold results obtained with each child and the corrected or gestational age (GA) at the time the follow-up tests were conducted. EOAE, ABR, and MLR testing was conducted under sedation (chloral hydrate). Infant S.G. was seen for follow-up testing at 3.6 mos corrected age; G.P. at 2 mos, 5 mos, and 9 mos corrected age; C.W. at < 1 mo and 4 mos corrected age; and C.P. < 1 mo and 3.6 mos corrected age. TEOAEs, and also DPOAEs in some cases, were obtained for each ear with all four infants. Figure 1 shows the DPOAE records obtained with infant G.P. using the ILO92 (top record) and the Bio-logic Scout (lower record) systems. This infant failed TEOAE screening in the left ear at 5 months of age but passed at 9 months. The fail was attributed to an ear canal obstruction or middle ear condition based on the finding by the child's pediatrician of cerumen and an opaque tympanic membrane the day before our testing. Immittance measures could not be completed.

ABR test results recorded prior to discharge from the ISCN with infant S.G., the VLBW child, were reported as absent—no recognizable or reproducible waveforms—to click stimuli presented at 85 dB nHL. On follow-up ABR testing at a corrected age of 3.6 mos., wave I was clearly identifiable to

TABLE 2. Summary of ABR and MLR Findings at Follow-Up

Name	*Age (Months) and Description*
S.G.	(3.6 mo) ABR: Wave V at 40 dB nHL, delayed III-V MLR: 10 db nHL
	Impression: Improvement when compared to ISCN ABR results. Abnormal waveform morphology and latency suggest disruption of neural synchrony.
G.P.	(2.0 mo) ABR: Wave I, delayed decreased later components MLR: 40 dB nHL
	(5.0 mo) ABR: Wave I, delayed decreased later components MLR: 40 db nHL
	(9.0 mo) ABR: Wave I, delayed decreased later components
	Impression: Disruption of neural synchrony.
C.W.	(< 1 mo) ABR: Wave I, delayed decreased later components MLR: 20 dB nHL atypical and delayed
	(4.0 mo) ABR: Wave I delayed decreased later components MLR: 40 db nHL
	Impression: ABR and MLR responses abnormal indicating auditory brainstem and thalamo-cortical pathway involvement.
C.P.	(< 1 mo) ABR: Wave V 50 dB nHL MLR: 70 db nHL
	(3.6 mo) ABR: Wave V 50 dB nHL MLR: 70 dB nHL
	Impression: Improvement noted in responses from rostral brainstem areas.

