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Effects of Hypoxic-Ischemic Encephalopathy and Whole-Body Hypothermia on Neonatal Auditory Function: A Pilot Study

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Abstract

We assessed the effects of hypoxic-ischemic encephalopathy (HIE) and whole-body hypothermia therapy on auditory brain stem evoked responses (ABRs) and distortion product otoacoustic emissions (DPOAEs). We performed serial assessments of ABRs and DPOAEs in newborns with moderate or severe HIE, randomized to hypothermia ($n = 4$) or usual care ($n = 5$). Participants were five boys and four girls with mean gestational age (standard deviation) of 38.9 (1.8) weeks. During the first week of life, peripheral auditory function, as measured by the DPOAEs, was disrupted in all nine subjects. ABRs were delayed but central transmission was intact, suggesting a peripheral rather than a central neural insult. By 3 weeks of age, peripheral auditory function normalized. Hypothermia temporarily prolonged the ABR, more so for waves generated higher in the brain stem but the effects reversed quickly on rewarming. Neonatal audiometric testing is feasible, noninvasive, and capable of enhancing our understanding of the effects of HIE and hypothermia on auditory function.

Keywords

Hypoxia-ischemia; hypothermia; auditory evoked potentials; otoacoustic emissions

Mild to moderate oxygen deprivation at birth temporarily depresses auditory function. More severe respiratory compromise associated with hypoxic-ischemic encephalopathy (HIE), prolonged ventilation, and persistent pulmonary hypertension increases the risk of a permanent hearing loss.¹ A severe hypoxic-ischemic episode can cause cochlear damage and retrocochlear neuronal lesions although isolated cochlear impairment is rare.^{2,3}

Progressive hearing losses as well as recovery of auditory function have been reported following severe respiratory compromise,^{4–6} suggesting that rescue therapies might be of benefit during a labile period after the primary insult. Balkany et al have reported improved immediate and long-term auditory function in rats cooled to ameliorate the loss of function associated with cochlear implant insertion trauma.⁷ Selective head cooling and whole-body

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cooling are promising interventions that may reduce the high rates of mortality and neurodevelopmental morbidity associated with neonatal encephalopathy.^{8–10} In the largest published whole-body hypothermia trial, asphyxiated newborns randomized to hypothermia had an 18% absolute reduction in death or moderate/severe disability at 18 to 22 months of age as compared with controls.⁸

The effects of hypothermia on the auditory system have been studied in humans undergoing cooling for heart surgery. Lowering the core body temperature prolongs auditory brain stem evoked responses (ABRs), more so for the more rostrally generated waves.^{11–15} ABR and otoacoustic emission (OAE) amplitudes decrease and ultimately disappear with a lowering of temperature.^{16,17} Cooling may also decrease middle ear compliance.¹⁸ In heart patients, ABRs and OAEs return to normal upon rewarming.

The etiology and development of hearing loss in human newborns with HIE are not well understood. It is also unclear whether the promise of hypothermia therapy in reducing death and moderate or severe disability extends to the auditory system. Although recent multi-center hypothermia trials assessed hearing outcomes upon follow-up, they were not designed to provide detailed information concerning auditory function in the immediate postnatal period when the HIE newborn is presumably vulnerable but responsive to therapy. We report preliminary results on the auditory function of a small group of HIE newborns participating in the largest published multicenter trial evaluating whole-body hypothermia as a rescue therapy.⁸

Methods

Participants

All infants from Children's Memorial Hermann Hospital and Lyndon B. Johnson Hospital in Houston, Texas who participated in the National Institutes of Child Health and Human Development Neonatal Research Network whole-body hypothermia trial were screened and eligible for inclusion in this study.⁸ All of the following criteria were required for enrollment in the hypothermia trial: gestational age ≥ 36 weeks; need for resuscitation at birth secondary to poor respiratory effort or a diagnosis of encephalopathy; signs of perinatal asphyxia, defined by severe acute intrapartum acidosis, or in the absence of blood gases, a history of an acute perinatal event and an Apgar score at 10 minutes of ≤ 5 or need for assisted ventilation at birth. In addition, to be eligible, infants required evidence of moderate or severe encephalopathy on a standardized modified neurological exam.

