Cochlear Microphonic and Summating Potential Responses from Click-Evoked Auditory Brain Stem Responses in High-Risk and Normal Infants

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Abstract

Background: Examination of cochlear and neural potentials is necessary to assess sensory and neural status in infants, especially those cared for in neonatal intensive care units (NICU) who have high rates of hyperbilirubinemia and thus are at risk for auditory neuropathy (AN).

Purpose: The purpose of this study was to determine whether recording parameters commonly used in click-evoked auditory brain stem response (ABR) are useful for recording cochlear microphonic (CM) and Wave I in infants at risk for AN. Specifically, we analyzed CM, summating potential (SP), and Waves I, III, and V. The overall aim was to compare latencies and amplitudes of evoked responses in infants cared for in NICUs with infants in a well-baby nursery (WBN), both of which passed newborn hearing screening.

Research Design: This is a prospective study in which infants who passed ABR newborn hearing screening were grouped based on their birth history (WBN and NICU). All infants had normal hearing status when tested with diagnostic ABR at about one month of age, corrected for prematurity.

Study Sample: Thirty infants (53 ears) from the WBN [mean corrected age at test = 5.0 weeks (wks.)] and thirty-two infants (59 ears) from the NICU (mean corrected age at test = 5.7 wks.) with normal hearing were included in this study. In addition, two infants were included as comparative case studies, one that was diagnosed with AN and another case that was diagnosed with bilateral sensorineural hearing loss (SNHL).

Data Collection and Analysis: Diagnostic ABR, including click and tone-burst air- and bone-conduction stimuli were recorded. Peak Waves I, III, and V; SP; and CM latency and amplitude (peak to trough) were measured to determine if there were differences in ABR and electrocochleography (ECochG) variables between WBN and NICU infants.

Results: No significant group differences were found between WBN and NICU groups for ABR waveforms, CM, or SP, including amplitude and latency values. The majority (75%) of the NICU group had hyperbilirubinemia, but overall, they did not show evidence of effects in their ECochG or ABR responses

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when tested at about one-month corrected age. These data may serve as a normative sample for NICU and well infant ECochG and ABR latencies at one-month corrected age. Two infant case studies, one diagnosed with AN and another with SNHL demonstrated the complexity of using ECochG and otoacoustic emissions to assess the risk of AN in individual cases.

Conclusions: CM and SPs can be readily measured using standard click stimuli in both well and NICU infants. Normative ranges for latency and amplitude are useful for interpreting ECochG and ABR components. Inclusion of ECochG and ABR tests in a test battery that also includes otoacoustic emission and acoustic reflex tests may provide a more refined assessment of the risks of AN and SNHL in infants.

Key Words: auditory-evoked potentials, diagnostic techniques, otoacoustic emissions, pediatric audiology

Abbreviations: ABR = auditory brain stem response; AN = auditory neuropathy; CM = cochlear microphonic; DPOAE = distortion product otoacoustic emission; ECochG = electrocochleography; NICU = neonatal intensive care unit; OAE = otoacoustic emission; SD = standard deviation; SNHL = sensorineural hearing loss; SNR = signal-to-noise ratio; SP = summating potential; TEOAE = transient-evoked otoacoustic emission; WBN = well-baby nursery

INTRODUCTION

Abnormal auditory brain stem responses (ABRs) in the presence of normal otoacoustic emissions (OAEs) have been associated with histories of prematurity, hyperbilirubinemia, and ototoxic drug exposure in infants in the neonatal intensive care unit (NICU) (Berg et al, 2005). Rance et al (1999) reported that the most common risk factor in a group of 20 children diagnosed with auditory neuropathy (AN) was neonatal hyperbilirubinemia. Jiang et al (2012) found that NICU infants tested in the first week after birth at 37–42 weeks (wks.) gestation displayed a significant increase in the Wave III–Wave V interval of the ABR, but the peripheral hearing status of those infants was not described. Reversible ABR abnormalities are common among high-risk infants because of temporary auditory dysfunction, secondary to external and middle-ear pathology, delayed central nervous system maturation or improvement as hyperbilirubinemia resolves (Psarommatis et al, 2011).

Examination of the cochlear microphonic (CM) and summating potential (SP) in comparison to Waves I, III, and V may be useful to identify the site of lesion in infants with abnormal ABR. The CM and SP are most clearly recorded with transtympanic electrocochleography (ECochG). However, these components are also present, albeit at lower amplitudes in extratympanic ABR recordings. An advantage of combined ECochG and ABR recording is the ability to simultaneously measure components from the hair cells to the upper brain stem. Arslan et al (1983) recommended ABR and ECochG recordings to fully assess hearing function in children. Although ECochG is not traditionally used to assess hearing in infants, it may be more readily measured in infants than in older children and adults, and thus could be a complementary tool to the ABR. However, normative data from a noninvasive extratympanic clinical protocol that reliably records ECochG potentials are needed. Data for ECochG components in normal-hearing NICU infants compared with well infants is particularly relevant because NICU infants are at higher risk for AN. A study of CM was reported by (Shi et al, 2012) in 36 infants and children diagnosed with AN who had absent ABRs and present CMs. No studies of CM and SP recordings have previously been reported in normal-hearing NICU populations.

AN is a heterogeneous hearing disorder of the inner hair cells, auditory nerve synapses or auditory nerve, in the presence of relatively normal outer hair cell function. The disorder was originally termed "AN" (Starr et al, 1996), based on the perplexing combination of normal OAE combined with markedly abnormal or absent ABR (Starr et al, 1996; 2001; Santarelli and Arslan, 2002). In 2008, the term was expanded by a consensus conference (Hayes and Sininger, 2008) to recognize the diversity of etiologies, including the inner hair cells, the synapse between inner hair cells and the VIII nerve fibers, or the spiral ganglion neurons. More recently, with increased evidence about the pathophysiologic mechanisms specific to presynaptic and postsynaptic disorders, it has become more clear that the original term "AN" is the more appropriate term (Rance and Starr, 2015; Moser and Starr, 2016). Because there are a variety of presentations of AN, its diagnosis can sometimes be elusive, especially at birth. Accurate diagnosis of AN relies on objective neurophysiological measures of cochlear hair cell and auditory nerve functions, imaging of auditory nerve/brain stem, and behavioral audiologic measures (Rance and Starr, 2015). Infants referred from newborn screening programs may undergo multiple tests before the disorder is properly diagnosed, by which time the infant may already be delayed in speech and language developmental milestones (Petty and Huffman, 2014). In addition to abnormal ABR, elevated or absent acoustic reflexes in ears with detectable CM and/or OAE responses is consistent with AN (Berlin et al, 2005).

Normative data have not previously been reported comparing ECochG components in well and NICU

infants of similar ages without hearing loss. Because infants cared for in the NICU are at higher risk for AN due to high rates of hyperbilirubinemia and other risk factors for neural deficits (as in the NICU group in this study), this is a clinically relevant population to provide normative data, although normative data can also help to screen for AN in the normal newborn population. The purpose of this study was to define normal CM, SP, and waveform components at longer latencies from combined click-evoked ECochG and ABR for assessment of infants. The overall aim was to investigate neurodevelopment by comparing latencies and amplitudes of these evoked responses in infants cared for in NICUs with those in a well-baby nursery (WBN). Individual cases of a NICU baby with AN and a well baby with sensorineural hearing loss (SNHL) are presented to illustrate application of the normative data.

MATERIALS AND METHODS

Participant Enrollment and Demographics

This study was part of a longitudinal, prospective multiyear project to evaluate the use of a wideband acoustic immittance test battery (wideband absorbance and acoustic reflexes) in conjunction with distortion product OAE (DPOAE) and ABR testing to identify middle-ear, cochlear, and neural hearing loss in infants and children. Infants who passed a two-stage newborn hearing screening were enrolled from the WBN and NICU at Good Samaritan Hospital and the NICU at Cincinnati Children's Hospital Medical Center. The two-stage screening protocol in the WBN consisted of transient-evoked OAE (TEOAE, clicks at 80 dB SPL) followed by an automated ABR (clicks at 35-dB nHL) if the infant did not pass the TEOAE test. Infants enrolled in the NICU were tested with a screening ABR test combined with either a TEOAE or DPOAE test. Infants in the WBN were tested within 24–48 hours after birth, whereas infants from the NICU were tested once they were healthy enough for discharge.

The WBN study group included 30 infants born between 36 and 41 wks. of gestation [mean = 38.9 wks.; standard deviation (SD) = 1.4 wks.] with a mean corrected age at test of five wks. (SD = 2.4 wks.; range = 0.4–11.3 wks.). All data reported used corrected age, for which the 38 wks. of postmenstrual date was considered to be full term. The corrected age was calculated by subtracting the difference between gestational age at birth and 38 wks. from the chronological age. The NICU study group comprised 32 infants born between 28 and 41 wks. gestation (mean = 33.9; SD = 3.5 wks.) with a mean corrected age at ABR testing of 5.7 wks. (SD = 2.7) ranging from 0.9 to 13 wks.