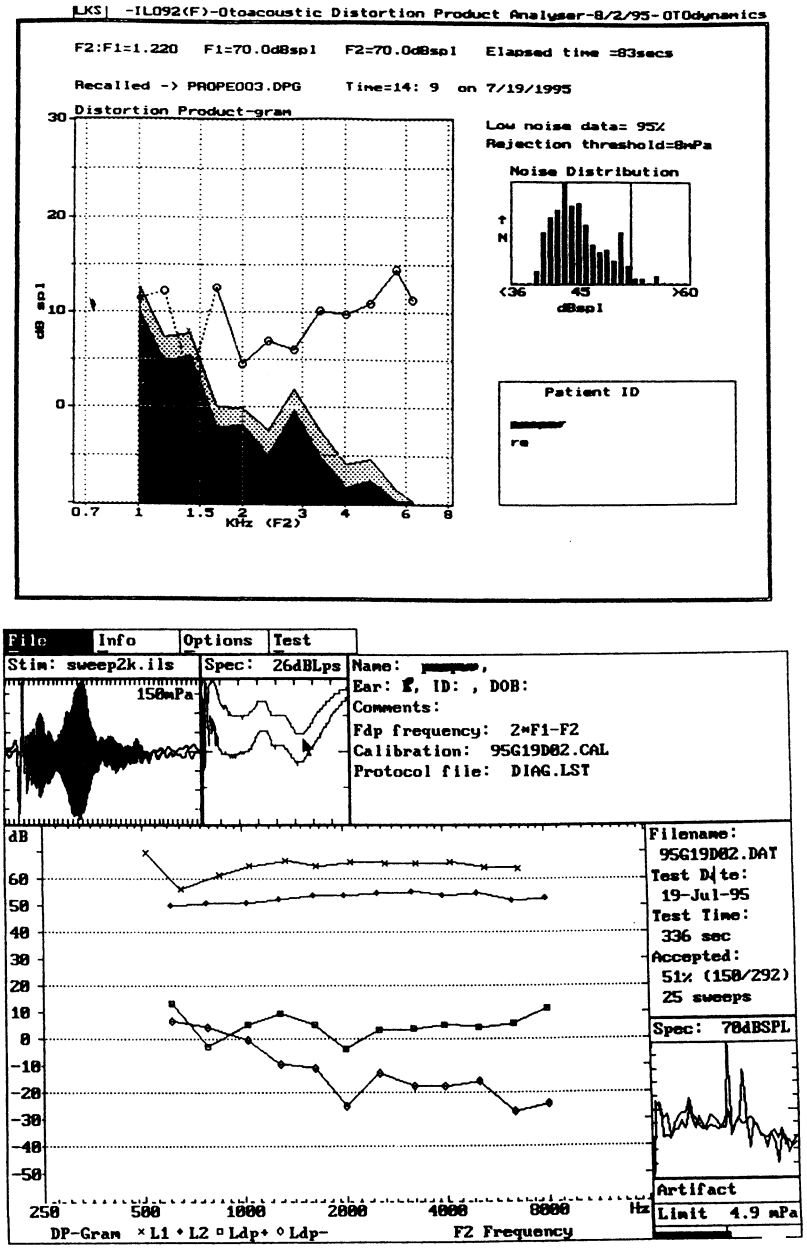

Figure 1. Distortion product otoacoustic emission records obtained with infant G.P. at age 9 months. Upper record obtained using the ILO 98 system; lower record obtained using the Bio-logic Scout system. Note the presence of low-frequency physiologic noise beginning at 1,000–1,500 Hz in this sedated infant.

an 80 dB nHL click stimulus and waves III and V to a click stimulus at 40 dB nHL, but absolute latencies for waves III and V were delayed. The presence of waves I, III, and V appears to represent reversal or improvement over the initial ABR records obtained prior to discharge from the ISCN. An MLR to click stimuli presented at 10 dB nHL is consistent with functional thalamo-cortical pathway neural activity and good hearing sensitivity. The ABR records obtained prior to discharge from the ISCN for the remaining three infants were also reported as either absent wave V or at best, a possible

wave I and a poorly identified prolonged wave V response with poor replicability or reproducibility to click stimuli at intensity levels up to 95 dB nHL. Follow-up ABR and MLR tests with infant C.P. conducted at less than 1 month of age and at age 3.6 months yielded wave V responses in both ears at 50 dB nHL. Again, as with infant S.G., identifiable wave V responses at 50 dB nHL represent what appears to be reversal of initial findings. Further follow-up testing should confirm whether infants S.G. and C.P. demonstrate the reversal of the "central" ABR abnormality associated with some high risk infants (Stockard & Stockard, 1981; Stockard, Stockard, Kleinberg, & Westmoreland, 1983).

