Auditory Brainstem Response Morphology and Analysis in Very Preterm Neonatal Intensive Care Unit Infants

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Objectives/Hypothesis: Analysis of auditory brainstem response (ABR) in very preterm infants can be difficult owing to the poor detectability of the various components of the ABR. We evaluated the ABR morphology and tried to extend the current assessment system.

Study Design: Prospective cohort study.

Methods: We included 28 preterm very low birth weight infants admitted to the neonatal intensive care unit of Sophia Children’s Hospital. ABRs were measured between 26 and 34 weeks postconceptional age. The presence of the following ABR parameters was recorded: the ipsilateral peaks I, III and V, the contralateral peaks III and V, and the response threshold.

Results: In 82% of our population, a typical “bow tie” response pattern was present as a sign of early auditory development. This bow tie pattern is the narrowest part of the response wave and is predominantly characterized by the ipsilateral negative peak III. This effect may be emphasized by the contralateral peak III. The bow tie pattern is seen approximately 0.1 milliseconds before the ipsilateral peak III. From 30 weeks postconceptional age onward, a more extensive morphologic pattern is recorded in 90% of the infants. A flow chart was designed to analyze the ABR morphology of preterm infants in an unambiguous stepwise fashion.

Conclusions: A typical bow tie pattern preceding peak III seems to be the earliest characteristic of the developing ABR morphology in preterm infants. As ABR characteristics will improve with increasing age, neonatal hearing screening should be postponed until after 34 weeks.

Key Words: ABR, analysis, preterm, infant.
Level of Evidence: 2a.

INTRODUCTION
Auditory brainstem response (ABR) measurement is an important tool in diagnosing hearing impairment in infants. ABR waves reflect the conduction of a neural signal as a result of a sound stimulus along the auditory nerve and different levels of the brainstem.

The auditory system matures from the periphery to the cortex. Cochlear maturity is achieved around term birth. The central conduction time, reflected by the I-V interval, is reported to mature from 11 to 18 months up to 3 to 5 years of age.

To adequately diagnose hearing impairment in infants, age-adjusted normal values are required. Several fitting models have been described that correct ABR latencies for postconceptional age. In very preterm infants, this may not be sufficient because of the poor detectability of various components of the ABR. Not many data are available for this group of infants. Only Amin et al. gathered a considerable amount of data. They proposed a system that categorizes the ABR waveforms in infants younger than 32 weeks postconceptional age. One limitation is that it is a rather basic system based on identifiable peaks III and V. They did not include contralateral response data in their analysis. Not much is reported about the presence and development of contralateral ABR traces at this very young age. Salamy et al. mention that the development of the contralateral response starts around 34 weeks postconceptional age. This suggests that the contralateral response cannot contribute to the analysis of wave morphology before this age. It also suggests a different maturational process of the contralateral pathways.

Second, Amin’s system does not include information about the response threshold. Because of the poor detectability and smaller amplitudes of the peaks and poor measurement conditions, response thresholds are often difficult to determine. Yet, when a clear ABR waveform is present at lower stimulus intensities, this provides valuable additional information. It may be an indication that the maturation of the auditory system is in a succeeding developmental stage.

The aim of our study was to describe the ABR morphology in very preterm infants in a more accurate way than is available until now. To extend the current assessment system by evaluating ABR response thresholds and the contralateral ABR traces, more specific
ABR measurement in preterm neonates.

MATERIALS AND METHODS

Subjects
Twenty-eight preterm infants admitted to the neonatal intensive care unit (NICU) of Sophia Children’s Hospital were included between March 1, 2009, and August 31, 2010. Postconceptional age at time of ABR measurement ranged from 26 to 34 weeks. All infants with very low birth weight (<1,500 g) were eligible for this study unless they had congenital anomalies (including chromosomal disorders) or metabolic disease. All ABR measurements were recorded in the second or third postnatal week. Informed consent was obtained from the parents. The study was approved by the local ethics committee.

Study Setting
The Sophia Children’s Hospital is a tertiary care center in Rotterdam, the Netherlands. In 2008, the life birth number in the Netherlands was 184,634, of which 4,003 infants required NICU care, of which 639 were admitted to the NICU at Sophia’s Children’s Hospital (all deceased infants are excluded from these admittance numbers).