The demographics and risk factors for the two groups are provided in Table 1. In contrast to the WBN group that had a 20% prevalence of risk factors (primarily family history), 96% of the NICU infants had at least

Table 1. Demographics of Infants with Normal Hearing Cared for in the WBN and NICU

Variable	Nursery Group	
	WBN	NICU
Gestational age at birth (wks.): mean (SD), range	38.9 (1.4), 36.0–41.0	33.9 (3.5), 28.0–41.0
Corrected age at test (wks.): mean (SD), range	5.0 (2.4), 0.4–11.3	5.7 (2.7), 0.9–13.0
Gender: N (%)		
Male	20 (66.7)	17 (53.1)
Female	10 (33.3)	15 (46.9)
Race: N (%)		
Black or African American	9 (30.0)	10 (31.2)
White or Caucasian	20 (66.7)	19 (59.4)
Other	1 (3.3)	3 (9.4)
Ethnicity: N (%)		
Hispanic/latino	0 (0.0)	1 (3.1)
Non-hispanic/latino	30 (100.0)	31 (96.9)
Risk factors*: N (%)		
Family history	5 (16.7)	1 (3.1)
Stigmata	0 (0.0)	0 (0.0)
Intrauterine infection	0 (0.0)	2 (6.3)
Ototoxic drugs (gentamicin)	0 (0.0)	19 (59.4)
Hyperbilirubinemia	2 (6.7)	24 (75.0)
NICU > 5 days	0 (0.0)	28 (87.5)
Low birth weight	0 (0.0)	7 (21.9)
Any risk factors present: N (%)	6 (20.0)	31 (96.9)

N = number.

*Percentages add up to >100% because of multiple risk factors for some infants.

one risk factor for hearing loss, with NICU stay >5 days (87.5%), hyperbilirubinemia (75%), and ototoxic medication (gentamicin, 59.4%) recorded as the most common risk factors.

Test Protocol

Ethical approval of the research protocol was granted by the Institutional Review Boards of Cincinnati Children's Hospital Medical Center and Good Samaritan Hospital. Informed consent was obtained from the parent(s) of all infants before participation. All testing was completed within an electrically shielded audiometric sound booth by a licensed pediatric research audiologist. Testing was scheduled at approximately one month of age, although it occurred later in some cases because of rescheduling or illness. Preparation instructions were sent out before the appointment. Caregivers were instructed to keep the infant awake and to delay feeding until after arrival at the outpatient clinic. Whenever possible, testing was scheduled in accordance with the infant's sleep schedule. Testing was completed after bottle or breast feeding while the infant was in a state of natural sleep or quiet wakefulness in their caregiver's arms or resting in an infant carrier.

An otoscopic examination was performed to ensure the ear canal was patent. Wideband absorbance was measured from 0.25 to 8 kHz using a research system with custom software, a Titan probe, and modified AT-235 tympanometry hardware (Interacoustics AT-235 and Titan probe, Middelfart, Denmark). Detailed descriptions of test procedures and results from normal-hearing infants are described in Keefe et al (2015) and Hunter et al (2015). Wideband acoustic reflex threshold measurements were obtained with the same hardware using procedures described in the study by Hunter et al (2017b) and Keefe et al (2016).

Diagnostic ABRs were measured using a Vivosonic Integrity V500 System (Version 5.2, Toronto, ON, Canada). The Vivosonic system uses a Bluetooth® amplifier, which substantially reduces electrical artifacts at the amplifier, an advantage for obtaining better quality ECochG and ABR waveforms. Recording details are provided in (Elsayed et al, 2015) and are summarized in the following paragraphs. The recording montage used three disposable pre-gelled electrodes placed at the high middle forehead (+), the ipsilateral mastoid (−), and the contralateral mastoid (ground). The interelectrode impedance was maintained at <5 kΩ. Air-conduction stimuli were presented via insert earphones (Etymotic Research ER-3A, Elk Grove Village, IL) using pediatric ear foam tips, trimmed as necessary to accommodate newborn ear canals. Bone-conduction stimuli were presented with a hand-held Radioear B-71 bone vibrator (Radioear Corp, New Eagle, PA). Click stimuli (100 μsec) were presented at a rate of 37.1/sec to the test ear through an insert earphone. Click stimuli were delivered at 70-dB nHL, referenced to 38-dB peak equivalent SPL (peSPL) with broadband contralateral masking noise applied as needed at 10 dB above the level of the test stimulus. Air- and bone-conduction tone-burst thresholds were measured at 0.5, 1, 2, and 4 kHz using Blackman-gated tones presented at 37.1/sec. At a minimum, air-conduction thresholds were obtained at 1 and 4 kHz with a bone-conduction threshold obtained for at least one corresponding frequency. Normal hearing was defined as air-conduction thresholds of 30-dB nHL or better at 1 and 2 kHz and 20-dB nHL or better at 4 kHz. Although tone-burst results were not analyzed for the present study, they were used to confirm normal hearing.

Signal averaging using the default Kalman weighting algorithm was used with the high-and low-pass filter cutoff frequency set at 0.03 and 3 kHz, respectively. Kalman weighting reduces myogenic artifact, important for lightly sleeping or awake infants. A "split-alternating" protocol was used to record the rarefaction (R), condensation (C), and alternating averages separately, which enabled the comparison of polarities and the ability to correlate waveforms for reliability measures. After the testing commenced, the whole-wave correlation was measured between the peak of Wave I and the trough of Wave V on the alternating polarity tracing. A whole-wave correlation coefficient of 0.60 was set as the lower acceptable limit for inclusion in the study. R and C waveforms were subtracted to determine when the residual noise was flat relative to the averaged waveform (<0.15 μV). To distinguish from stimulus artifact that may be present, CM onset was measured after the 0.9 msec acoustic delay in the earphone tubing after subtracting the condensation waveform from the rarefaction waveform. A total of 14 ears (10 NICU and 4 WBN) were excluded because of low-waveform cross-correlation values (<0.60) and an additional four ears were excluded because of abnormal ABR status (2 WBN and 2 NICU).

DPOAE testing was completed using the Vivosonic Integrity system (Version 5.2, Toronto, ON, Canada) with an ILO P40-UG probe. In situ calibration was performed in each ear using the default program 1-kHz calibration tone before testing followed by DPOAE acquisition. DPOAE level and noise levels were measured at seven f_2 frequencies in descending order (8, 5.5, 4, 3, 2, 1.5, and 1 kHz) with primary-tone stimulus levels of 65-dB SPL (L1) and 55-dB SPL (L2), and an f_2/f_1 frequency ratio of 1.22 (Gaskill and Brown, 1990; Abdala, 1996; Stover et al, 1996). The averaging time was set at 12 sec per stimulus pair per trial. The measurement accuracy was set to "accurate" on the Vivosonic device so that the DPOAE signal required to be stable for 0.4 sec within ±1 dB from its median SPL. DPOAEs were included only if data for at least the five highest frequencies were obtained. The signal-to-noise

ratio (SNR) was calculated by subtracting the mean DPOAE noise level from the mean DPOAE signal level at each f_2 test frequency. Pass criteria require both the DPOAE signal and SNR levels to be greater than the 20th percentile obtained from infants with normal hearing (Hunter et al, 2017a) at three of five DPOAE f_2 test frequencies [2, 3, 4, 5.5, and 8 kHz (Blankenship et al, 2017)]. Nine ears did not meet the DPOAE pass criteria (six WBN and three NICU) and therefore were excluded from analysis.

Statistical Analysis

Waveform Analysis

ABR waveforms, including the rarefaction, condensation and alternating polarity averages, were analyzed separately for each ear. Figure 1 displays ABR waveforms from a healthy WBN infant including the alternating polarity (top), condensation and rarefaction tracings overlaid (middle), and condensation minus rarefaction tracing (bottom). ABR Waves I, III, and V, and SP amplitudes and latencies were measured using the alternating polarity ABR waveform (Figure 1, top). ABR peak components I, III, and V were identified as the final data point on the waveform preceding the negative slope (Hall, 2007, p. 128). Wave I, III, and V amplitudes were measured as the difference between peak amplitude to the subsequent lowest trough. In cases of multiple peaks, the last peak before the trough was marked. The SP was identified as the ledge preceding the ABR Wave I peak. The SP peak amplitude was calculated using the average amplitude over a prestimulus baseline of 1–2 msec (Ge and Shea, 2002). ABR and SP latencies were calculated from stimulus onset to the latency of the marked peak. Absolute SP, Wave I, and Wave V amplitudes were used to calculate the Wave V/I and SP/AP amplitude ratios.