In contrast, infants C.W. and G.P. failed to show the reversals in ABR recordings seen in the records of infants S.G. and C.P. In addition to abnormal ABR recordings, MLR findings obtained with infant C.W. were judged atypical suggesting possible involvement of the thalamo-cortical auditory pathway. ABRs recorded for infants G.P. and C.W. were characterized by a high amplitude cochlear microphonic (CM) and possible wave I, possible wave II but absent, delayed, or decreased in amplitude later components. The ABR records of infant G.P. are compared at corrected ages 5 mos and 9 mos in Figure 2. The two waveforms shown in each record are replications obtained at an intensity level of 80 dB nHL. Presence of waves I and II of normal latency would be strong evidence of neural response from the distal and proximal (brainstem) portion of the eighth nerve, in turn, presumptive evidence of cochlear function. In addition, it is sometimes possible to identify a cochlear microphonic (CM) in the ABR recording as an onset response preceding wave I. Since the CM is a receptor potential generated within the cochlea, mainly the outer hair cells, and follows the waveform of the stimulus, reversing the polarity of the stimulus from condensation to rarefaction or rarefaction to condensation should reverse the polarity (upward or downward deflection) of the response. Also, latency of wave I may shift slightly with increased stimulus rates whereas CM will not. Verification of a CM response would be additional evidence of cochlear activity. In Figure 2, the wave immediately following onset of the stimulus is presumed to be the CM response because switching from a condensation to a rarefaction click produced a reversal of the polarity of the waveform. Figure 2 also illustrates the difficulty an examiner may face when trying to judge whether there is a real change in the ABR record over time; i.e., is there evidence of a change in neural response with the implication of a more favorable prognosis?

Table 3 summarizes the pre- and perinatal history of the four infants. As expected with infants requiring admission to an ISCN, each presented with a number of medical conditions, some of which have

TABLE 3. Summary of Medical History

Name	
S.G.	15-year-old mother, little prenatal care C-section GA 25 wks Birthweight 885 g Apgar 5/8 RDS Peak bilirubin level: 4.9 mg/dL Phototherapy 5 days (ampicillin and gentamycin)
G.P.	39-year-old mother; gestational diabetes GA 35 wks Birthweight 2615 g Apgar 8/8 Respiratory distress (assisted ventilation—no apnea) Hyperbilirubinemia: peak bilirubin levels 14.9 mg/dL Phototherapy 5 days Direct hyperbilirubinemia: 12.2 mg/dL (day 7) 15.2 mg/dL (day 8)
C.W.	28-year-old mother: Rhesus hemolytic disease Antenatal transfusion C-section GA 33 wks Birthweight 2370 g Apgar 8/8 Bilirubin level: 7.2 mg/dL (2 hrs age), 15.5 mg/dL (42 hrs age) Exchange transfusion (ampicillin and gentamycin)
C.P.	34-year-old mother Rh sensitization (intrauterine transfusion) GA 34 wks Birthweight 2005 g Apgar 7/9 Moderate RDS Peak bilirubin level 12.4 mg/dL (4th day) Phototherapy 4 days Bilirubin level 15.9 mg/dL Exchange transfusion

GA: gestational age.
RDS: respiratory distress syndrome.

