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Cochlear microphonic and summing potential responses from click-evoked auditory brainstem 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 ABR are useful for recording CM and Wave I in infants at risk for AN. Specifically, we analyzed cochlear microphonic (CM), summing 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: Prospective study of infants that 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 1 month of age, corrected for prematurity.

Study Sample: Thirty infants (53 ears) from the WBN (mean corrected age at test = 5.0 weeks) and thirty-two infants (59 ears) from the NICU (mean corrected age at test = 5.7 weeks) with normal hearing were included in this study. In addition, two infants were included as comparative

*Data collected while employed at Cincinnati Children's Hospital Medical Center

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Conflicts of Interest

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 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 when tested at about 1 month corrected age. These data may serve as a normative sample for NICU and well infant ECoChG and ABR latencies at 1 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: Cochlear microphonic and summing potentials 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.

Keywords

Auditory evoked potentials; pediatric audiology; otoacoustic emissions; diagnostic techniques

INTRODUCTION

Abnormal auditory brainstem evoked 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 due to temporary auditory dysfunction, secondary to external and middle ear pathology, delayed central nervous system maturation or improvement as hyperbilirubinemia resolves (Psarommatidis et al., 2011)..

Examination of the cochlear microphonic (CM) and summing potential (SP) in comparison to Waves I, III and V may be useful to identify 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 brainstem.

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 non-invasive extratympanic clinical protocol that reliably records ECoChG potentials are needed. Data for ECoChG components in normal-hearing NICU infants compared to 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 “auditory neuropathy” (Starr et al., 1996), based on the perplexing combination of normal OAE combined with markedly abnormal or absent ABR (Starr et al., 1996; Starr et al., 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 ‘auditory neuropathy’ is the more appropriate term (Rance and Starr, 2015; Moser and Starr, 2016). Since there are a variety of presentations of AN, its diagnosis can sometimes be elusive, especially at birth. Accurate diagnosis of auditory neuropathy relies on objective neurophysiological measures of cochlear hair cell and auditory nerve functions, imaging of auditory nerve/brainstem, and behavioral audiological 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 has 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 SNHL are presented in order to illustrate application of the normative data.

MATERIALS AND METHODS

Subject Enrollment and Demographics

This study was part of a longitudinal, prospective multi-year project to evaluate the use of a wideband acoustic immittance test battery (wideband absorbance and acoustic reflexes) in conjunction with distortion product otoacoustic emission (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 otoacoustic emission (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, while infants from the NICU were tested once they were healthy enough for discharge.

The WBN study group included 30 infants born between 36 to 41 weeks gestation (mean = 38.9 wks; standard deviation SD = 1.4 wks.) with a mean corrected age at test of 5 weeks (SD = 2.4 wks.; Range = 0.4 to 11.3 wks.). All data reported used corrected age, for which the 38 weeks post-menstrual date was considered to be full term. The corrected age was calculated by subtracting the difference between gestational age at birth and 38 weeks from the chronological age. The NICU study group was comprised of 32 infants born between 28 to 41 weeks gestation (mean = 33.9; SD 3.5 wks.) with a mean corrected age at ABR testing of 5.7 weeks (SD = 2.7) ranging from 0.9 to 13 weeks.

The demographics and risk factors for the two groups are provided in Table I. In contrast to the WBN group that had a 20% prevalence of risk factors (primarily family history), ninety-six percent of the NICU infants had at least 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 prior to 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 due to re-scheduling or illness. Preparation instructions were sent out prior to 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 measured with the same hardware using procedures described in (Hunter et al., 2016; 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 ECoG and ABR waveforms. Recording details are provided in (Elsayed et al., 2015) and are summarized below. The recording montage used three disposable pre-gelled electrodes placed at the high middle forehead (+), the ipsilateral mastoid (–) and the contralateral mastoid (ground). The inter-electrode impedance was maintained at less than 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 μs) were presented at a rate of 37.1 per second to the test ear through an insert earphone. Click stimuli were delivered at 70 dB nHL, referenced to 38 dB peSPL (peak equivalent SPL) 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 per second. 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 employed 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, condensation and alternating averages separately, which enabled the comparison of polarities and the ability to correlate waveforms for reliability measures. After 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. Rarefaction and condensation waveforms were subtracted to determine when the residual noise was flat relative to the averaged waveform (below 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 fourteen ears (10 NICU and 4 WBN) were excluded due to low waveform cross-correlation values (< 0.60) and an additional four ears were excluded due to 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 prior to 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 seconds per stimulus pair per trial. The measurement accuracy was set to “accurate” on the Vivosonic device so that the DPOAE signal was required to be stable for 0.4 seconds within ± 1 dB from its median SPL. DPOAEs were included only if data for at least the five highest frequencies were obtained. The 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, 2017) at 3 of 5 DPOAE f_2 test frequencies (2, 3, 4, 5.5, 8 kHz; (Blankenship, 2017). Nine ears did not meet the DPOAE pass criteria (6 WBN and 3 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-rarefaction tracing (bottom). ABR Waves I, III, and V and SP amplitudes and latencies were measured using the alternating polarity ABR waveform (Fig. 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), pg. 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 pre-stimulus baseline of 1 to 2 ms (Ge and Shea Jr, 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 (Fig. 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 (Fig. 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 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 ms,