ABR Measurement
ABR measurements were recorded in the NICU. All children were in natural sleep or in calm conditions throughout the assessment. Both ears were sequentially tested. ABRs were recorded using a Centor USB Racia-Alvar system (Manufactured by: Racia-Alvar, France. Distributed by: MedCat, the Netherlands). Responses were recorded using silver cup electrodes placed at both mastoids with a reference at the vertex and a ground electrode on the forehead and then band pass filtered. A band-filter was used with cutoff frequencies of 20 Hz and 3 kHz. The repetition frequency was 29 Hz. Click stimuli were used with alternating polarity. Click stimuli were presented starting at a level of 90 dB nHL. When no response was found, stimulus level was increased to 100 dB nHL. The level was decreased with step sizes of 20 dB until no response was found. The response threshold was defined as the lowest level at which a replicable response was found. The response latencies (in milliseconds) were obtained by establishing the peak of the wave (at 90 dB nHL) and reading out the digitally displayed time. The interobserver difference of peak latencies had to be ≤0.3 milliseconds, and the average of the two latencies was used. The response peaks were sometimes poorly reproducible; in that case, the combination of traces at various stimulation intensities was used to establish the presence of a peak. The fact that a combination of traces was needed to establish the presence of a peak reflects a level of insecurity, which is common when analyzing new data. When a peak can be confirmed in several traces, this is an indication that the observation is no result of chance. Dealing with these aspects is an important process in understanding and analyzing new data. The ipsilateral (stimulated side) and contralateral (not stimulated side) response traces were recorded. For each trace, the test retest values are displayed, as a measure of recording accuracy. Two specialized audiologists independently interpreted the ABR waves, and in case of disagreement the audiologists arrived at a consensus. For the analysis, only the results of the best ear of each infant were included to prevent the negative influence of possible hearing loss on ABR morphology.

Possible hearing loss was diagnosed consequently by neonatal hearing screening using automated ABR (AABR). Otoacoustic emission (OAE) measurement was not conducted in the NICU for technical reasons; mechanical ventilation and surrounding noise made it impossible to obtain reliable OAE measurement.

Statistical Analysis
The SPSS 15 (SPSS Inc., Chicago, IL) statistical package was used for the analysis. For dichotomous values, the Pearson $\chi^2$ was used. $P$ values ≤.05 were considered statistically significant.

RESULTS
The 28 studied preterm infants had a median postconceptional age at birth of 28.3 weeks (interquartile range, 26.6–29.4 weeks). The median birth weight was 878 g (interquartile range, 718–1,010 g). All ABR measurements were conducted in the NICU between the 7th and 23rd postnatal day when infants were stable enough to undergo the examination. The median postconceptional age at time of ABR measurement was 30.1 weeks (interquartile range, 28.7–33 weeks). AABR hearing screening was conducted after 34 weeks postconceptional age in most infants. A few infants were tested between 31 and 33 weeks postconceptional age upon discharge. All except one infant passed the AABR neonatal hearing screening (96%). Hearing loss has been confirmed in this infant. ABR results improved from a maximum hearing loss in one ear and a sensorineural hearing loss in the other ear to a sensorineural hearing loss of 40 dB nHL in both ears with an additional conductive component. Two infants died during the course of follow-up.

Two specialized audiologists independently interpreted the ABR waves. When identifiable, the ipsilateral peaks I, III, and V, the contralateral peaks III and V, and the response threshold were established. In contrast to ABR measurement at later ages, peak III instead of V was shown to be the most characteristic peak. A typical “bow tie” pattern is the earliest characteristic that appears just before peak III (Fig. 1). It is the narrowest distance between the ipsilateral and contralateral response waves with a characteristic appearance. The negative peak preceding peak III is the soundest characteristic of this pattern. The positive peak III, if present, follows after approximately 1 millisecond. The contralateral peak III can emphasize the bow tie pattern. In Figure 2, typical ABR traces with a bow tie pattern are presented for different postconceptional age groups. With increasing postconceptional age, the latency of the bow tie shortens, and more peaks become identifiable. With increasing postconceptional age, the latencies of the peaks also decrease. In Table I, the latencies of peaks III and V, the III-V interval, and the threshold levels are presented for different postconceptional age groups. After primary analysis the interobserver concordance was 89%. The audiologists arrived at a full consensus at final analysis.
Based on the observed characteristics of the ABR morphology, a flow chart was designed to analyze the ABR morphology of preterm infants in an unambiguous stepwise fashion (Fig. 3). The best ear of each infant was included in the analysis. A classification was made based on the extensiveness of the response. In type I, no response is found. In type II, a typical bow tie pattern is observed. In type III, a contralateral response can be found as well as a bow tie pattern. In type IV, clear ipsilateral peaks (often peaks III and/or V) are identified as well as a contralateral response. A contralateral response (type III) was identified in 68% of the infants, even before 30 week postconceptional age in some cases. A more extensive morphologic pattern (type IV), with reproducible ipsilateral peaks was seen in 57% of the infants.

In Figure 4 the division of the response types is described for different postconceptional age groups. A more extensive morphologic pattern develops with increasing postconceptional age. Especially between 29 and 30 weeks postconceptional age in some cases. A more extensive morphologic pattern (type IV), with reproducible ipsilateral peaks was seen in 57% of the infants.

Interpretation of ABR results in adults and older infants is largely dependent on peak V, which is the clearest and strongest peak. The peripheral to central maturation of the auditory system results in a weaker projection of peak V in these preterm infants. This was even more clearly observed in our data. Instead of peak V, a broad negative ipsilateral peak III response appeared to be the best identifiable and most consistent characteristic. Especially in combination with a contralateral peak, this results in a typical bow tie pattern. The typical bow tie pattern can also be found in older infants younger than 30 weeks postconceptional age and infants who are 30 weeks postconceptional or older is statistically significant ($P = .004$).