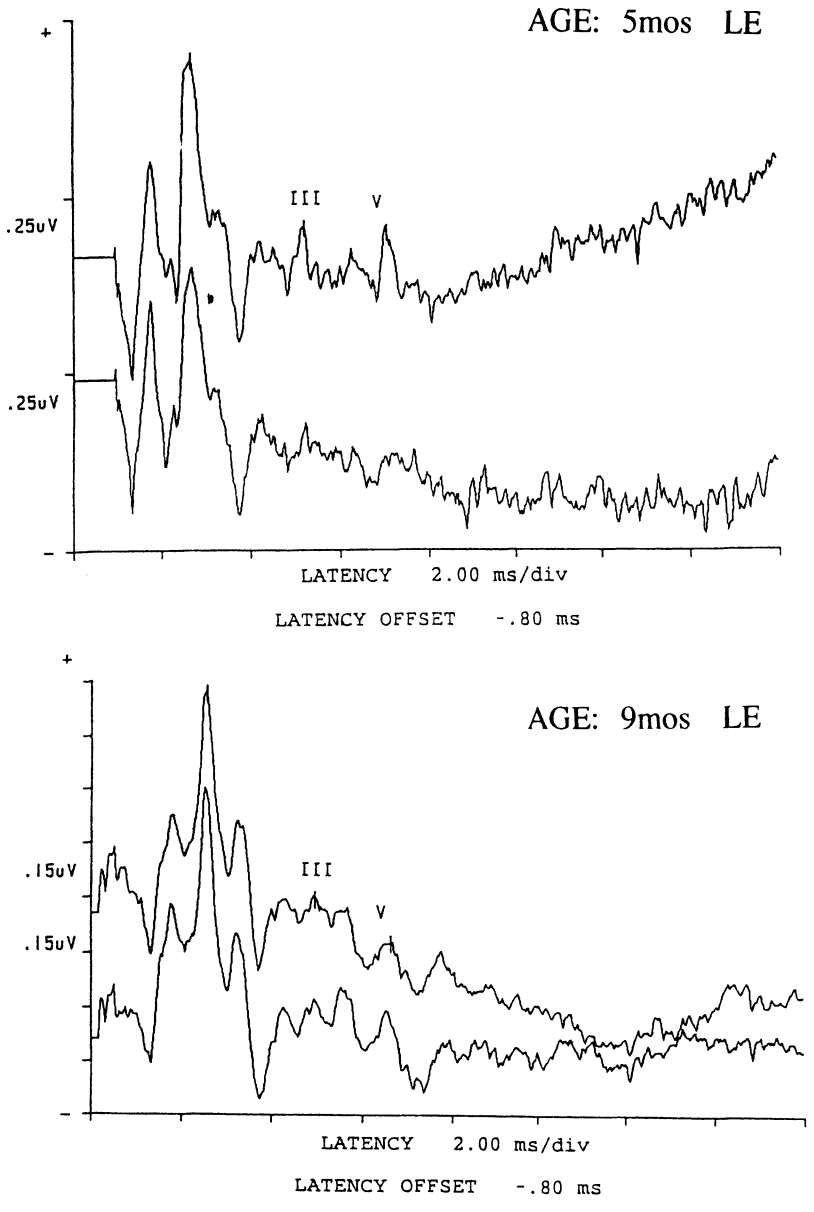

Figure 2. Auditory brainstem response record obtained with infant G.P. at corrected age 5 months (upper record) and at corrected age 9 months (lower record). Stimulus latency offset is .8 msec. The cochlear microphonic (CM) can be seen occurring immediately after stimulus onset.

been variously associated with neurodevelopmental disorders including hearing loss. All four infants were preterm; one had a left frontal cystic periventricular leukomalacia detected by ultrasound at 3 weeks of age; two were low birthweight, one very low birthweight; three were diagnosed as having a respiratory distress syndrome, two received ampicillin and gentamicin, and three had hyperbilirubinemia necessitating either exchange transfusion or phototherapy. By strict definition, the only indicators associated with sensorineural and/or conductive hearing loss for use with neonates birth to 28 days listed in the Joint Committee on Infant Hearing 1994 Position Statement (American Academy of Pediatrics, 1995) were: birth weight less than 1,500 grams (infant S.G.),

possible ototoxic aminoglycoside (infants S.G. and C.W.), and hyperbilirubinemia requiring exchange transfusion (infants C.W. and C.P.). A third infant (G.P.), also diagnosed with hyperbilirubinemia, received a 5-day course of phototherapy but no exchange transfusion. The fourth infant (S.G.) also received a 5-day course of phototherapy for what was apparently judged "physiological" jaundice, usually a benign and self-limited condition.

DISCUSSION

Our finding of normal otoacoustic emissions and abnormal brainstem responses in neonates has been reported previously. Vohr et al. (1993) in a footnote stated:

> A rare exception is the infant with a normally functioning cochlea and damage along the cranial nerve VIII pathway (retrocochlear or central). Such an infant may have normal evoked otoacoustic emissions, but an abnormal brainstem response and may show what appears to be sensitivity loss on behavioral measures. (p. 62)