The protocol was approved by the University of Texas Health Science Center Committee for the Protection of Human Subjects. Parents of 9 of 21 eligible study infants provided written informed consent and participated in this substudy. Five were in the control arm of the trial (usual care), and four were in the cooling arm. The four infants in the cooling arm were systemically cooled to a core body temperature of 33.5°C within 6 hours of birth using a cooling blanket (Blanketrol II Hyper-Hypothermia System, Cincinnati Sub-Zero, Cincinnati, Ohio). Hypothermia was maintained for 72 hours at this temperature, followed by gradual rewarming over a 6-hour period (0.5°C per hour) until the core temperature reached 36.5°C . Core temperature was monitored by an esophageal probe and skin temperature by an abdominal probe.

Procedures

The instrumentation used to record the distortion product otoacoustic emissions (DPOAEs) and the ABR recordings is described elsewhere.¹⁹ The software programs for generating the DPOAEs were EMAN (Neely and Liu, Omaha, NE) and CUBeDISP™ (Etymotic Research,

Elk Grove Village, IL), modified to add capabilities including artifact rejection and response detection. Custom software generated the ABR stimuli (100- μ s rarefaction clicks) and recorded the responses. The recorded electroencephalograph (EEG) was amplified 100,000 times and band-pass filtered with a P511K A.C. preamplifier (Astro-Med, West Warwick, RI) with the 3-dB cutoffs at 100 Hz and 3 kHz.

Newborn testing was conducted at the bedside at both study sites. Auditory testing was conducted after scheduled testing for the parent protocol if the infant's medical condition permitted and test equipment was available. Prior to the DPOAE and ABR evaluations, otoscopy was performed to ensure an unobstructed ear canal and drum with no obvious signs of pathology. All surviving infants were evaluated at 18 to 30 months of age. Data on vision and audiometric outcomes (ABRs) were obtained, and standardized neurological and developmental testing was performed by trained examiners masked to intervention status.⁸

After positioning the DPOAE probe in the external ear canal and achieving a good fit, DPOAEs were generated by simultaneously presenting two sinusoids differing in frequency (the lower frequency primary is f_1 and the higher-frequency primary is f_2) and recording the sound pressure in the sealed ear canal. DPOAEs were recorded to a range of stimulus frequencies ($f_2/f_1 = 1.2$; $f_2s =$ from 1.1 to 11.4 kHz) presented at 65 dB sound pressure level (SPL) at the measurement plane of the probe microphone. Each stimulus pair was presented for a total of 4096 artifact-free milliseconds. A fast Fourier transform was calculated on the time-averaged response and the amplitudes of the distortion product ($2f_1 - f_2$) and noise (estimated by the mean amplitude of the three lower- and higher-frequency bins adjacent to the distortion product) were measured.

A DPOAE was considered a response and not noise if it exceeded the noise level by 10 dB or more. DPOAE thresholds at select frequencies were evaluated if there was a response at those frequencies with stimulus levels = 65 dB SPL. The threshold determination procedure used is described elsewhere.²⁰ Replicate responses were recorded to each stimulus level presented. DPOAE thresholds were defined by the lowest level L1 primary associated with DPOAE "responses" from both replicates.

The ABR was recorded after scheduled amplitude EEG testing conducted as part of the parent protocol. Only the ear easiest to access at the time of the first recording was tested because of the challenging recording conditions and limited recording time. The contralateral C3 or C4 electrode was used as the noninverting electrode with ipsilateral A2 or A1 as the inverting electrode. The ground electrode was Fz. Impedances were measured before and after testing and were ≤ 5 k Ω .