Next, the rarefaction and condensation ABR tracings were overlaid to identify stimulus artifact and the CM (Figure 1, middle). These components can be identified by comparing the phase reversal of the rarefaction (R) and condensation (C) recordings. The dashed lines indicate CM onset and offset (the initial and final crossings of the condensation and rarefaction tracings). The duration of the CM was defined as the interval from the onset time of the phase reversal after the initial stimulus artifact, to the time at which the phase reversals were no longer visually apparent (Shi et al, 2012). CM amplitude was measured using the method described by Shi et al (2012), in which the difference waveform (C-R/2) from peak to trough was determined for the largest wave within the duration of the CM (Figure 1, bottom). Because it can be difficult to distinguish CM from stimulus artifact, the tubing was clamped so as to attenuate the sound stimulus to determine whether responses

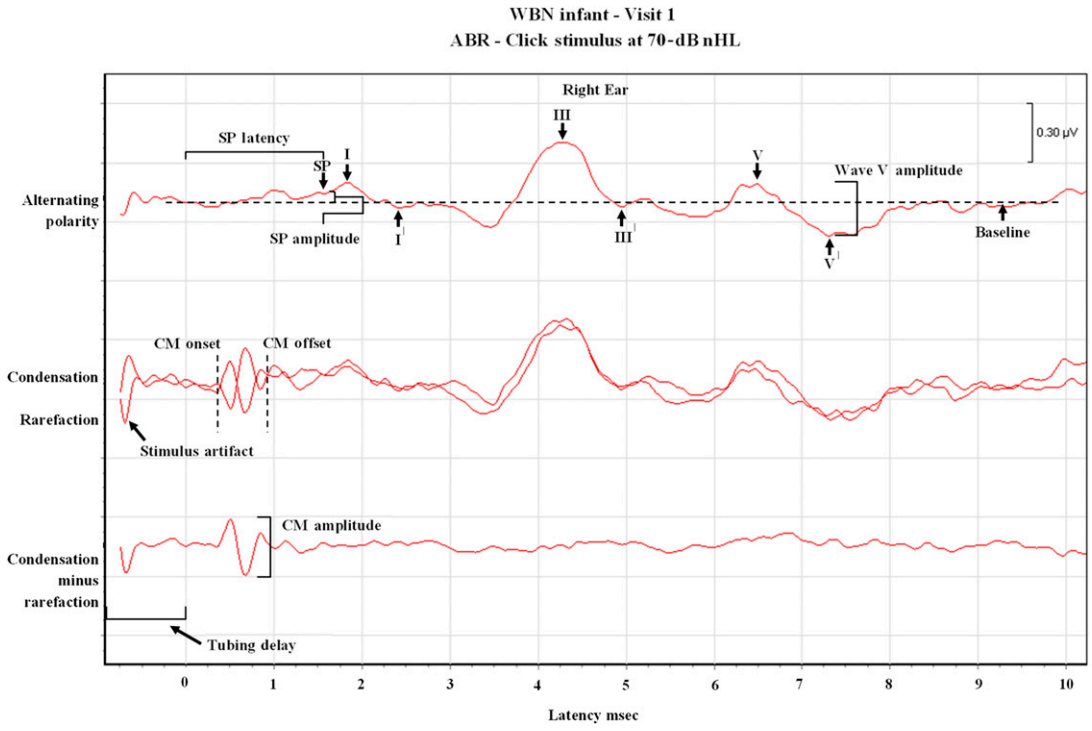

Figure 1. ABR waveforms recorded from the right ear of a healthy WBN infant at 70-dB nHL using click stimuli. Alternating, condensation, rarefaction, and condensation minus rarefaction waveforms are displayed in the top, second and third, and bottom tracings, respectively. ABR Wave I, III, and V neural components along with the SP are identified in the top tracing. The second and third tracings are overlaid to identify the CM onset and offset which are marked with dashed lines. The bottom or fourth tracing represents the condensation minus rarefaction tracing and was used to measure CM amplitude. (This figure appears in color in the online version of this article.)

were due to stimulus artifact or CM. When this was done, it was apparent that the stimulus artifact was seen in the early portion of the waveform, as marked in Figure 1 for latencies <0 msec, whereas the later reversals in the waveforms up to about 1 msec were CM components because they disappeared when the tubing was clamped (not displayed).

WBN and NICU Group Comparisons

Independent-sample *t*-tests were conducted to determine if there were mean differences in ABR and ECochG variables (amplitude and latencies) between left and right ears for the WBN and NICU groups separately. Independent samples *t*-tests revealed no significant mean differences in ABR and ECochG amplitudes and latencies between the left and right ears for the WBN or the NICU group ($p > 0.05$). Therefore, left and right ear data were combined to form a WBN and NICU group. Next, group comparisons using independent samples *t*-tests were conducted to determine if there were mean differences in ABR and ECochG variables between the WBN and NICU infants. Data were analyzed with SigmaPlot Version 13.0 (Systat Software, San Jose, CA).

RESULTS

Analysis of the ABR results showed clearly measurable waves for 112 individual ears, including 53 WBN and 59 NICU ears. The SP was not present in six NICU and three WBN ears. The CM was not present in one NICU ear. Descriptive statistics and results of independent samples *t*-tests for the ABR and ECochG recording parameters, amplitude, and latencies for the WBN and NICU study group are displayed in Table 2. All variables, with the exception of Wave V amplitude, failed the test of normality as assessed by Shapiro–Wilk test ($p < 0.05$). Therefore, Mann–Whitney rank sum tests were conducted to determine if there were group differences between WBN and NICU infants, and these median group difference values are discussed in the following paragraphs. Thus, median rather than mean values are presented for subsequent group comparisons. No significant differences were found between median whole waveform correlation coefficient values for the WBN compared with the NICU group ($p = 0.353$). However, NICU infants had a significantly lower number of equivalent sweeps ($p \leq 0.001$) and total number of sweeps ($p = 0.002$) than WBN infants.

With regard to ABR amplitude, group comparisons revealed no significant differences in median amplitude values for Wave I, Wave V, or the Wave V/I ratio. For ECochG component amplitudes, group comparisons revealed no significant median differences in SP amplitude, SP/AP, or CM amplitudes. Analyses indicated no significant median differences in ABR or ECochG component latencies between WBN and NICU infants.

Case Studies

Two case studies that were challenging to diagnose because of conflicting test results were examined relative to

Table 2. ECoG and ABR Descriptive Statistics for Infants Cared for in the WBN and NICU

ECoG and ABR Variables	Nursery Group												
	WBN						NICU						
	N	Mean	SD	Median	5th %	95th %	N	Mean	SD	Median	5th %	95th %	*p*-Value
Recording parameter													
Number of sweeps	53	2,673	1,095	2,256	1,656	5,170	59	2,230	1,071	1,840	1,040	5,632	0.002
NES	53	2,038	524	2,019	1,530	3,436	59	1,562	599	1,535	797	2,594	<0.001
Correlation	53	0.83	0.08	0.85	0.64	0.92	58	0.81	0.09	0.84	0.63	0.93	0.353
Amplitude													
Wave I	53	0.16	0.05	0.16	0.08	0.24	59	0.16	0.07	0.15	0.05	0.29	0.735
Wave V	53	0.28	0.09	0.28	0.12	0.44	59	0.29	0.10	0.29	0.12	0.48	0.315
Wave V/I ratio	53	1.86	0.77	1.69	1.05	3.69	59	2.22	1.49	1.79	0.70	5.33	0.420
SP/AP ratio	50	0.28	0.18	0.24	0.02	0.69	53	0.32	0.27	0.27	0.05	0.70	0.337
SP	50	0.04	0.03	0.04	0.00	0.09	53	0.04	0.03	0.04	0.01	0.09	0.461
CM	53	0.24	0.09	0.23	0.10	0.40	58	0.26	0.13	0.28	0.08	0.53	0.508
Latency*													
Wave I	53	1.62	0.23	1.57	1.40	1.99	59	1.62	0.12	1.59	1.44	1.88	0.236
Wave III	53	4.34	0.23	4.30	3.99	4.84	59	4.38	0.36	4.33	4.04	4.82	0.677
Wave V	53	6.67	0.35	6.62	6.10	7.19	59	6.62	0.26	6.57	6.31	7.14	0.372
SP	50	1.36	0.24	1.31	1.05	1.90	53	1.32	0.14	1.36	1.11	1.55	0.580
CM onset	53	0.42	0.11	0.47	0.19	0.58	58	0.46	0.09	0.50	0.25	0.55	0.085
CM off set	53	1.16	0.28	1.07	0.77	1.67	58	1.28	0.50	1.31	0.68	1.88	0.133
CM duration	53	0.73	0.30	0.70	0.23	1.35	58	0.82	0.51	0.86	0.23	1.39	0.322

* = milliseconds; AP = action potential; DNT = did not test; NES = number equivalent sweeps.

the normative ECochG and ABR ranges. The test battery approach was used in these cases to diagnose type of hearing loss.