Norton (1993) reported evaluating eight children in whom ABR was either absent or present only at 80 or 90 dB nHL and who had good TEOAEs. Information as to whether any of the children had been screened by ABR or EOAE at birth was not given but it is possible that comparable ABR/TEOAE findings would have been obtained had neonatal screening been done. One child was described as a preterm (34 wk GA) male who was in an NICU for 8 weeks because of respiratory distress syndrome, hyponatremia, and hyperbilirubinemia. At 10 months of age, the infant failed an ABR test (no identifiable wave V at 80 dB nHL, possible wave I at 60 dB nHL). When tested at 13 months of age, he presented as an alert and engaging infant with delayed motor development, mild cerebral palsy, and inconsistent responses to auditory stimuli. No ABR was observed at 90 dB nHL in either ear; however, robust TEOAEs were recorded for both ears. At approximately 14 months of age, reliable sound-field VRA responses were obtained at 20 to 25 dB HL for band-pass noise (500, 1K, 2kHz) and 4 kHz tone-pips. He was enrolled in a parent-infant program for hearing-impaired children and receiving auditory training and speech and language stimulation. Norton (1993) concluded that "the full implication of severely elevated ABR thresholds or absent ABR in the presence of robust TEOAEs will only become evident after we have followed these children for several years" (p. 70).

Identification through the combined use of EOAE and ABR of what appears to be normal peripheral but impaired central auditory function in at-risk newborns raises a number of questions. Our observations address two, at least in part. First, can we begin to identify prenatal or neonatal factors that could possibly place newborns at risk for the condition? Second, is an absent or elevated threshold ABR and present EOAE an early sign of some form of permanent eighth nerve neuropathy or brainstem conduction defect described in older children and young adults or simply a reversible "central" ABR abnormality?

On the question of possible causative factors, the occurrence of hyperbilirubinemia requiring exchange transfusion or phototherapy in three of the four infants in our series, the apparent need for phototherapy with the fourth infant, together with the several notations in the literature of the occurrence of hyperbilirubinemia in infants and children who demonstrate paradoxical audiological findings, raises the possibility of an association between hyperbilirubinemia and the occurrence of this special form of hearing impairment in preterm and LBW infants. Severe sensorineural hearing loss and central nervous system deficits such as choreoathetotic cerebral palsy, seizures, and mental retardation were at one time relatively common sequelae of hyperbilirubinemia. Current medical management, however, including exchange transfusions in cases of hemolytic disease (Rh or ABO blood incompatibility between fetal red blood cells and maternal antibody) and phototherapy has significantly reduced the

occurrence and severity of bilirubin encephalopathy (kernicterus) in term infants. Less well understood, however, are the toxic effects of low and moderate levels of bilirubin on the central nervous system of premature and LBW infants.

Bilirubin (literally red bile, a blood waste product) is formed from the breakdown of hemoglobin molecules. Newly formed bilirubin binds to serum albumin and is carried to the liver where it is conjugated (combined) with other molecules to form a detoxified product that is excreted in the bile. An estimated 60% of healthy term infants for the first few days of postnatal life have an increase or accumulation of unconjugated bilirubin, so-called "physiologic" jaundice, until liver and bowel functions mature sufficiently for independent conjugation and excretion of bilirubin. Most newborns develop visible jaundice at serum bilirubin levels of 7–8 mg/dL with the bilirubin level usually peaking by the third or fourth postnatal day. In healthy term infants, the statistical upper limit for unconjugated bilirubin levels approximates 13–15 mg/dL while bilirubin levels above 20 mg/dL may pose some risk of hyperbilirubinemia, usually defined as bilirubin toxicity or neonatal jaundice with possible pathological outcome (Cashore, 1993). Phototherapy reduces jaundice and hyperbilirubinemia and should be considered if the bilirubin level exceeds 12–17 mg/dL and recommended if the bilirubin level exceeds 15–20 mg/dL on the second or third postnatal day (American Academy of Pediatrics, 1994). Unconjugated bilirubin in the skin absorbs light energy and is converted to an isometric water soluble form that then can be excreted by the kidney without conjugation. Exchange transfusion is recommended if intensive phototherapy fails and if the bilirubin level exceeds 20–25 mg/dL; exchange transfusion and intensive phototherapy are recommended if the bilirubin level exceeds 25–30 mg/dL on the second or third postnatal day (American Academy of Pediatrics, 1994).