**DISCUSSION**

We developed a flow chart to analyze the morphology of the ABR results of 28 preterm infants in an unambiguous way. We found that in 82% of infants, a typical bow tie response pattern is present, dominated by a negative peak III. The presence of a more extensive morphologic response type increases with increasing postconceptional age. From 30 weeks postconceptional age onward, an ipsilateral and/or contralateral response is present in 90% of the infants in their best ear.

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infants or adults, but the clearer peaks III and V make it less easy to identify. In these preterm infants, it seems to be the clearest and earliest characteristic of the ABR waveform and should be the first pattern to look for when measuring ABR in very young preterms.

Interpretation of ABR results using the flow chart results in a reliable ABR analysis at an early developmental stage. The stepwise analysis from a basic ABR morphology to a more extensive response type ensures that no ABR characteristics will be missed. The analysis can be difficult owing to the broader peaks and poorer reproducibility; however, an unambiguous characterization was found for most infants. As a result of the immature auditory system, a longer time span had to be considered to identify peak latencies. Sometimes the combination of traces at various stimulation intensities had to be used to establish the presence of a peak. We chose to report only the results of the best hearing ear to prevent the negative influence of possible hearing loss on ABR morphology. Absence of this pattern did not correlate with a hearing loss, as 96% of infants passed the AABR screening.

The ABR peak latencies that we found are comparable to the results found by Amin et al.9 Before 29 weeks, the number of infants with identifiable peaks was limited, therefore data of peak latencies and the III-V interval are presented beyond this age. A clear age-dependent decline of peak III and V latencies, III-V interval, and ABR response threshold is observed. These results indicate the well-known ongoing maturational processes of the auditory system in infants.

Because peak I is rarely identifiable in these infants, the III-V interval, instead of the I-V interval, was used as a measure of the central conduction time or auditory maturation. Interpeak intervals are not as much influenced by conductive hearing losses as individual peak latencies. Because tympanometry was not performed and peak I was often not identifiable, the degree of conductive hearing losses and its influence on peak latencies cannot be established.

Although peaks become identifiable around 30 weeks postconceptional age, threshold levels are still increased as a result of ongoing maturation or possible hearing loss. Threshold levels will decrease during the following weeks. In our data from 31 weeks postconceptional age, thresholds become closer to the normal range. However, in certain cases no threshold can be established, suggesting a delayed maturation or congenital hearing loss. This confirms that neonatal hearing screening should be postponed until after 34 weeks.

The auditory system is known to develop in a peripheral to central fashion.1 Cochlear maturity is achieved a few weeks before term birth. Axonal myelin formation and synaptic efficacy result in maturation of the auditory pathways in the brainstem during the first months of life.2 When applied to the ABR response, this implies a small or absent age dependency of peak I and large age dependency of later peaks and intervals. The earlier and clearer identification of peak III compared to peak V in our preterm population is line with the peripheral to central maturation of the auditory system. As peak V is generated in the colliculus inferior, around 30 weeks postconceptional age an important step in the maturation of the colliculus inferior takes place. The central conduction time, reflected in the I-V or III-V intervals, is also known to decrease with increasing postconceptional age as a result of maturation.

Jiang et al. suggested that very preterm infants without perinatal complications have an advanced peripheral development of the brainstem but a retarded central development.11,12 Their findings were based on the fact that the III-V interval of preterm infants was much more prolonged than the I-III interval compared to term infants. This may be the result of early sound stimulation ex utero, which could lead to accelerated myelination and peripheral auditory maturation. This may be another explanation for the strong expression of
peak III in our population. Unfortunately we were unable to gather enough information on peak I latency in this population to study the various interpeak intervals.

In the 1980s, the contralateral ABR response was reported to emerge around 34 weeks postconceptional age. However, we found a contralateral response in 86% of infants from 29 weeks postconceptional age onward. Even at 26 to 27 weeks postconceptional age, a contralateral response is found in some cases. This implies development of contralateral pathways in a very early stage. Salamy et al. reported that the contralateral response develops in a rostrocaudal fashion, with peaks IV and V being the most pronounced in early life. In our population, similar to the ipsilateral response, peak III seems to be the earliest and most prominent of the contralateral response peaks. As a result of early measurement in the immature auditory system, apparently peak V is not yet as strongly and clearly developed and therefore less frequently measurable in our population.

A limitation of our study may be that hearing loss may have influenced the interpretation of the ABR morphology. However, 96% of the infants passed AABR neonatal hearing screening.

CONCLUSION
We developed a flow chart to analyze the ABR results in very preterm infants. Peak III seems to be the most prominent and earliest identifiable peak in both the ipsilateral and contralateral ABR traces. From 30 weeks postconceptional age onward, an extensive ABR morphology was seen in 90% of our population. Threshold levels and identifiable peaks will improve during the following weeks; therefore neonatal hearing screening should be postponed until after 34 weeks.

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