AN Case Study

The following case describes history, newborn screening, and audiologic test results obtained at three and eight months of age from an infant that was enrolled in the same study, but was diagnosed with bilateral AN and so was excluded from the normative sample. The infant was born at 29 wks. of gestation and had several risk factors for hearing loss, including prematurity, a history of G6PD (a glucose deficiency disorder), and double-exchange blood transfusion for hyperbilirubinemia. His mother reported that he has an elder brother with G6PD and AN diagnosed at birth that improved over time. His elder brother now has normal hearing and normal ABR results. Before discharge from the NICU, this infant passed the DPOAE screening; however, he was referred on the automated ABR screening bilaterally.

At approximately three months of age, otoscopy, ambient absorbance, DPOAE, acoustic reflex, and diagnostic ABR tests were completed (see Figures 2 and 3). Otoscopy showed that ear canals were patent and clear of debris. Figure 2A displays ambient absorbance results plotted over normative values (model mean estimated 95% confidence intervals obtained from normal infants; Hunter et al, 2015). Absorbance was less than the normal range from 0.25 to 2 kHz in the right ear and decreased in the left ear to <0.5 kHz. Acoustic reflex testing was conducted using broadband noise in the left and right ipsilateral condition. Acoustic reflex thresholds (not shown) were absent at the highest level presented, which was 80-dB SPL in both ears.

Figure 2B displays DPOAE signal level and SNR values plotted over infant normative data (Hunter et al, 2017a) and cutoff values for diagnosis of infants with hearing loss reported by Blankenship et al (2017). The cutoff values shown in Figure 2B provide balanced sensitivity and specificity (as the cutoff value for DPOAE signal level is that level closest to the point of symmetry of the receiver–operator characteristic curve and similarly for the cutoff value of SNR) for detection of hearing loss of 30-dB HL or greater. Right ear DPOAE amplitudes met or exceeded the cutoff criteria at 3, 4, 5.5, and 8 kHz. The right ear SNR was low at all frequencies except 3 and 5.5 kHz, possibly because of abnormally low wideband absorbance from 0.25 to 2 kHz (Panel A). In the left ear, the DPOAE responses displayed low amplitude from 1 to 3 kHz with normal DPOAE signal levels and SNR obtained from 4 to 8 kHz. The SNR was greater than the cutoff criteria in the left ear between 3 and 8 kHz. Decreased absorbance and negative middle-ear pressure in the right ear were evidence of middle-ear dysfunction that likely affected the DPOAE signal level amplitude.

Figure 3 displays ABR waveforms at three months of age in response to click stimuli presented at 70 dB nHL. ABR waveforms displayed very abnormal morphology, with no identifiable peaks (Wave I, III, and V) but with a clear CM present bilaterally. For the left and right ear, respectively, the CM latencies are as follows: CM onset (0.14 and 0.42 msec), offset (1.96 and 1.91 msec), and total duration (1.82 and 1.49 msec). Comparison to the 5th–95th percentiles obtained from NICU infants show that only the CM onset in the right ear was in the normal range. The CM onset in the left ear displayed an earlier onset, the CM offset in both ears was delayed, and the total CM duration in both ears was prolonged. The CM amplitude was 0.20 and 0.14 μV in the left and right ears, respectively, both of which are within the 5th–95th percentile obtained from NICU infants.

ABRs were also recorded to click stimuli at 80- and 90-dB nHL (right ear) and 99-dB nHL (left ear) as well as to tone-burst stimuli at various intensity levels (not displayed). ABR results at 80- and 99-dB nHL also revealed no identifiable peaks with only the CM present bilaterally. However at 90-dB nHL, a delayed and poorly formed possible Wave V was present. Tone-burst responses for the right ear showed a threshold of 95-dB nHL for 0.5-kHz tone-burst stimuli with no response observed at 1, 2, and 4 kHz. In the left ear, responses were obtained at 105- and 104-dB nHL at 0.5 and 1 kHz with no response at 2 and 4 kHz. In both ears, a large CM was observed for tone bursts and Wave V, when present, was delayed and poorly formed. Partially present DPOAEs and absent acoustic reflexes in conjunction with absent or poor ABR waveform morphology with a large CM is consistent with AN, which was later diagnosed by an audiologist and neuro-otologist in a team approach.

At approximately eight months of age, ABR testing was repeated to evaluate changes with development. Ambient absorbance results displayed in Figure 4A indicate normal middle-ear function from 0.5 to 4 kHz bilaterally with decreased absorbance <0.5 and >4 kHz. The gray fill pattern of normative responses in Figure 4A represents a different baseline compared with that in Figure 2A for younger infants. Acoustic reflex testing was conducted using broadband noise in the left and right ipsilateral condition. An elevated acoustic reflex threshold of 80-dB SPL was obtained in the left ear and no response was obtained at the maximum SPL of 80 dB in the right ear. Although it was surprising that a reflex was recorded to BBN in the left ear, albeit at an elevated threshold, no data have been previously reported for BBN acoustic reflexes recorded using the absorbance method (Hunter et al, 2017b; Keefe et al, 2016) in patients with AN. Figure 4B displays DPOAE signal level and SNR values plotted over infant normative data (Hunter et al, 2017a) and symmetry cutoff values reported by Blankenship et al (2017). DPOAE signal levels for both the left and right ear were below the symmetry cutoff values at all frequencies

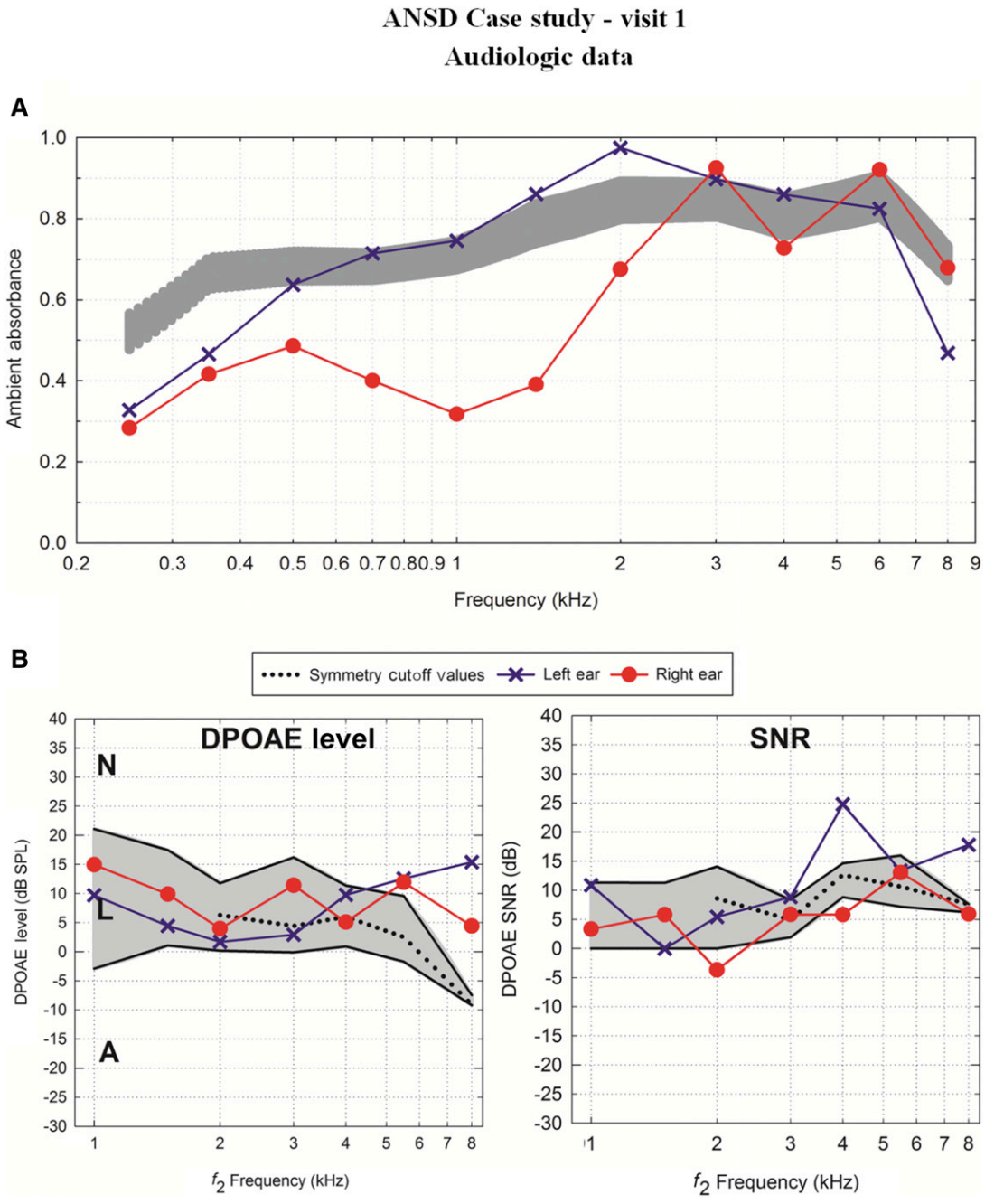

Figure 2. Audiologic test results for a three-month-old infant diagnosed with bilateral AN. Panel A displays left and right ear ambient absorbance as a function of frequency (0.25–8 kHz). The light gray–shaded region represents normative range based on the model mean estimated 95% confidence intervals obtained from normal infants (Hunter et al, 2015). Panel B displays left and right ear DPOAE signal level and SNR values obtained at the same study visit. The gray-shaded region represents the area of overlap between the distributions of the 90th percentile from hearing-impaired infants and the 10th percentile obtained from normal-hearing infants at approximately one month of age (Blankenship et al, 2017). DPOAE signal level and SNRs that are above the symmetry cutoff values (dotted line) are consistent with normal outer hair cell function and those plotted below are consistent with abnormal function. In addition, overall DPOAE amplitude can be further categorized as normal (N), low (L), or absent or abnormal (A). (This figure appears in color in the online version of this article.)

tested and were markedly decreased relative to the three-month DPOAE results. Therefore, DPOAE responses would be categorized as abnormal or absent for both ears. Reduction of DPOAEs over time has been reported in some cases of AN, and may have occurred because of outer hair cell damage associated with severe hyperbilirubinemia in this case. Middle-ear dysfunction does not appear to explain the decrease in DPOAE levels.