In premature and LBW infants the risk of kernicterus and permanent sequelae may be much higher at serum bilirubin levels below those thought to be safe for term infants. A postmortem study (Gartner, Snyder, Chabon, & Bernstein, 1970) found in 9 of 14 LBW infants with peak bilirubin levels ranging from 9.4 to 15.6 mg/dL pathologic evidence of kernicterus, namely yellow staining and necrosis of brain cells of nuclei of the lower brainstem and thalamus. The unexpected occurrence of kernicterus in some premature infants (a control group without pathological evidence of kernicterus had peak bilirubin levels ranging from 8.8 to 17.2 mg/dL) at what had been thought to be low bilirubin levels, the possible role of anoxia in the etiology of kernicterus, and the possibility that undetected kernicterus could contribute neurologic abnormalities that become evident later in life, are among the major questions raised by this study that are still being investigated. A more recent and larger study (Ahdab-Barmada & Moossy, 1984) identified kernicterus in 97 of 630 (approximately 15%) of autopsied neonates. Mean bilirubin levels ranged from 6.5 mg/dL in the group at GA 20–24 weeks to 13.9 mg/dL in the 37–40 week GA group. The topography of the selective neuronal damage in the premature infants with low levels of bilirubin and kernicterus was similar to that found in newborns with high levels of bilirubin. Ahdab-Barmuda and Moossy concluded that although prematurity and asphyxia are conditions that appear to potentiate kernicterus in neonates with low levels of serum bilirubin, clinical correlates and predictive indices remain to be defined. Efforts to determine whether bilirubin alone can cause hearing impairment or if additional factors such as asphyxia place certain preterm or LBW infants at higher risk include studies utilizing the Gunn rat animal model (Shapiro, 1994; Silver, Kapilulnik, & Sohmer, 1995). The Gunn rat has an autosomal, recessive inability to convert toxic to nontoxic bilirubin. A possible contributory effect of asphyxia on neonatal jaundice in the Gunn rat has recently been reported by Silver et al. (1995).

ABR has proven to be one of the chief means in clinically establishing the vulnera-

bility of the auditory brainstem to kernicterus and in identifying so-called soft signs of neurobehavioral changes attributable to low or moderate levels of bilirubin in preterm or LBW infants. Chisin, Perlman, and Sohmer (1979) were among the first to provide evidence for damage to the auditory nerve while the cochlea was spared in cases of hearing loss following neonatal hyperbilirubinemia by recording a response from the cochlear hair cells (the cochlear microphonic) in 13 patients with histories of neonatal hyperbilirubinemia and in whom no neural response from the auditory nerve and brainstem could be recorded by ABR. At the time of examination, the subjects, ranging in age from 9 months to 22 years, all had behavioral evidence of a moderate to severe hearing loss suggesting that "hearing loss" following neonatal hyperbilirubinemia is permanent. Also, all had relatively high bilirubin levels ranging from 16 to 42.5 mg/dL. Later studies, however, of full-term neonates with hyperbilirubinemia due to hemolytic disease found that abnormal ABR findings (an absent wave IV–V or a prolonged I–V interpeak latency associated with increased brainstem conduction time) usually resolved, suggesting that bilirubin toxicity was a transitory condition (Gupta, Hans, & Anand, 1990; Nakamura et al., 1985; Nwaesei, VanAerder, Boyden, & Perlman, 1984; Perlman et al., 1983). In some infants ABR wave changes appeared to be rapidly reversible after exchange transfusion. Wennberg, Alhfors, Bickers, McMurtry, and Shetter (1982) noted by serial ABRs a reversal of apparent total deafness during exchange transfusion. De Vries, Lary, Whitelaw, and Dubowitz (1987) also recorded serial ABRs in infants with elevated bilirubin levels, noting that two infants had normal ABRs despite high bilirubin levels and that although some improvement in ABR amplitude immediately following exchange transfusion was observed in one infant, in three of four infants in whom some recovery was noted, an absent or very poor wave I at 60 and 40 dB was still evident at 6 months of age.