Stimuli were 100- μ s clicks presented at three different stimulus rates, two conventional (constant interstimulus intervals) rate stimuli (10.01/s and 30.20/s) and a maximum length sequence (MLS). The MLS consisted of 256 clicks presented at pseudorandomly varying interclick intervals (half were separated by 2.2 ms with the remaining 128 clicks separated by integer multiples of 2.2 ms). The responses to 1500 clicks for the conventional stimuli and 75 MLSs (256 clicks/MLS \times 75 sequences = 19,200 clicks) were averaged to improve the signal to noise ratio.

The clicks for all three stimuli were presented at 90 dB peak equivalent sound pressure level (peSPL). Replicate responses were recorded to each stimulus. If reproducible responses were not recorded at 90 dB peSPL, the level of the stimuli was incremented by 10 dB to a maximum of 110 dB peSPL. If the responses replicated, the two replicates were averaged for the final scoring. The latencies and amplitudes of waves I, III, and V were scored. Those waves are the most robust of the ABR waves.

Only the recorded responses to the 10.01/s stimuli are presented because the results were similar for all stimulus rates presented and because normative data were available for the 10.01/s results. Using Gorga et al's normative data,²¹ z-scores were calculated for wave I, III, and V latencies and the I–V (III–V) interwave latency interval. The z-scores were used to estimate the probabilities that the recorded ABRs were from Gorga et al's normative distributions (a one-tailed test, $\alpha = 0.025$). Adjustments were made for rate and level differences between the recorded data and Gorga et al's norms.

Results

Table 1 provides baseline characteristics for our nine study subjects. Five newborns were randomized to usual care and four to hypothermia therapy. The two groups were comparable in gestational age, sex, Apgar scores, cord pH, and severity of encephalopathy.

DPOAE

Table 2 summarizes the DPOAE results in the newborn period. At an age when almost all newborns have robust DPOAEs, DPOAEs could not be reliably recorded at all frequencies from any of these newborns. The specificity of screening DPOAEs in the newborn period is 0.90 or better.²² Thus, the probability all nine study newborns were tested as false-positives is very small $(1.00 - 0.90)^9 = 0.000000001$. None of the study infants had outer ear canal or eardrum obstructions/pathology by otoscopy to account for these results.

Two of the study newborns (cases 4 and 6) had reliable DPOAEs recorded at a few frequencies in the first week after birth. The reliable DPOAEs (signal-to-noise ratios > 10 dB) were recorded at high frequencies ($f_2 = 6.4$ kHz for case 4 and $f_{2s} = 7.5, 8.6,$ and 9.9 kHz for case 6). They were of considerably lower amplitude than the DPOAEs recorded at those frequencies from those same newborns several weeks later. Both recordings were conducted after cooling and during or shortly after rewarming. No other study newborns had reliable DPOAEs in the first week after birth.

For three of the study newborns, additional auditory testing was conducted more than 3 weeks after birth but before hospital discharge (bold text in Table 2). Despite failing to produce DPOAEs shortly after birth, more than 3 weeks later reliable DPOAEs were recorded (Fig. 1). The emissions in the midrange of the assessed frequencies were of relatively low amplitude. The meaning of these low-amplitude, midfrequency emissions is unclear, although Jiang et al have also reported that low-amplitude and missing emissions were more likely at midfrequencies (1 to 5 kHz in their sample) in newborns after perinatal HIE.²³ Threshold DPOAEs were also assessed for these three infants when reliable DPOAEs were recorded. They were within normal limits for infants of their ages. Case 6's midfrequency DPOAE thresholds were slightly elevated relative to those of the other two infants (especially at 4 kHz) but still consistent with “normal” cochlear function.

ABR

ABRs were recorded in the first 8 days after birth from all but one of the study newborns (see Table 3). However, the null hypothesis that the recorded waveforms belonged to Gorga et al's normative sample was rejected for the ABR waves I ($p = 0.0168$), III ($p = 0.0089$), and V ($p = 0.0091$) recorded right after birth by Wilcoxon signed-rank test with continuity correction (absent measurements were assigned the probability associated with the longest latency wave recorded assuming that an absent response should be scored as less likely than any recorded response).