Figure 5 displays ABR waveforms at eight months of age in the same AN infant in response to click stimuli presented at 80-dB nHL. ABR waveforms were abnormal bilaterally with no identifiable peaks (Wave I, III,

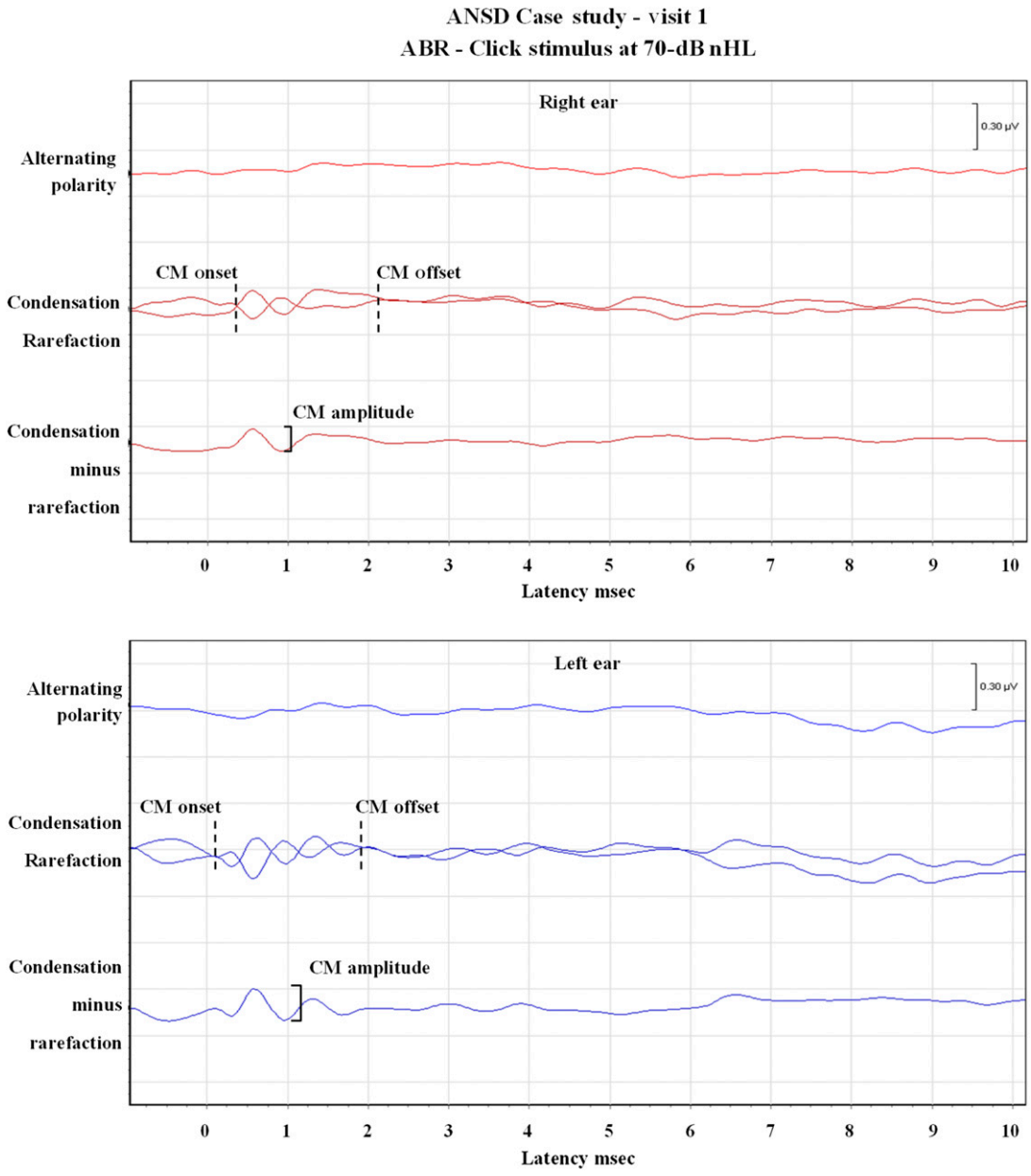

Figure 3. ABRs waveforms obtained from a three-month-old infant with bilateral AN in response to click stimuli presented at 70-dB nHL. Alternating, condensation, rarefaction, and condensation minus rarefaction waveforms are displayed in the top, second and third, and bottom tracings, respectively. CM onset and offset are marked with dashed lines and the CM amplitude is identified in the bottom tracing (bracket). (This figure appears in color in the online version of this article.)

and V) with the CM present bilaterally. Thus, no improvement in the click response was found compared with the ABR at three months of age. However, the CM was still clearly present in both ears. For the left and right ear, respectively, the CM latencies are as follows: CM onset (0.26 and 0.16 msec), offset (1.28 and 1.15 msec), and total duration (1.02 and 0.99 msec). On comparison to the 5th–95th percentiles obtained from NICU infants, only the CM onset in the right ear was outside of the normal range. When compared with the three-month ABR results, the CM onset increased by 0.12 msec in the left ear and decreased by 0.26 msec in the right ear. The CM offset and total duration decreased by 0.68 and 0.8 msec in the left ear and decreased by 0.76 and 0.5 msec in the right ear. The CM amplitude was 0.40 and 0.50 µV in the left and right ear, respectively, both of which are at the upper range of the 5th–95th percentile obtained from NICU infants. Compared with the three-month ABR results, the CM amplitude increased from 0.2 to 0.4 µV in the left ear and increased from 0.14 to 0.50 µV in the right ear, although the amplitude increase from 70- to 80-dB nHL likely accounted for this change.

ABR responses to tone-burst stimuli (not shown) displayed abnormal waveform morphology for the

