

Auditory Brainstem Response in Term and Preterm Infants with Neonatal Complications: The Importance of the Sequential Evaluation

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Abstract

Introduction Literature data are not conclusive as to the influence of neonatal complications in the maturational process of the auditory system observed by auditory brainstem response (ABR) in infants at term and preterm.

Objectives Check the real influence of the neonatal complications in infants by the sequential auditory evaluation.

Methods Historical cohort study in a tertiary referral center. A total of 114 neonates met inclusion criteria: treatment at the Universal Neonatal Hearing Screening Program of the local hospital; at least one risk indicator for hearing loss; presence in both evaluations (the first one after hospital discharge from the neonatal unit and the second one at 6 months old); all latencies in ABR and transient otoacoustic emissions present in both ears.

Results The complications that most influenced the ABR findings were Apgar scores less than 6 at 5 minutes, gestational age, intensive care unit stay, peri-intraventricular hemorrhage, and mechanical ventilation.

Conclusion Sequential auditory evaluation is necessary in premature and term newborns with risk indicators for hearing loss to correctly identify injuries in the auditory pathway.

Keywords

- ▶ neonatology
- ▶ evoked potentials
- ▶ auditory brainstem

Introduction

Neonatal hearing screening in newborns with complications should be performed using the evoked otoacoustic emissions (OAE) and auditory brainstem response (ABR) because they are complementary tools and together provide a complete evaluation of the auditory system.^{1,2} The ABR test is a noninvasive neurophysiologic assessment of brainstem maturation in babies and could be a useful electrophysiologic test to verify neuronal myelination in preterm infants.³

Furthermore, the ABR has shown fewer false-positives and lower referral rates compared with OAE, is less sensitive to

noise and middle ear disorders even in very premature infants, and is an essential tool in the diagnosis of hearing loss in the pediatric population.^{4–7}

The ABR in neonates may have a high variability of response. The frequently observed prolonged latencies can be considered normal due to the characteristics of the maturation process of the auditory system, explained by the hypothesis that the structures that generate the ABR core components take more time to completely mature.^{8–10} Therefore, the literature remains unclear whether these changes in the ABR responses would be permanent, thus indicating hearing loss, or whether they could be normalized with increasing age.^{11–14}

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According to Kohelet et al,¹⁵ the ABR response in full-term and preterm newborns of the same chronological age was similar, regardless of gestational age. Nevertheless, Sleifer et al observed that absolute and interpeak latencies were statistically different between 4-month-olds and 12-month-olds.¹⁶ At 20 months, only wave I was similar. The authors concluded that the maturation of the auditory pathway occurs in a different way between full-term and preterm newborns, and that gestational age must be considered in the ABR analysis, mainly in infants younger than 20 months. In a recent study, Roopakala et al compared the ABR results in 25 preterm and 25 full-term infants and observed a significant increased latency of ABR waveform V in preterm infants.³

However, the ABR response in full-term and preterm newborns may be impacted by neonatal complications that are considered of risk for hearing loss and, consequently, may delay the maturation process.¹⁷ Most of the studies show the influence of neonatal complications that are considered of risk for hearing loss in the ABR results. Some authors reported that neonates with transient low Apgar scores had a significant increase in I to V interval at very high click rates in the first 3 days of life.¹¹ In another study, very low-birth-weight infants had prolonged interpeak III to V.¹² The ABR in extremely preterm infants with bronchopulmonary dysplasia showed a significant increase in wave V and interpeak intervals I to V and particularly III to V.¹³ Extremely low birth weight and mechanical ventilation may, as well, cause abnormal ABR.¹⁴

The question is whether these ABR findings will be recovered with increasing age or neurodevelopment. The objective of this study was to understand the real influence of neonatal complications considered of risk for hearing loss, in infants, using the sequential ABR evaluation.

Methods

Study Population

This historical cohort study was conducted in a tertiary referral center from October 2008 to October 2010. The inclusion criteria were: treatment at the Universal Neonatal Hearing Screening Program of the local hospital; at least one risk indicator for hearing loss according to the Joint Committee on Infant Hearing¹⁸; presence in both evaluations (the first upon neonatal unit discharge, and the second at 6 months of age); all the ABR latencies; transient otoacoustic emissions confirmed in both ears; consent form signed by the newborn's parents or guardians.

For comparison, gestational age was divided into three categories: term ≥ 37 weeks, premature between 31 and 36 weeks, and extremely premature < 31 weeks.