In contrast, the V-I interwave latency interval for the study sample did not significantly differ from Gorga et al's normative values ($p = 0.1422$). The V-III latency interval results also indicate that brain stem transmission times did not differ in the study infants from the normative values ($p = 0.4469$ by the Wilcoxon signed-rank test). The cases that had no recorded waves were dropped from these analyses.

Four study infants were tested at least 3 weeks after birth (bold text of Table 3). HIE newborn ABRs within the first 8 days after birth tended to be prolonged or absent compared with those from a normative sample of infants of similar gestational age. By 3 weeks of age those differences in ABR waves were attenuated.

One of the hypothermia-treated newborns (case 6) had ABR recordings (1) 2 hours after the onset of therapy (esophageal temperature = 33.4°C), (2) after 26 hours of hypothermia therapy (esophageal temperature = 33.4°C), (3) 15 minutes after completing rewarming from hypothermia (esophageal temperature = 36.2°C recorded 4 hours before terminating rewarming), and (4) 3 weeks after birth. Figure 2 presents the ABRs of this infant to the 100 dB peSPL 10.01/s stimuli at these four times. The vertical lines on the figures indicate the latencies of the three prominent waves (I, III, and V) from the first recording just after beginning hypothermia.

Between the first and second recording 24 hours later, the latencies of all three waves increased slightly. Recovery from birth and normal development over this time interval have been associated with a reduction in ABR latencies.²⁴ The recorded latency increase seemed to be more pronounced for waves III and V (higher in the auditory pathway) than wave I (the auditory nerve is the generator for wave I). Right after rewarming, there was a reduction in wave III and V latencies compared with the first recording. Three weeks after birth, wave III and V latencies had decreased further with little change in wave I latency.

Outcomes at 18 to 30 Months

Of the four HIE newborns undergoing hypothermia therapy in the study sample, all had depressed auditory function shortly after birth, one infant died in the newborn period, and the other three recovered auditory function to have normal hearing at 18 to 30 months of age. Of the three survivors, one had normal neuromotor and Bayley examinations (mental development index [MDI] = 97 and psychomotor development index [PDI] = 95) at 18 to 30 months, one was moderately delayed on the Bayley MDI (77) but otherwise was normal (normal neuromotor exam and a Bayley PDI = 99), and one had a profound motor impairment (abnormal neuromotor exam and a Bayley PDI < 50 and a Bayley MDI = 81). All surviving hypothermia-treated newborns had normal vision at 18 to 30 months.

Of the five control HIE newborns not receiving hypothermia therapy, all had depressed auditory function shortly after birth, one died, one was hearing impaired, and three had normal hearing at 18 to 30 months. Of the four surviving controls, one had low Bayley scores (79 on both the MDI and PDI) with a normal neuromotor exam. A second control had a delayed Bayley PDI (66) and abnormal neuromotor exam with less obvious cognitive delay (Bayley MDI = 79). The other two surviving controls were considered unscorable on the Bayley, receiving MDI and PDI scores < 50. They also had abnormal neuromotor exams. All surviving controls had normal vision at 18 to 30 months.

Discussion

This study confirms that auditory function is transiently disrupted in almost all newborns with moderate to severe HIE. Outer hair cells as assessed by DPOAEs were a site of insult, although middle ear involvement could not be ruled out. Rebillard et al have demonstrated that DPOAEs

are temporarily suppressed by inducing hypoxia.²⁵ Jiang et al reported reduced or absent DPOAEs (especially at 1 to 5 kHz) in term newborns after perinatal hypoxia-ischemia.²³

The ABR waveform was delayed, although the interwave intervals were normal. These results suggest a cochlear insult that spared the auditory brain stem pathway. Normal brain stem transmission was unexpected given the results of ABR studies by Jiang et al and postmortem histopathologic studies.^{3,25,26} The effects Jiang et al recorded increased by day 3 after birth and then recovered (faster for wave I than wave V) with subtle deficits remaining at 1 month. The persisting deficits they observed were small and may have been too subtle to detect with our small sample size.