while the later reversals in the waveforms up to about 1 ms were CM components, since 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 II. All variables, with the exception of Wave V amplitude, failed the test of normality as assessed by Shapiro-Wilk's test ($p < .05$). 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 below. 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 to the NICU group ($p = 0.353$). However, NICU infants had a significantly lower number of equivalent sweeps ($p = <0.001$) and total number of sweeps ($p = 0.002$) compared to 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 due to conflicting test results were examined relative to the normative ECoChG and ABR ranges. The test battery approach was used in these cases to diagnose type of hearing loss.

Auditory Neuropathy Case Study—The following case describes history, newborn screening and audiologic test results obtained at 3 and 8 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 weeks 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 older brother with G6PD and auditory neuropathy diagnosed at birth that improved over time. His older brother now has normal hearing and normal ABR results. Prior to discharge from the NICU, this infant passed the DPOAE screening, however he referred on the automated ABR screening bilaterally.

At approximately 3 months of age, otoscopy, ambient absorbance, DPOAE, acoustic reflex, and diagnostic ABR tests were completed (See Figures 2 and 3). Otoscopy showed ear canals were patent and clear of debris. Figure 2A displays ambient absorbance results plotted over normative values (model mean estimated 95 percent confidence intervals obtained from normal infants; Hunter et al., 2015). Absorbance was below the normal range from 0.25 to 2 kHz in the right ear and decreased in the left ear below 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, 2017) and cut-off values for diagnosis of infants with hearing loss reported by Blankenship, 2017. The cut-off values shown in Figure 2B provide balanced sensitivity and specificity (as the cut-off value for DPOAE signal level is that level closest to the point of symmetry of the receiver-operator characteristic curve, and similarly for the cut-off value of SNR) for detection of hearing loss of 30 dB HL or greater. Right ear DPOAE amplitudes met or exceeded the cut-off 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 due to abnormally low wideband absorbance from .25 to 2 kHz (Panel A). In the left ear, the DPOAE responses displayed low amplitude from 1–3 kHz with normal DPOAE signal levels and SNR obtained from 4–8 kHz. The SNR was above the cut-off criteria in the left ear between 3–8 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 3 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 ms), offset (1.96 and 1.91 ms), and total duration (1.82 and 1.49 ms). Comparison to the 5th to 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 μ V in the left and right ears, respectively, both of which are within the 5th to 95th percentile obtained from NICU infants.

ABRs were also recorded to click stimuli at 80 and 90 dB nHL (right ear) and 99 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 8 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 below 0.5 and above 4 kHz. The gray fill pattern of normative responses in Figure 4A represents a different baseline compared to 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. While 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., 2016; Keefe et al., 2016) in patients with AN. Figure 4B displays DPOAE signal level and SNR values plotted over infant normative data (Hunter, 2017) and symmetry cut-off values reported by Blankenship et al. (2017). DPOAE signal levels for both the left and right ear were below the symmetry cut-off values at all frequencies tested and were markedly decreased relative to the 3 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 due to 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 8 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, and V) with the CM present bilaterally. Thus, no improvement in the click response was found compared to the ABR at 3 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 ms), offset (1.28 and 1.15 ms), and total duration (1.02 and 0.99 ms). Upon comparison to the 5th to 95th percentiles obtained from NICU infants, only the CM onset in the right ear was outside of the normal range. When compared to the 3 month ABR results, the CM onset increased by 0.12 ms in the left ear and decreased by 0.26 ms in the right ear. The CM offset and total duration decreased by 0.68 and 0.8 ms in the left ear and decreased by 0.76 and 0.5 ms in the right ear. The CM amplitude was 0.40 and 0.50 μ V in the left and right ear respectively, both of which are at the upper range of the 5th to 95th percentile obtained from NICU infants. Compared to the 3 month ABR results, the CM amplitude increased from 0.2 to .4 μ V in the left ear and increased from 0.14 to .50 μ V 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 displayed) displayed abnormal waveform morphology for the patient's age. At supra-thresholds 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, while screening ABR was absent. The CM recordings were clearly present on multiple ABRs, while 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 since outer hair cells are often affected by that condition.

Sensorineural Hearing Loss Case Study—The following case study/report describes pertinent case history and audiologic test results obtained at 1 month of age from an infant that was diagnosed 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 1 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 below 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 the majority of test frequencies. DPOAEs based on signal level and SNR were only present at 4 and 5.5 kHz. In the left ear, DPOAE responses displayed low or absent amplitude from 1–8 kHz and acceptable SNR only at 5.5 kHz.