Audiological Assessment

For the ABR analysis, the rarefaction click stimulus was presented by the 3 Ω insertion phone, with intensity of 80-dB nHL (normal Hearing Level) and a presentation rate of 20.1 c/s (clicks/seconds) with a bandpass filter of 100 and 3,000 Hz and average of 1,024 stimuli on Interacoustics EP15

Eclipse (Interacoustics A/S, Assens, Denmark). Duplicate recordings were made in response to each stimulus condition to examine reproducibility. The ABR was captured through electrocardiogram disposable electrodes (Neuroline, Ambu A/S, Balthorpakken, Denmark), after cleaning the skin with electrocardiogram/electroencephalograph abrasive gel (NUPREP, Weaver and Company, Aurora, USA). The impedance level was kept between 1 and 3 k Ω for the electrodes; the active electrode was positioned in F_z, the reference electrode in M₁ and M₂, and the ground electrode in F_{pz}. No sedatives were used.

Variable and Statistical Analyses

Predictor variables included gender, gestational age, birth weight $< 1,500$ g, low Apgar score, infection, intensive care unit (ICU) stay, hyperbilirubinemia, peri-intraventricular hemorrhage, use of mechanical ventilation and ototoxic medication. Outcome variables included absolute latencies (I, III, and V) and interpeak latencies (I to III, III to V, and I to V) of the ABR in both ears.

ABR change (in percentage) at 6 months of age (moment 2) was calculated in relation to the ABR performed upon hospital discharge (moment 1) using the following expression: $\text{ABR at 6 months of age} - \text{ABR postdischarge} / \text{ABR postdischarge} \times 0.100\%$.

The relation between risk indicator for hearing loss and variation of ABR were analyzed using Mann-Whitney and Kruskal-Wallis test, followed by Dunn for multiple comparisons of the gestational age. Statistical analysis was performed with SPSS v15 and Graph Pad Prism v5 software (SPSS Inc., Chicago, IL, USA). A *p* value of < 0.05 was accepted as statistically significant.

Ethics

This study was approved by the Research Ethics Committee, process no. 402/08.

Results

A total of 114 newborns, 51 (45%) girls and 63 (55) boys, met the inclusion criteria. Other sample data are shown in ► **Table 1**.

► **Table 2** shows that Apgar score lower than 6 in the first minute, gestational age, and ICU stay best correlated with the variation of the absolute ABR latencies ($p < 0.05$).

► **Table 3** shows that ICU stay, peri-intraventricular hemorrhage, mechanical ventilation, and gestational age showed the best relationship to the interpeak variation ($p < 0.05$).

Discussion

The objective of our cohort study was to verify the real influence of the neonatal complications considered of risk for hearing loss, by analyzing the variation of the ABR parameters between two moments: at hospital discharge and at 6 months of age. This second evaluation moment was chosen based on the need of an early diagnosis of hearing loss and intervention by 6 months of age. Obviously, children

Table 1 Description of the 114 newborn according to gestational age and risk indicators for hearing loss

Variables	n (%)
Gestational age < 31 wk	29 (25%)
Gestational age 32–36 wk	49 (43%)
Gestational age ≥ 37 wk	36 (32%)
Birth weight < 1,500 g: no	79 (69%)
Birth weight < 1,500 g: yes	35 (31%)
Apgar < 4 (1 min): no	59 (52%)
Apgar < 4 (1 min): yes	55 (48%)
Apgar < 6 (5 min): no	94 (82%)
Apgar < 6 (5 min): yes	20 (18%)
Infection: no	71 (62%)
Infection: yes	43 (38%)
Intensive care units: no	38 (33%)
Intensive care units: yes	76 (67%)
Hyperbilirubinemia: no	109 (96%)
Hyperbilirubinemia: yes	05 (4%)
Peri-intraventricular hemorrhage: no	101 (89%)
Peri-intraventricular hemorrhage: yes	13 (11%)
Mechanical ventilation: no	53 (46%)
Mechanical ventilation: yes	61 (54%)
Ototoxic drugs: no	74 (65%)
Ototoxic drugs: yes	40 (35%)

with a history of hearing risk indicators are more likely to have hearing impairment and then require periodic evaluation even if they had an initial normal auditory assessment.^{18,19}

Newborns with risk indicators for hearing loss have some coexistent neonatal complications. However, such complications are not considered by most of the studies, which compare only one risk indicator in healthy babies in only one moment or in the first days of life.

This study intended to show the real influence of risk indicators coexisting with prematurity or not and yet clarify whether the findings in the first evaluation remain abnormal in the second one even with increasing age, considering the present risks. Therefore, in this study, an ABR follow-up was performed in two moments, the first at hospital discharge and the second at 6 months of age, to assess whether these possible alterations are transient or permanent.