Newborns with severe HIE are at a significantly increased risk for sensorineural hearing loss. The incidence of significant bilateral hearing loss is ~2 to 4 per 1000 newborn infants.²⁷ In our small sample of nine HIE newborns, even the one infant confirmed with sensorineural hearing impairment is consistent with prior literature suggesting that these newborns are at increased risk for permanent hearing loss. However, our results and those reported by Jiang and colleagues do not address the few severe HIE newborns who do develop permanent hearing loss. The effect of the severity of HIE, the loss of auditory function, the recovery from that loss, and the persistence of deficits in a small proportion of HIE newborns are not well understood.

The neonatal effects of hypothermia on DPOAEs or ABRs in HIE newborns have not been reported previously. The effects of hypothermia on ABRs of HIE newborns we reported are comparable to those of cardiovascular patients cooled for heart surgery.^{11–15} Cooling prolonged the latency of the ABR. The prolongation was more pronounced for waves III and V (higher in the auditory pathway) than wave I. Rewarming reversed those effects. In rats, hypothermia reduced abnormalities in the auditory system associated with a severe perinatal ischemic episode.²⁸ The only newborns in our study who had reliable DPOAEs during the first 8 days after birth were newborns cooled and then rewarmed. However, those DPOAEs were reduced in amplitude and restricted to the higher frequencies tested. These trends suggest that cooling may hasten recovery from the transient deficits associated with HIE.

The protective effects of hypothermia on auditory function have not been studied in detail. The methodologies used in this study are well suited to doing so. They represent a noninvasive and relatively inexpensive complement to future trials with a substantial return in understanding and improving auditory function in HIE newborns.

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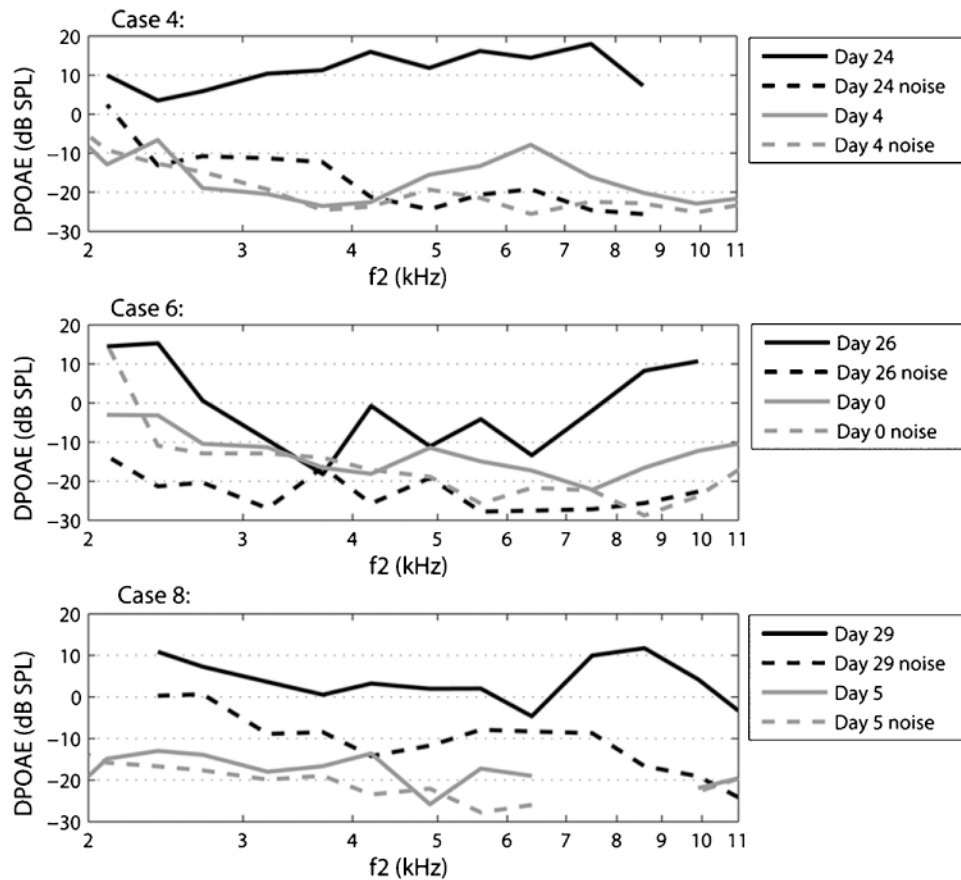