Figure 7 displays ABR waveforms from the infant with SNHL at 1 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 supra-threshold 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 ms, respectively, for the left ear, and 2.66, 4.85, and 6.62 ms, 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 to WBN infants. With regard to ABR amplitude, Wave I (0.14 and 0.011 μ V), Wave V (0.14 and .019 μ V), and the Wave V/I ratio (1.0 and 1.73 μ V) for the left and right ear respectively, were all

within the 5th to 95th percentile obtained in WBN infants. In addition, the left and right ear CM onset (0.37 and 0.37 ms), offset (1.46 and 1.65 ms), and total duration (1.09 and 1.28 ms) were all within the 5th to 95th percentile obtained in NICU infants. The CM amplitude (0.13 and 0.14 μ V) 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 difference 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 sensorineural hearing loss.

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 to 97/s) showed higher amplitude SP compared to slower rates (7–19/s), using a filter setting similar to the present study (3–3000 Hz). The rate in the present study was intermediate, at 37/s, due to 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/s 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 tonebursts 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 under 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

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 ($4.11 \mu\text{V} \pm 0.57 \mu\text{V}$) reported for a group of 1–7 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 extra-tympanic, non-invasive electrode to obtain recordings, while Santarelli et al. (2008) recorded SP amplitudes with trans-tympanic ECoG. Trans-tympanic ECoG 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 non-invasive measure is more suitable because it is more comfortable for the infant and does not require sedation. Non-invasive extra-tympanic ECoG 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 to mastoid or nape of neck electrodes (Ferraro and City, 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 criteria, and did not average to a set number of sweeps, but to what was needed in order 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. Since a non-invasive 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 due to 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 uncanceled CM. The SP often appears as a small shoulder or deflection immediately prior to 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 since the mechanisms for OAEs and CMs differ. Thus, examination of specific normative ranges for CM are important in

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 3 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. Additionally, the recording techniques, in particular, the use of extra-tympanic surface electrodes and the moderate intensity stimulus level are also specific to these normative ranges. The use of transtympanic electrodes and stimuli such as tonebursts 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). Since 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, ECoG has advantages and disadvantages, but with the use of non-invasive 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. While comparisons of CM, SP and Wave I, III and V are very helpful to evaluate 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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Abbreviations:

ABR	Auditory Brainstem Response
AN	Auditory Neuropathy
CM	Cochlear Microphonic
ECochG	Electrocochleography
NICU	Neonatal Intensive Care Unit
nHL	Normal Hearing Level
OAE	Otoacoustic Emission
SD	Standard Deviation
SNR	Signal-to-Noise Ratio
SNHL	Sensorineural Hearing Loss
SPL	Sound Pressure Level
SP	Summating Potential
WBN	Well-Baby Nursery

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Figure 1.

Auditory brainstem response 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.

Figure 2.

Audiologic test results for a 3 month-old infant diagnosed with bilateral auditory neuropathy (AN). Panel A displays left and right ear ambient absorbance as a function of frequency (0.25 to 8 kHz). The light gray shaded region represents normative range based on the model mean estimated 95 percent 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 1 month of age (Blankenship et al., 2017). DPOAE signal level and SNRs that are above the symmetry cut-off 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).

Figure 3.

Auditory brainstem responses waveforms obtained from a 3 month-old infant with bilateral auditory neuropathy (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).

Figure 4. Audiologic test results for an 8 month-old infant diagnosed with bilateral auditory neuropathy (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 cut-off values, and abbreviations.

Figure 5.

Auditory brainstem responses waveforms obtained from an 8 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.

Figure 6.

Audiologic test results for a 1 month-old infant diagnosed with bilateral sensorineural hearing loss (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 cut-off values, and abbreviations.

Figure 7.

Auditory brainstem responses waveforms obtained from a 1 month-old infant with bilateral sensorineural hearing loss (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).

TABLE I.

Demographics of infants with normal hearing cared for in the WBN and NICU

Variable	Nursery Group	
	WBN	NICU
Gestational Age at Birth (weeks): Mean (SD), Range	38.9 (1.4), 36.0 to 41.0	33.9 (3.5), 28.0 to 41.0
Corrected Age at Test (weeks): Mean (SD), Range	5.0 (2.4), 0.4 to 11.3	5.7 (2.7), 0.9 to 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)

NICU = Neonatal Intensive Care Unit; WBN = Well-Baby Nursery; SD = Standard Deviation; N = Number.

* Percentages add up to more than 100% due to multiple risk factors for some infants.

Table II.

ECoG and ABR descriptive statistics for infants cared for in the WBN and NICU

ECoG and ABR Variables	Nursery Group						NICU						P-value
	WBN												
	N	Mean	SD	Median	5th %	95th %	N	Mean	SD	Median	5th %	95th %	
Recording Parameter													
# of Sweeps	53	2673	1095	2256	1656	5170	59	2230	1071	1840	1040	5632	0.002
NEQ	53	2038	524	2019	1530	3436	59	1562	599	1535	797	2594	<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