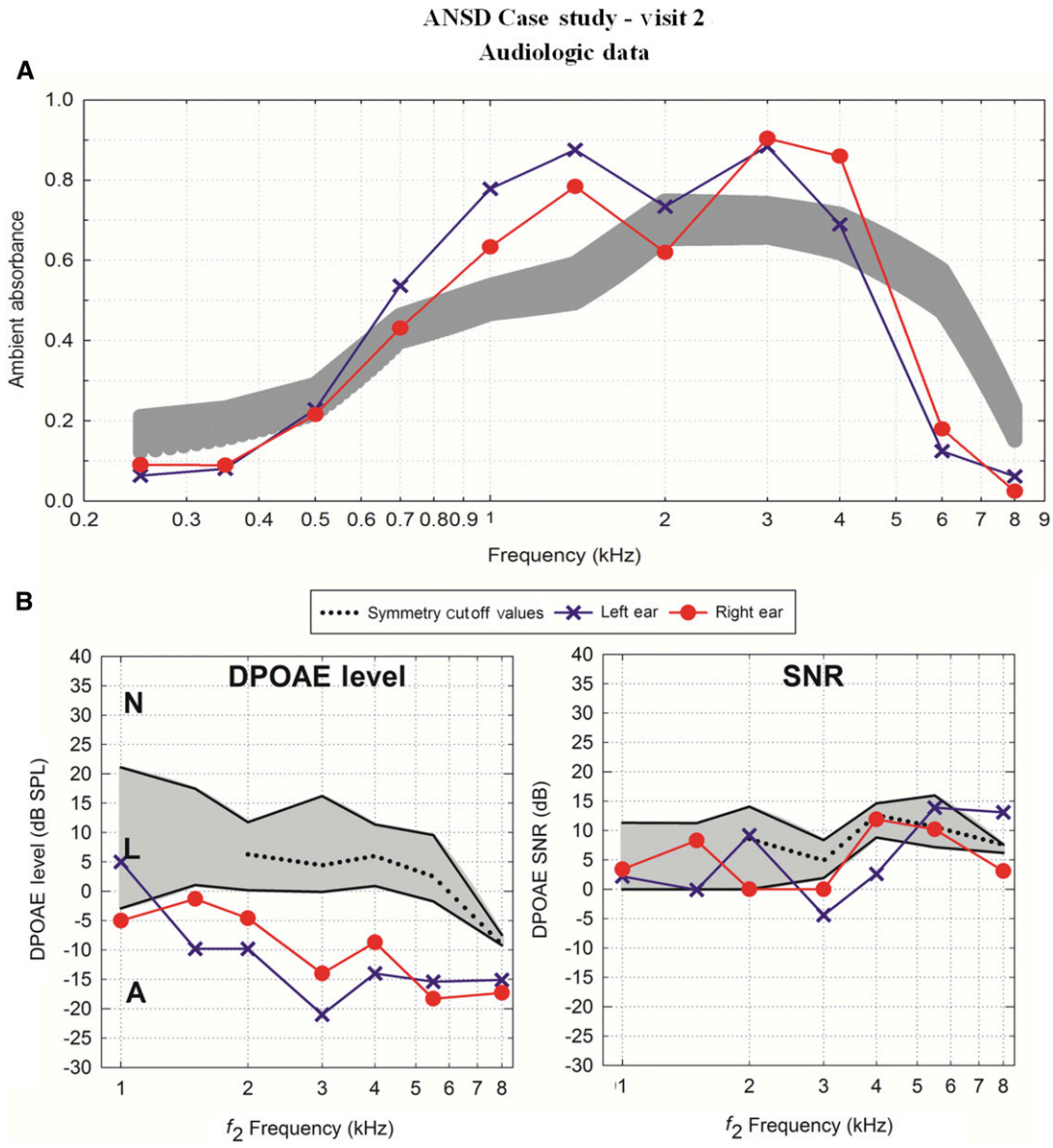

Figure 4. Audiologic test results for an eight-month-old infant diagnosed with bilateral AN, including ambient absorbance (Panel A) and DPOAE signal level and SNR responses (Panel B). See Figure 2 for a detailed description of shaded regions, symmetry cutoff values, and abbreviations. (This figure appears in color in the online version of this article.)

patient's age. At suprathresholds levels, there were some repeatable waveforms; however, they had a markedly abnormal appearance, delayed latency, and therefore were not marked as ABR peaks. At 4 kHz, an air-conduction response was obtained at 50-dB nHL with no response obtained via bone conduction at 60-dB nHL. At 1 kHz, no response was obtained at 100-dB nHL. Tone-burst ABR responses were not measured for 0.5 or 2 kHz in the right ear. In addition, ABR responses to tonal stimuli were not able to be obtained in the left ear.

In summary, the presence of OAEs in combination with present CM and absent acoustic reflexes in this case strengthened the diagnosis. Because OAEs can change over time, obtaining a baseline recording is critically important. In this case, screening OAEs were present, whereas screening ABR was absent. The CM recordings were clearly present on multiple ABRs, whereas the acoustic reflexes were initially absent, and then were elevated at a later test using the wideband absorbance technique. The OAEs became abnormal over time, which may be due to the hyperbilirubinemia history because outer hair cells are often affected by that condition.

SNHL Case Study

The following case study/report describes pertinent case history and audiologic test results obtained at one month of age from an infant that was diagnosed

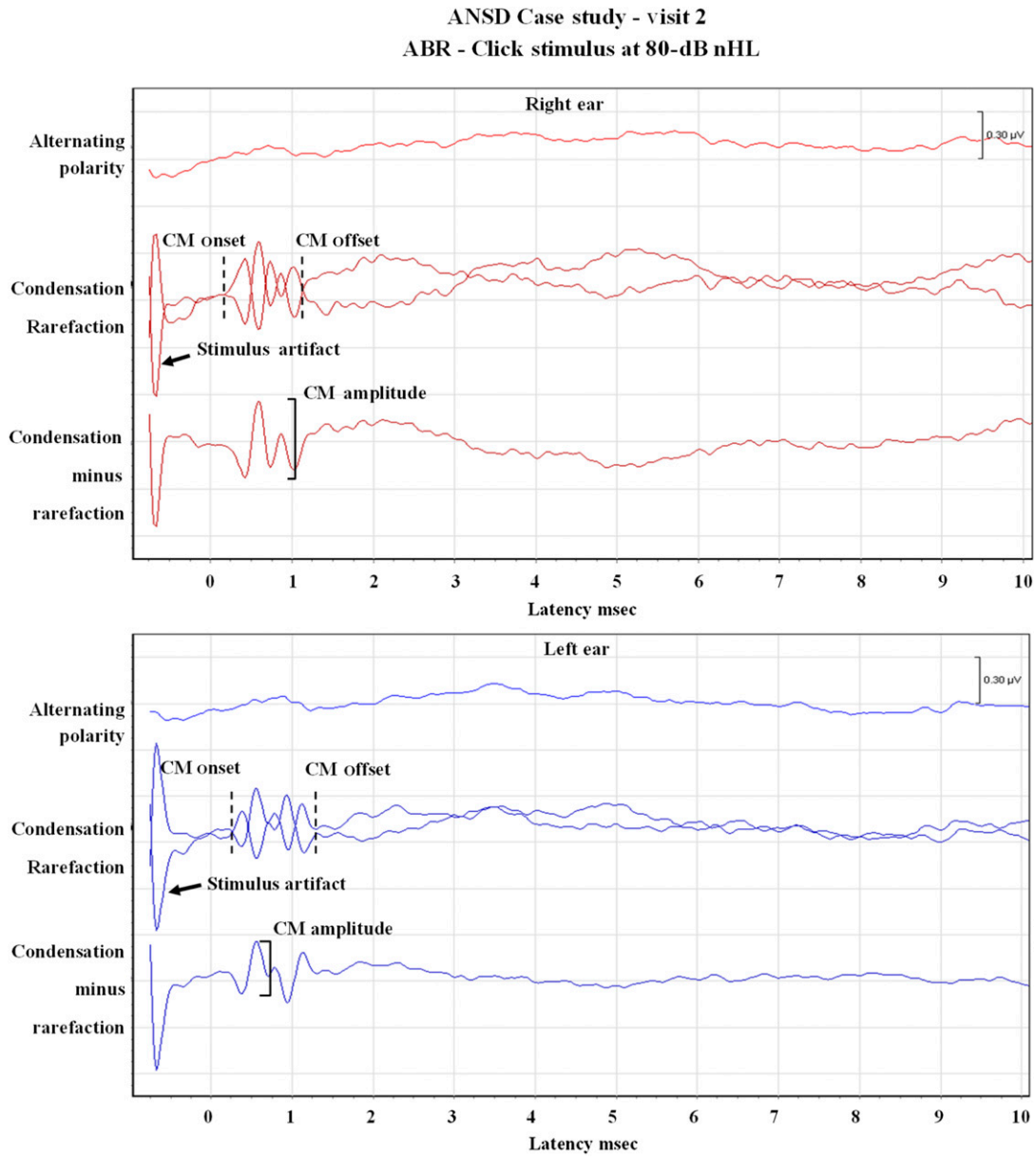

Figure 5. ABR waveforms obtained from an eight-month-old infant with bilateral AN in response to click stimuli presented at 80-dB nHL. Alternating, condensation, rarefaction, and condensation minus rarefaction waveforms are displayed in the top, second and third, and bottom tracings, respectively. CM onset and offset are marked with dashed lines; the CM amplitude is identified in the bottom tracing (bracket). A large stimulus artifact can also be seen in the condensation and rarefaction tracings. (This figure appears in color in the online version of this article.)

with a moderate SNHL. This child was born at full term with no birth complications and referred on the newborn hearing screening bilaterally (combined DPOAE and automated ABR screening). The mother reported a family history of hearing loss on the father's side, including an uncle with hearing loss and a cousin with Down syndrome, as well as family members with epilepsy.