While there is evidence from ABR findings that acute brainstem bilirubin toxicity may be transient or reversible through exchange transfusion or phototherapy, several recent studies have documented long-term neurodevelopmental handicapping conditions in preterm or LBW children with low or moderate bilirubin levels. Neurodevelopmental outcome at 2 years of age in 831 preterm or small-for-gestational age infants with hyperbilirubinemia, documented as part of a prospective national survey conducted in the Netherlands, showed that 10.7% had what were termed minor handicaps (developmental quotient between 80–90 and/or mild cerebral palsy and/or slight hearing defects and/or mild retinopathy) and 5.4% a major handicap (developmental quotient less than 80 and/or severe cerebral palsy and/or severe hearing defects and/or severe retinopathy) (van de Bor, van Zeben-van der Aa, Verloove-Vanhorick, Brand, & Ruys, 1989). Although audiological examinations were only done when clinically indicated, thus possibly missing minor hearing defects, hearing defects were found in 3.5% of the children with bilirubin levels in the 5.9–8.7 mg/dL range, 3.6% in the 8.8–11.6 mg/dL range, and 4.1% in the 11.7–14.6 mg/dL range.

In an editorial review, Newman and Maisels (1989) listed among the strengths of the van de Borg et al. study the large sample size, 100% follow-up of surviving children, inclusion of children who received treatment of hyperbilirubinemia with phototherapy and/or exchange transfusion, and consideration of possible confounding variables including intracranial hemorrhage. Weaknesses noted include whether the so-called minor handicaps noted at a corrected age of 2 years will be present or less obvious by 4 to 7 years of age, that the measures of intracranial hemorrhage were crude, and that the bilirubin determinations were performed only when there was clinical indication. Newman and Maisels also pointed out that in evaluating the apparent association between bilirubin and brain damage observed in the van de Bor et al. study, it is critical to ask whether the association is real. If so, is it causal? And if causal, what should be done? Newman and

Maisels summarized that the evidence presented by the van de Bor et al. study is not overwhelming, but it does suggest a causal relationship between maximal bilirubin concentration and neurodevelopmental outcome, although the magnitude of the effect may be small. To the question of therapeutic recommendations, Newman and Maisel replied that nothing much should be done because the van de Bor study did not provide enough evidence to conclude a strong association between maximal bilirubin concentration and neurologic handicap, and that in other studies, association has not been consistent. They also pointed out that there is no evidence that reduced maximal bilirubin concentration would also reduce the incidence of neurologic handicap. Newman and Maisels concluded with the recommendation that the observations of van de Bor et al. be confirmed with additional observational studies.

Vohr (1990), in a review article, outlined evidence for the use of ABR measures, infant cry analysis, and behavioral assessment scales for the identification of the subtle or soft neurobehavioral or neurosensory possibly long-term effects of low and moderate levels of bilirubin in term and preterm neonates. ABR measures with a cohort of 50 term infants showed that wave I was normal but that wave III and the interpeak latency (IPL) of waves I–III are sensitive to moderate levels of bilirubin, defined as 10 to 20 mg/dL. For the entire cohort of infants, bilirubin levels correlated with prolongation of the latency of waves III, V, and the IPL of waves I–III and I–V. Correlation analysis also showed an interactive relationship among the ABR, cry, and behavioral findings suggesting a diffuse effect of bilirubin on the brainstem. Vohr recommended further studies be conducted to identify the risk of lower levels of bilirubin, the safe duration of exposure, and whether reversals in clinical findings occur in premature and LBW infants relative to neurobehavioral or neurosensory disorders.