Results show that ABR latencies and interpeaks were higher in extremely preterm infants than in full-term newborns, confirming other published results.^{3,16,17} Apparently, this difference decreases with increasing age, possibly due to the maturational process.¹⁶ Sleifer et al reported differences between these children, with very similar results at 24 months of age.¹⁶ Furthermore, Turchetta et al observed an improvement over time of the estimated hearing threshold in ABR follow-up in preterm and full-term newborns.²⁰

In the second assessment, when we analyzed the percentage of changes between these two moments, extremely premature infants showed greater reduction in the absolute latency of wave I in both ears. Despite the statistical significance, this finding has no clinical relevance, because the values are similar to those in older children and healthy adults.^{10,17} This result shows that the peripheral transmission matures faster as compared with subsequent waveforms and the same reasoning cannot be applied to reductions of interpeaks I to III, III to V, and I to V between the two assessments due to improper myelination of auditory pathway and improper efficacy of higher-order neurons in infant population.²¹

Table 2 The *p* values of the relation between the variation of ABR absolute latencies and gestational age as well as risk indicators for hearing loss

Characteristics	Right ear			Left ear		
	I	III	V	I	III	V
Apgar < 6 (5 min): no (<i>n</i> = 94) × yes (<i>n</i> = 20)	0.433	0.016	0.164	0.032	0.006	0.026
GA: <31 wk (<i>n</i> = 29) × 32–36 wk (<i>n</i> = 49) × ≥ 37 wk (<i>n</i> = 36)	0.018 ^a	0.683	0.217	0.043	0.278	0.258
ICU: no (<i>n</i> = 38) × yes (<i>n</i> = 76)	0.320	0.025	0.815	0.134	0.157	0.907
BW < 1,500 g: no (<i>n</i> = 79) × yes (<i>n</i> = 35)	0.110	0.636	0.606	0.054	0.654	0.958
Apgar < 4 (1 min): no (<i>n</i> = 59) × yes (<i>n</i> = 55)	0.814	0.195	0.107	0.187	0.171	0.053
Infection: no (<i>n</i> = 71) × yes (<i>n</i> = 43)	0.255	0.338	0.309	0.684	0.312	0.205
Hyperbilirubinemia: no (<i>n</i> = 109) × yes (<i>n</i> = 5)	0.841	0.668	0.447	0.140	0.175	0.533
PIVH: no (<i>n</i> = 101) × yes (<i>n</i> = 13)	0.107	0.206	0.380	0.083	0.820	0.199
MV: no (<i>n</i> = 53) × yes (<i>n</i> = 61)	0.084	0.154	0.360	0.201	0.666	0.189
Ototoxic drugs: no (<i>n</i> = 74) × yes (<i>n</i> = 40)	0.764	0.960	0.204	0.667	0.838	0.268
Sex: F (<i>n</i> = 51) × M (<i>n</i> = 63)	0.468	0.346	0.174	0.934	0.401	0.130

Abbreviations: ABR, auditory brainstem response; BW, birth weight; GA, gestational age; ICU, intensive care unit; MV, mechanical ventilation; PIVH, peri-intraventricular hemorrhage.

^a < 31 ≠ ≥ 37 (Dunn test for multiple comparisons).

Table 3 The *p* values of the relation between the variation of ABR interpeaks and gestational age as well as risk indicators for hearing loss

Characteristics	Right ear			Left ear		
	I-III	III-V	I-V	I-III	III-V	I-V
ICU: no (<i>n</i> = 38) × yes (<i>n</i> = 76)	0.003	0.004	0.907	0.022	0.117	0.514
PIVH: no (<i>n</i> = 101) × yes (<i>n</i> = 13)	0.459	0.077	0.070	0.297	0.028	0.026
MV: no (<i>n</i> = 53) × yes (<i>n</i> = 61)	0.006	0.558	0.079	0.162	0.282	0.041
GA: <31 (<i>n</i> = 29) × 32–36 (<i>n</i> = 49) × ≥ 37 (<i>n</i> = 36)	0.066	0.006 ^a	0.984	0.434	0.307	0.767
BW < 1,500 g: no (<i>n</i> = 79) × yes (<i>n</i> = 35)	0.252	0.324	0.842	0.468	0.580	0.144
Apgar < 4 (1 min): no (<i>n</i> = 59) × yes (<i>n</i> = 55)	0.220	0.203	0.065	0.527	0.226	0.276
Apgar < 6 (5 min): no (<i>n</i> = 94) × yes (<i>n</i> = 20)	0.159	0.890	0.200	0.994	0.127	0.329
Infection: no (<i>n</i> = 71) × yes (<i>n</i> = 43)	0.944	0.309	0.781	0.617	0.420	0.276
Hyperbilirubinemia: no (<i>n</i> = 109) × yes (<i>n</i> = 5)	0.410	0.609	0.171	0.934	0.678	0.552
Ototoxic drugs: no (<i>n</i> = 74) × Yes (<i>n</i> = 40)	0.891	0.059	0.311	0.854	0.152	0.381
Sex: F (<i>n</i> = 51) × M (<i>n</i> = 63)	0.180	0.514	0.067	0.268	0.227	0.065

Abbreviations: ABR, auditory brainstem response; BW, birth weight; GA, gestational age; ICU, intensive care unit; MV, mechanical ventilation; PIVH, peri-intraventricular hemorrhage.