Figure 1. Distortion product otoacoustic emission (DPOAE) waveforms in three study newborns (cases 4, 6, and 8) tested within the first week and repeated more than 3 weeks after birth. Despite failing to produce DPOAEs shortly after birth, all three study newborns tested after 3 weeks had reliable DPOAEs. All cases demonstrated high amplitudes at the lowest and highest frequency ranges. The emissions in the midrange of the assessed frequencies for cases 6 and 8 were of relatively low amplitude.

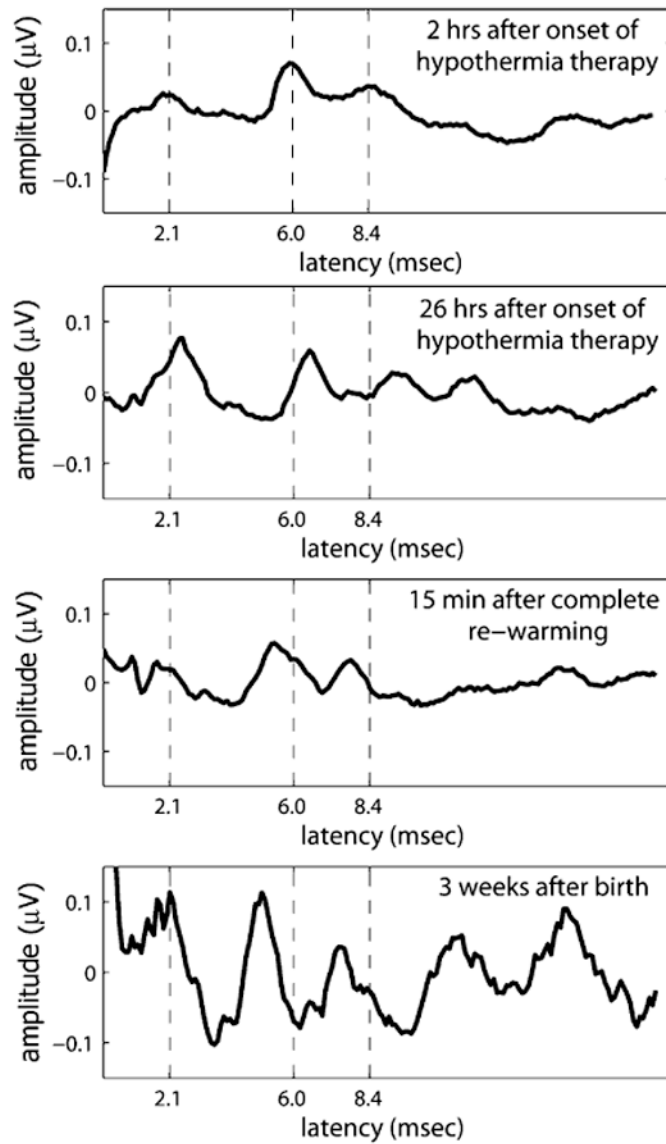


Figure 2.

Serial brain stem evoked response (ABR) recordings from a subject (case 6) during and following hypothermia therapy. The dashed vertical lines indicate the latencies of the three prominent waves (I, III, and V) from the first recording 2 hours after the onset of hypothermia therapy. Following 26 hours of hypothermia, the latencies increased slightly. Immediately following complete rewarming, there was a reduction in waves III and V latencies as compared with the first recording. The ABR latencies 3 weeks later suggest a further decrement in wave III and V latencies with little additional change in wave I latency.