Clearly, the question of a possible relationship or association between low and moderate elevations of serum bilirubin and the development of subtle or soft signs of neurodevelopmental handicapping conditions remains controversial. Observational studies can best be described as marked by inconsistencies. Furthermore, findings including data from postmortem studies, obtained on infants prior to 1982 are suspect because of the known relationship of benzyl alcohol to kernicterus, intraventricular hemorrhage, and mortality in preterm infants. In 1982, an illness marked by gasping respirations, metabolic acidosis, neurologic deterioration, hematologic abnormalities, and death was described among small preterm infants who received large cumulative amounts of fluid containing benzyl alcohol (an agent to inhibit the growth or multiplication of bacteria) to flush intravascular catheters. Unfortunately, the cumulative dose inadvertently dispensed to small preterm infants in an estimated one third or more neonatal intensive care units could exceed the recommended safe limit for adults. With the discontinuation of the use of benzyl alcohol in nurseries, a significant decrease was noted in the incidence of kernicterus, intraventricular hemorrhage, and death. Jardine and Rogers (1989) reported that while the incidence of kernicterus among preterm infants in their nursery averaged 25–31% prior to the withdrawal of benzyl alcohol, kernicterus abruptly disappeared after its withdrawal. Benzyl alcohol, rather than moderate-level elevations in serum bilirubin levels, may have been the principal unrecognized factor in the development of kernicterus in many preterm infants prior to 1992.

While the factors influencing bilirubin toxicity in newborns, particularly preterm infants, are complex and not completely understood, it may be possible using neurophysiological measures to develop new criteria for the treatment of neonatal jaundice in infants with relatively low or moderate serum bilirubin levels. The goal would be the forecasting and averting of bilirubin neurotoxicity, thus reducing the potential for central nervous system damage. Perlman and Frank (1988) suggested that "finer tools" such as ABR, visual and somatosensory

event-related potentials, cry analysis, and magnetic resonance imaging may prove useful as either predictors of kernicterus or as outcomes with which biochemical predictors can be correlated.

CONCLUSIONS

Our data suggest a possible association between the objective findings of absent or abnormal ABR and present EOAEs and the occurrence of hyperbilirubinemia or low or moderate levels of bilirubin in preterm or otherwise at-risk infants. The question of whether these findings present in the neonatal period are markers of long-term neurodevelopmental or neurosensory handicapping conditions remains open. Clearly, it will be necessary to follow infants that present during the neonatal period with absent or elevated ABR and present EOAEs through their school years in order to answer questions raised by our findings and those of several other studies about the relationship between low and moderate levels of bilirubin and some form of hearing or auditory handicapping deficit. Establishing a relationship between our observations on neonates and an auditory nerve or brainstem conduction deficit characterized by normal or near-normal hearing thresholds and severely reduced auditory perceptual or speech processing skills will require, ideally, periodic assessments that include behavioral audiological testing with emphasis on specialized forms of auditory and speech discrimination measures, neurophysiological testing incorporating ABR, MLR and the late auditory event-related potentials, and standardized developmental speech, language, and learning measures. Additional studies are needed to address questions about the possible contributory effects of other conditions or factors, asphyxia and aminoglycosides as prime examples, on bilirubin neurotoxicity in neonates.

The possible association between a screening ABR fail and an EOAE pass and the auditory processing deficits that have been documented in school-age children and young adults raises questions about whether EOAE, as recommended in the NIH Consensus Statement (1993), should be universally employed as the initial screening tool when screening infants in a special care nursery. In our limited sample, the four ISCN infants would not have been identified if EOAE screening had been the initial screening procedure. All would have passed, an ABR would not have been ordered, and the possible auditory nerve or auditory brainstem conduction abnormality not detected. The protocol that recommends EOAE as the initial screening method with ABR follow-up for fails may be effective and economical with a well-baby population but may not be for the at-risk ISCN population. The question is whether the purpose of the screen is to identify cochlear (sensory) or both cochlear and retrocochlear (neural) hearing impairment. Programs engaged in or planning a hearing screening program with an ISCN population should give serious consideration to using the ABR intensity series protocol outlined by Galambos et al. (1994). This proven protocol requires that an estimate of threshold be obtained immediately if the infant fails an initial 60 dB nHL or 30 dB nHL test in either ear. To this we would add EOAE testing at the time the ABR threshold series is done. In this way, an estimate of threshold for each ear along with test results suggesting either peripheral (cochlear) or central (neural) impairment can be entered into the hospital record and plans made for follow-up services.

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