A diagnostic ABR was completed at approximately one month of age along with immittance testing (ambient absorbance and acoustic reflexes) and DPOAEs. Otoscopy results indicate that the ear canals were patent and clear of debris. Immittance testing displays decreased absorbance <1 kHz in the right ear and normal absorbance in the left ear at all frequencies with the exception of 2 kHz (see Figure 6A). Acoustic reflex testing was conducted using an ipsilateral broadband noise activator revealed a threshold of 75-dB SPL in the right and no response in the left ear at the maximum SPL of 80 dB. Figure 6B displays DPOAE signal level and SNR values as a function of f_2 test frequency from 1 to 8 kHz. Right ear responses showed low or absent DPOAE amplitude at most of the test frequencies. DPOAEs based on signal level and SNR were only present at 4 and 5.5 kHz. In the left ear, DPOAE responses

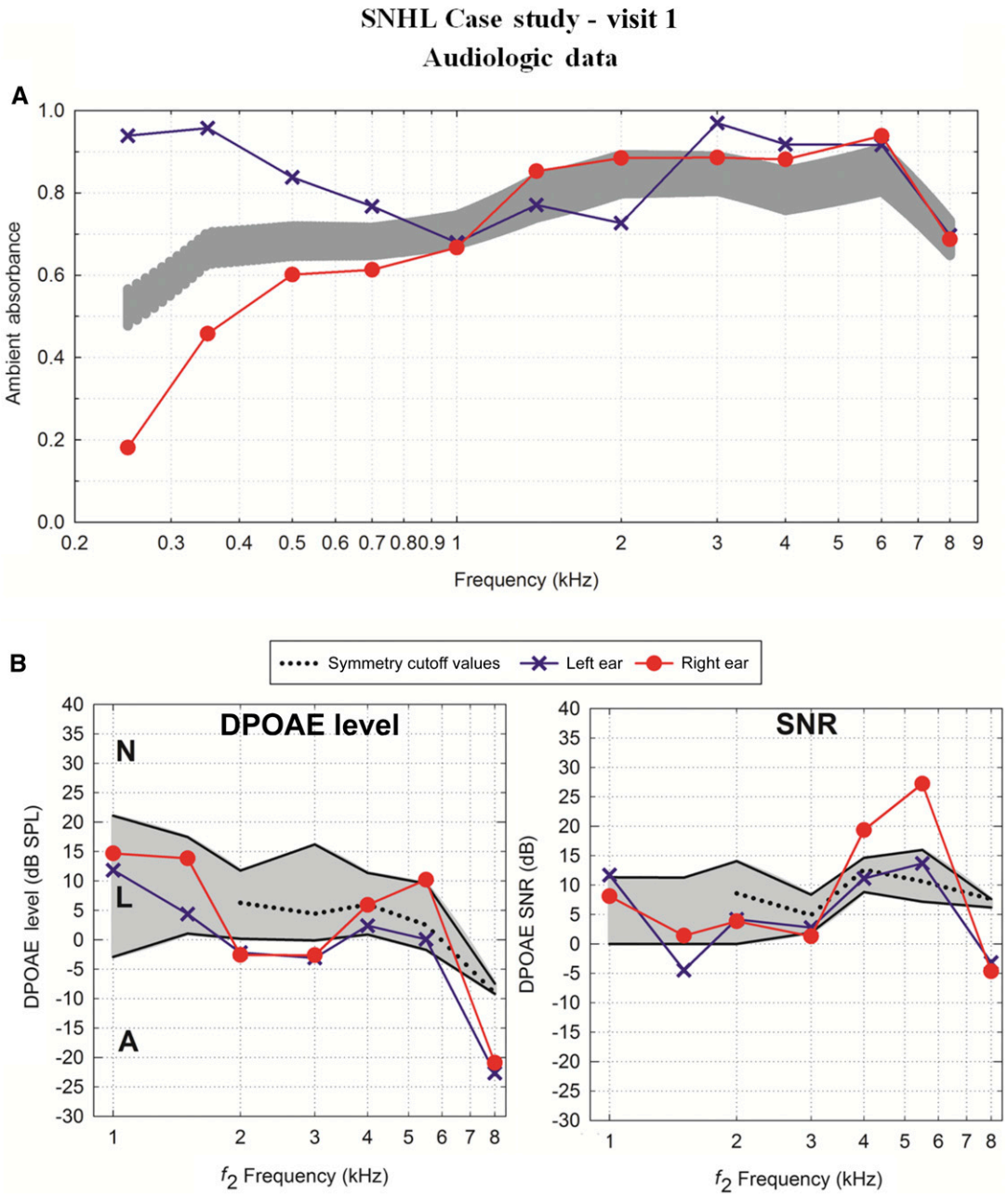

Figure 6. Audiologic test results for a one-month-old infant diagnosed with bilateral SNHL including ambient absorbance (Panel A) and DPOAE signal level and SNR responses (Panel B). See Figure 2 for a detailed description of shaded regions, symmetry cutoff values, and abbreviations. (This figure appears in color in the online version of this article.)

displayed low or absent amplitude from 1 to 8 kHz and acceptable SNR only at 5.5 kHz.

Figure 7 displays ABR waveforms from the infant with SNHL at one month of age in response to click stimuli presented at 70-dB nHL. ABR recordings were obtained in natural sleep and quiet state and were of acceptable quality. The ABR results at suprathreshold levels for click stimuli at 70-dB nHL were observed to have delayed waveform morphology for the patient's age with inter-peak latencies within normal limits and bilaterally symmetrical. ABR Wave I, III, and V latencies were 2.66, 4.41, and 6.75 msec, respectively, for the left ear, and 2.66, 4.85, and 6.62 msec, respectively, for the right ear. The ABR Wave I latency (left and right ear) and the Wave III latency (right ear only) were prolonged compared with WBN infants. With regard to ABR amplitude, Wave I (0.14 and 0.011 μV), Wave V (0.14 and 0.019 μV), and the Wave V/I ratio (1.0 and 1.73 μV) for the left and right ear, respectively, were all within the 5th–95th percentile obtained in WBN infants. In addition, the left and right ear CM onset (0.37 and 0.37 msec), offset (1.46 and 1.65 msec), and total duration (1.09 and 1.28

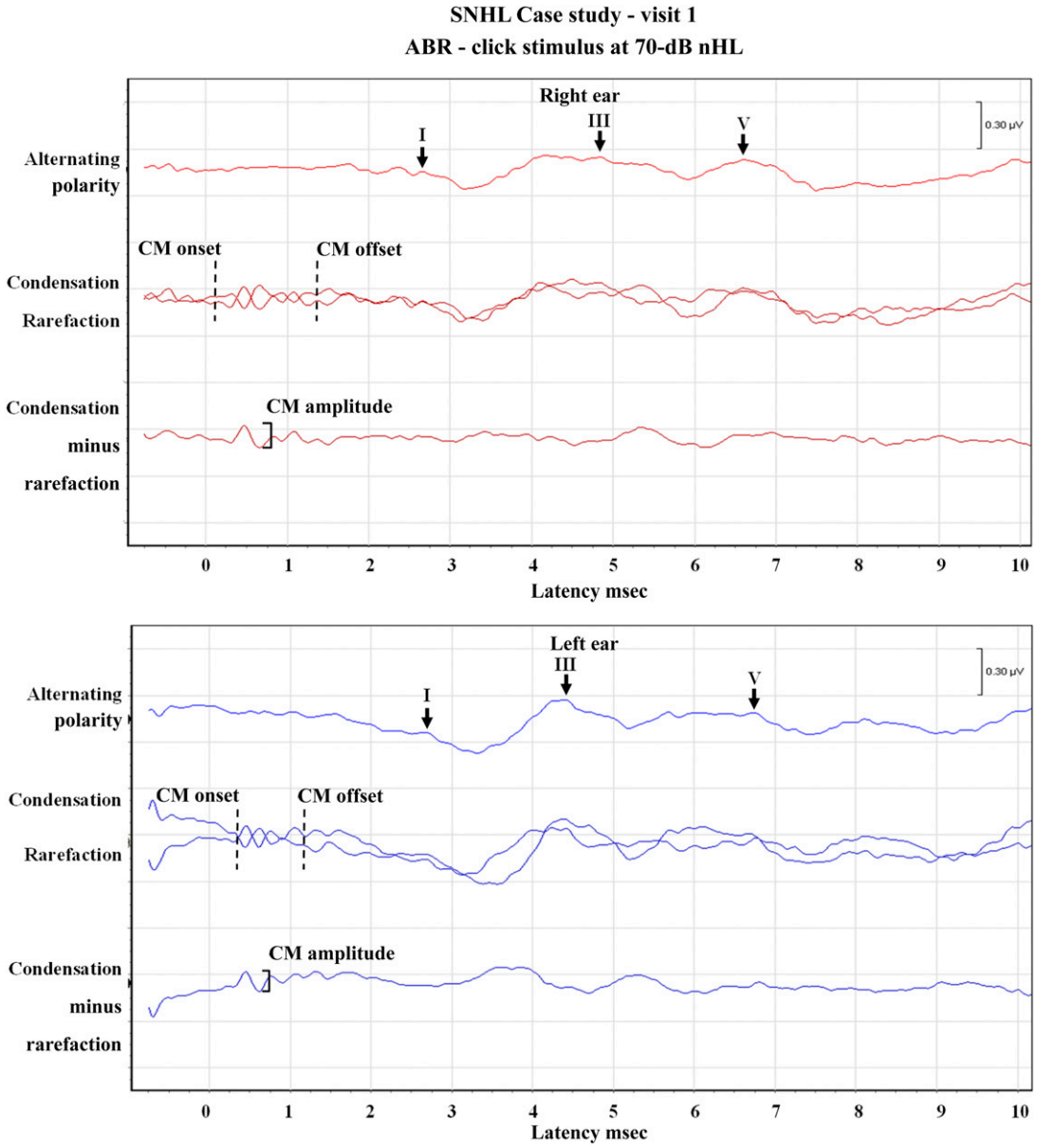

Figure 7. ABR waveforms obtained from a one-month-old infant with bilateral SNHL in response to click stimuli presented at 70-dB nHL. Alternating, condensation, rarefaction, and condensation minus rarefaction waveforms are displayed in the top, second and third, and bottom tracings, respectively. Wave I, III, and V can be identified in the alternating polarity tracing. The CM onset and offset are marked with dashed lines, the CM amplitude is identified in the bottom tracing (bracket). (This figure appears in color in the online version of this article.)

msec) were all within the 5th–95th percentile obtained in NICU infants. The CM amplitude (0.13 and 0.14 µV) was close to the 5th percentile of the normal sample. Thus, although this infant had SNHL, CM responses could still be recorded within the low-normal range. This is an unexpected finding, and was also reported by Santarelli et al (2008). The key differences between this infant and the infant with AN were the ABR waveform morphology and latencies, tone-burst thresholds, and acoustic reflex thresholds, relative to the CM responses.