Table 1

Baseline Characteristics

Patient	Hypothermia Therapy	Gestational Age (wk)	Birth Weight (g)	Sex	Apgar Scores	Cord pH	Sarnat Stage
Case 1	No	39	2035	F	1/1/3	6.83	Moderate
Case 2	No	40	3950	M	1/1/3	6.65	Severe
Case 5	No	37	2190	M	1/1/6	6.76	Moderate
Case 7	No	41	3470	M	2/4	6.63	Severe
Case 8	No	41	4885	F	2/5/7	6.63	Moderate
Case 3	Yes	37	2775	M	0/0/0	6.71	Severe
Case 4	Yes	40	3850	F	0/2/3	6.57	Moderate
Case 6	Yes	36	2910	M	2/2/4	6.98	Moderate
Case 9	Yes	39	3100	F	Unknown*	6.97	Severe

* Patient was born at an outside facility and no Apgar score was given by the provider.

Table 2
DPOAE Responses in the First 8 Days (A) and > 21 Days after Birth (B)

Patient	Hypothermia	Age (d)	Results
Case 1A	No	5	No response
Case 2A	No	4	No response
Case 5A	No	0, 8	No response
Case 7A	No	5	No response
Case 8A	No	5	No response
Case 8B	No	29	Normal
Case 3A	Yes	8	No response
Case 4A	Yes	3, 4	Limited response *
Case 4B	Yes	24	Normal
Case 6A	Yes	0, 2	Limited response †
Case 6B	Yes	26	Normal
Case 9A	Yes	4	No response

For three infants (shown in bold), additional auditory testing was conducted more than 3 weeks after birth but before hospital discharge. DPOAE, distortion product otoacoustic emission; SNR, signal-to-noise ratio; SPL, sound pressure level.

* For this newborn, at 4 days of age there was one DPOAE with a SNR > 10 ($f_2 = 6.4$ kHz, DPOAE = -7.84971 dB SPL, SNR = 17.701689 dB).

† For this newborn, at 2 days of age there were three DPOAEs with SNRs > 10 dB ($f_2 = 7.5, 8.6,$ and 9.9 kHz; DPOAEs = $4.3425698, -1.55086,$ and -7.3124399 dB SPL respectively; SNRs = $25.6857708, 21.66464,$ and 16.4055601 dB, respectively).

Table 3

ABRs in the First 8 Days (A) and > 21 Days after Birth (B)

Patient	Hypothermia	Age (d)	Wave I	Wave III	Wave V*	V-I interval	V-III interval
Case 1A	No	5	Absent	Delayed [‡]	Delayed	Missing	Normal
Case 2A	No	4.5 [‡]	Delayed	Delayed	Delayed	Normal	Normal
Case 5A	No	0.8	Absent	Delayed	Delayed	Prolonged	Prolonged
Case 7A	No	5	Delayed	Absent	Absent	Missing	Missing
Case 8A	No	5	Normal	Delayed	Delayed	Normal	Normal
Case 8B	No	29	Normal	Normal	Normal	Normal	Normal
Case 3A	Yes	8	Delayed	Delayed	Delayed	Normal	Normal
Case 4A	Yes	3.5	Delayed	Delayed	Delayed	Normal	Normal
Case 4B	Yes	24	Delayed	Delayed	Delayed	Normal	Normal
Case 6A	Yes	0, 1, 2	Normal	Normal	Normal	Prolonged	Normal
Case 6B	Yes	28	Normal	Normal	Normal	Normal	Normal
Case 9A	Yes	4	Absent	Absent	Absent	Missing	Missing
Case 9B	Yes	54	Delayed	Normal	Normal	Normal	Normal

For four infants (shown in bold), additional testing was conducted more than 3 weeks after birth but before hospital discharge. ABR, auditory brain stem evoked response.

* Wave V estimated by longest latency wave V in the sample.

[‡] Delayed and prolonged were defined by Z-scores indicating a long latency response unlikely ($p < 0.025$ by a one-tailed test) to be from Gorga's normative sample.

[‡] If newborns were evaluated on several occasions during the first 8 days, the last recorded, most mature responses were reported.