^a < 31 ≠ 32–36; < 31 ≠ ≥ 37 (Dunn test for multiple comparisons).

The percentage of change in interpeak latencies I to III and III to V was higher in preterm infants than in full-term infants, giving the impression that auditory maturation occurs more rapidly in preterm infants. Both showed change in the ABR values between the assessments, characterized by reduced latencies due to the maturation process. But in the second assessment, preterm infants had higher values, showing that the improvement might be related to the maturation of the auditory pathways that was not complete at birth and changed according to gestational age.^{20,22}

On the other hand, not only gestational age may cause ABR alterations, but other neonatal complications may as well contribute to auditory maturation impairment. Despite being frequently studied, both aspects are not considered concurrently.

These studies evaluated healthy babies, without risk indicators for hearing loss, although it is very common that preterm neonates have many associated risk factors, hence the need for a detailed analysis of the factors to which preterm infants may have been exposed and that may have contributed to these remaining differences after the end of maturation.

In this study, newborns whose Apgar score was less than 4 at 1 minute after birth and normal after 5 minutes showed no significant increase in the ABR latencies, but those infants who had a low Apgar score at 5 minutes after birth had significant differences in the absolute latency of wave III in both ears.

According to these findings, the low Apgar score at 5 minutes caused worse damages in the auditory pathway, despite increasing age. Jiang et al observed an increase in interpeak I to V only within the first 3 days of life, as well as normal results within 1 month of life for the newborns who

had a low Apgar score but had good recovery after 5 minutes.¹⁴ The authors highlighted that the ABR changes observed within the first 3 days of life are of little significance because they normalized with the development of the maturation process. Therefore, a low Apgar score at 1 minute poses low risk for auditory changes, and a persistently low score may affect the auditory pathways.

An interesting finding in this study that has not been reported in the literature is that the infants who had a longer ICU stay, without considering the primary status of such admission, presented clear alterations between the first and second ABR assessments. Reductions in the absolute latency of wave III in the right ear, interpeak I to III in both ears, and in interpeak III to V in the left ear were statistically significant between the first and second assessments.

Other conditions contribute to the ABR differences, such as peri-intraventricular hemorrhage, maternal infection, chorioamnionitis, and neonatal infection or sepsis. These conditions have been associated with the development of neonatal brain damage and adverse neurodevelopmental outcomes.^{23–26} In this study, alterations in the ABR components were observed in these infants, showing that the occurrence of this injury deserves special attention as its association with hearing loss is rarely reported in literature.

Likewise, the use of mechanical ventilation, regardless of the primary disease, changes the ABR recordings and is, therefore, a confounding factor along with other hearing risk indicators.^{14,27} This was observed in this study when newborns using mechanical ventilation showed reduced interpeak I to III for the right ear and reduced interpeak latency I to V for the left ear.

Nevertheless, other conditions frequently associated with hearing loss, such as low birth weight, infections,

hyperbilirubinemia with serum level requiring transfusion, and use of ototoxic drugs, showed no significance in the ABR parameters with increasing age.

Results showed that the waveform I is less sensitive to the injuries that occurred during pregnancy and/or neonatal complications. However, waves III and V, which characterize the maturation of axons and synaptic mechanisms in the brainstem level, are more likely to be affected by the risk analyzed in this study.²⁸ Therefore, the differences in the ABR responses between full-term and preterm newborns and with some risk indicators for hearing loss cannot only be due to nervous maturation, but might as well be caused by injuries occurred during pregnancy and/or neonatal complications.¹⁷

We believe that these findings bring an important contribution to clinical practice. Neonates with complications deserve more attention paid to auditory evaluation, because prematurity and neonatal complications may interfere in the ABR findings. The interpretation and/or standardization of the results may be uncertain if only one assessment is performed.

Conclusion

The complications that most impacted the ABR findings were: Apgar scores less than 6 at 5 minutes of birth, gestational age, ICU stay, peri-intraventricular hemorrhage, and mechanical ventilation.

The sequential auditory evaluation is necessary in preterm and full-term newborns with risk indicators for hearing loss to correctly identify injuries in the auditory pathway.

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