Tone-burst ABR thresholds for 0.5, 1, 2, and 4 kHz were obtained at 60-dB nHL for both left and right ears. Bone-conduction thresholds were obtained at 50-dB nHL at 4 kHz in the right ear, and at 60-dB nHL at 1 kHz in the left ear. ABR, DPOAE, and acoustic reflex results were consistent with a moderate degree of bilateral SNHL.

DISCUSSION

All measures of cochlear and neural potentials were similar between normal-hearing NICU infants and the healthy controls, recorded at a similar chronological age. The standard recording technique was able to simultaneously record the CM in 99% of NICU and well babies and the SP was present in 92% of NICU

and well babies, with no significant group differences. These recording techniques are supported by recent studies of the SP in human adults. Kennedy et al (2017) studied stimulus rate in amplitude of the human SP and reported that faster repetition rates (58–97/sec) showed higher amplitude SP than slower rates (7–19/sec), using a filter setting similar to the present study (3–3000 Hz). The rate in the present study was intermediate, at 37/sec, because of concerns about reducing Wave I and V amplitude at faster rates in newborns. Liberman et al (2016) used a 10–3000-Hz bandpass filter and click rates of 9.1 and 40.1/sec to record SP and AP measurements and reported that the higher click rate of 40.1/sec did not decrease the SP significantly. There are important differences between the studies as Kennedy used a continuous loop deconvolved technique and frequency-specific tone bursts in adults, but the general principles should apply for rate and filter settings. These results are consistent with the work of Jiang et al (2012) who showed that amplitudes for Waves I, III, and V did not differ significantly between a group of NICU infants and healthy newborns. However, although they found that Wave I and III latencies were similar to controls, Wave V latency was delayed in NICU infants. We did not find similar delays in latency for Wave V, possibly because we excluded infants with abnormal middle-ear function and cochlear hearing loss. Such peripheral factors can affect latency values. Because no significant differences were found between normal and NICU cases, the data are generalizable to both groups. The present finding regarding CM amplitude is in agreement with values reported by Young (2000) on the click-evoked CM amplitude obtained from 26 normal newborns, and also with amplitudes reported by Shi et al (2012) in a group of children <3 years of age using a similar extratympanic recording method. In the past, it has been difficult to identify a method capable of recording the CM without the hindrance of stimulus artifact. However, the consistency found across these studies helps establish normative values for CMs in infants and young children. This will support the use of the CM as a reliable indicator of the status of outer hair cells in clinical diagnosis of hearing function. Amplitudes of the CM in our group were smaller than those reported in children with severe to profound SNHL (Schoonhoven et al, 1999). However, Schoonhoven et al (1999) used a transtympanic recording method, so specific normative data are necessary for extratympanic recordings.

The mean SP amplitude recorded in the present study (0.04) is markedly lower than the value (4.11 ± 0.57 μV) reported for a group of 1- to 7-year olds (Santarelli et al, 2008). However, this difference may be explained by methodological differences. The most important difference was that the present study used an extratympanic, noninvasive electrode to obtain recordings, whereas Santarelli et al (2008) recorded SP amplitudes with transtympanic ECochG. Transtympanic ECochG provides a specific and sensitive measure of the cochlear potentials, which is useful when discriminating between hydropic and non-hydropic ears for Meniere's disease diagnosis (Sass, 1998). However, for screening infants, a noninvasive measure is more suitable because it is more comfortable for the infant and does not require sedation. Noninvasive extratympanic ECochG tends to have lower amplitude waveforms, due to the distance from the anatomic generator site, but it still enhances Wave I and the electrical potentials of the cochlea compared with mastoid or nape of neck electrodes (Ferraro, 2000).

The significant finding of a smaller number of equivalent sweeps needed in the NICU cases to reach acceptable inter-wave correlation was unexpected. We used a defined stopping criterion and did not average to a set number of sweeps, but to what was needed to achieve adequate correlation values. The mean and median correlation values are similar for the well and NICU infants, so it does not appear that the recordings were halted prematurely for the NICU infants. We do not have an explanation for this difference, but can conclude that NICU cases were at least as repeatable as well-baby cases and did not require significantly more averaging to obtain reliable results. Because a noninvasive recording was used in this study, it was sometimes difficult to separate the CM from stimulus artifact. An insert earphone was used and clicks were presented in split-sweep, alternating polarity to help identify the presence of stimulus artifact. The use of insert earphones also helps to separate artifact from CM because of the travel time for the stimulus and location relative to the recording electrode. However, when examining the combined waveform in which the CM is canceled, distortion of the SP can sometimes still result from uncancelled CM. The SP often appears as a small shoulder or deflection immediately before Wave I, so it can be difficult to identify. Because it is sometimes difficult to distinguish the SP from Wave I, some authors consider the two potentials as a single event, referred to as SP/CAP (Santarelli et al, 2008). Evoked response latencies are less variable than amplitudes across individuals, so latencies may be a more consistent measure to use when evaluating infants. Latency is not as affected by factors such as noise levels, placement of electrodes, and filter settings. In the present study, latencies of the SP, CM, Wave I, and V were also similar between the NICU and control groups.

In the case of the infant with AN who had present OAEs but later had abnormal OAEs, this type of case is not atypical. Santarelli et al (2008) reported that AN may present as an absent or abnormal ABR with preserved CM, sometimes in the presence of preserved OAEs, but not always. Absent OAEs in cases of AN may occur because the mechanisms for OAEs and CMs differ. Thus, examination of specific normative ranges for

CM is important in the evaluation of ABR recordings to determine if significant evidence of OHC function is present. When OAEs are absent, the CM, SP, and AP measures are particularly important. The case with SNHL and preserved but low-amplitude CM is also not atypical (Santarelli et al, 2008). Thus, these two cases do not fit the textbook description of AN and SNHL, but rather, reflect the realistic complexities that clinicians face in diagnosis and support the need for a test battery approach.

Limitations of this study are that the ABR recordings were made in a narrow age range from birth to about three months, and thus the normative ranges are applicable to this age range, generally during the most likely time of follow-up from newborn hearing screening. In addition, the recording techniques, in particular, the use of extratympanic surface electrodes and the moderate intensity stimulus level are also specific to these normative ranges. The use of transtympanic electrodes and stimuli such as tone bursts may be more sensitive for diagnosis of AN. Testing was done on only one session; thus, test–retest repeatability is an area for future study. We assessed repeatability by performing cross-correlations of the condensation and rarefaction waveforms. The variance (SD) of the SP, CM, and later waveforms were similar to previous studies in infants. Future studies comparing groups of infants with AN and SNHL are needed to determine the sensitivity and specificity of the CM and SP to differential diagnosis.

CONCLUSIONS

Infants who are admitted to the NICU are at significant risk for hearing impairment, especially those who were born early and/or are treated with ototoxic drugs and phototherapy for hyperbilirubinemia (Pourarian et al, 2012). Because the incidence of hearing loss and conditions such as AN is increased in this environment, neonatal hearing screening and diagnostic follow-up are critically important. Like any other auditory test, ECochG has advantages and disadvantages, but with the use of noninvasive recording techniques, there is no reason why it cannot be used as a complementary measure to the ABR and OAE during infant hearing assessment. This study demonstrated that CM and SP can be measured using standard clinical ABR techniques and surface electrodes at a moderate intensity level (70 dB nHL). Thus, once the clinician is familiar with cochlear potentials and comfortable with interpreting them in the split rarefaction/condensation recording technique, the presence of the CM relative to Wave I latency and amplitude may assist in identification of these early waveforms, and also in relation to Waves III and V. Although comparisons of CM; SP; and Wave I, III, and V are very helpful in evaluating possible AN, a test battery approach including OAE and acoustic reflexes is advised for thorough assessment of middle-ear, cochlear, and neural levels, as demonstrated in the two case studies included in this report.

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