Neonatal brainstem audiometry and early language development in preterm children

Jaana Antinmaa\textsuperscript{1,2,3}, Helena Lapinleimu\textsuperscript{2}, Jaakko Salonen\textsuperscript{4}, Suvi Stolt\textsuperscript{5}, Anne Kaljonen\textsuperscript{6}, Satu Jääskeläinen\textsuperscript{1}

Affiliations:
\textsuperscript{1}Department of Clinical Neurophysiology, Turku University Hospital and University of Turku, Turku, Finland
\textsuperscript{2}Department of Pediatrics and Adolescent Medicine, Turku University Hospital and University of Turku, Turku, Finland
\textsuperscript{3}Department of Pediatrics, The Hospital District of South Ostrobothnia, Seinäjoki, Finland
\textsuperscript{4}Department of Otorhinolaryngology, Turku University Hospital, Turku, Finland
\textsuperscript{5}Department of Psychology and Speech and Language Pathology (Logopedics), Faculty of Medicine, University of Helsinki
\textsuperscript{6}Department of Biostatistics, Faculty of Medicine, University of Turku, Turku, Finland

Address correspondence to:
Jaana Antinmaa, M.D.
Department of Clinical Neurophysiology, University of Turku
PO Box 52, 20521 Turku, Finland
Phone: +358 40 7618107
Fax: +358 2 313 3922
Email: jaana.antinmaa@utu.fi

Short running title: Neonatal BAEP and early language development

Citation information:
ABSTRACT

Aim: To study whether auditory function measured with brainstem auditory evoked potential and brainstem audiometry recordings in the neonatal period associates with language development one year later in preterm infants.

Methods: This retrospective study included 155 preterm infants (birth weight ≤1500 g and/or birth ≤32 gestational weeks) born between 2007 and 2012 at the Turku University Hospital. Auditory function was recorded at the mean corrected age of one month. Language development was evaluated at the mean corrected age of one year by using the Finnish version of the MacArthur Communicative Development Inventory.

Results: Infants with a longer interpeak interval I-V in the right ear in the neonatal brainstem auditory evoked potential recording had a smaller receptive lexicon size at one year (p=0.043) and were more likely to have an abnormal (≤17 words) receptive lexicon size (p=0.033). The absence of a contralateral response with right ear stimulation increased the risk for abnormal lexicon size (p=0.049).

Conclusion: The results suggest that impaired auditory function in the neonatal period in preterm infants may lead to a poorer language outcome one year later. Auditory pathway function assessment provides information for the identification of preterm children at risk for weak language development.

Key words: BAEP, language development, preterm
Key notes:

- Impaired neonatal auditory pathway function predicts weak language development one year later in preterm infants.
- Slow auditory processing increases the risk of an abnormal receptive lexicon 29-fold.
- Detectable contralateral response reduces the risk for poor receptive lexicon by 80%.
INTRODUCTION

The maturation of the auditory pathway can be disrupted by premature birth as many critical periods of brain development, including myelination and synaptogenesis, occur during the 27th gestational weeks onwards; consequently, for preterm children during the period when they are in a hospital environment (1,2). In addition to premature birth itself, brain development can be impaired for several reasons, including maternal infections and hypoxic ischemic encephalopathy (1). Neonatal intensive care unit (NICU) treatment is considered to be a risk factor for abnormal auditory maturation (3). Other risk factors are for example asphyxia (4), necrotizing enterocolitis (5), chronic pulmonary disease (6) and environmental noise (7).

Premature birth increases the risk of an adverse neurodevelopmental outcome (8) including delayed language development (9). At the corrected age of one year language abilities can be studied by gathering information about the number of words that the child understands (receptive lexicon). It has been discovered that the receptive lexicon size grows slower in prematurely born very low birth weight (VLBW) children compared to full-term children (10,11). The early weak receptive lexicon predicts the weak expressive lexicon and language abilities of preterm infants at two years of age (10–12).

Previous studies have concluded that especially a timely maturation of the auditory pathway is a prerequisite for normal language development (13). The maturation and function of the auditory pathway in neonates can be examined reliably and objectively with brainstem auditory evoked potentials (BAEP) and brainstem audiometry (BA) recordings. Slow conduction in auditory pathway has been shown to predict later language development (14). To our knowledge, only two studies so far have analyzed the association between early BAEP and BA recordings and later language development (14,15) and the Cox et al. study is rather old (15). In addition, the language abilities in both these studies were evaluated at the age of over two years, which is later in childhood than
in the present study; thus, there is need for further study in this area. The aim of the present study was to investigate the association between neonatal brainstem auditory function in neurophysiological recordings and receptive lexicon at the corrected age of one year in infants born preterm.

PATIENTS AND METHODS

Participants
In Turku University Hospital, 378 preterm infants (birth weight ≤1500 g and/or birth at ≤32 gestational weeks) were born between 2007 and 2012. A total of 155 preterm infants were included in the study (Figure 1). This retrospective register study included infants who had undergone a BAEP recording in the neonatal period (at the corrected age of ≤2.5 months) and whose lexical development had been evaluated by parents at the corrected age of one year. A total of 223 neonates were excluded from these analyses due to incomplete BAEP or receptive lexicon data (Figure 1). The information of early lexical development was gathered using the Finnish version of the MacArthur Communicative Development Inventory (CDI) (16,17). All the children were from Finnish speaking families. The procedure for this retrospective study was approved by the Hospital District of Southwest Finland Ethics Review Committee in 2010.

*The function of auditory pathway at the corrected age of one month*

BAEP and BA were recorded at the Department of Clinical Neurophysiology of Turku University Hospital in a quiet room by experienced event related potential technologists. The ear canals of the children were checked and cleaned before the recordings. All infants were naturally asleep or peacefully awake. An eight-channel Nicolet Viking IV (Nicolet Biomedical Instruments, Madison, Wisconsin, USA) was used to record the BAEP and BA of 25 infants (recorded mostly in 2007) and a Viking SelectTM (CareFusion, USA) was used for 130 infants. The recording electrodes were placed on both mastoids and the reference electrode at the vertex (Cz) anterior to the fontanel, and the ground on the
forehead (Fp2’). The stimulus was delivered to the ear canal with tubal insert earphones (Nicolet model TIP 300 Ohm). The length of the silicon tube of insert earphones was 153 mm and the size was selected according to the size of the infant’s ear canal.

In a BAEP recording, broadband rarefaction click stimuli were administered to the infant’s ear at an intensity of 85 dB nHL (stimulation rate 10.3 Hz) while the non-stimulated ear received masking white noise at 45 dB nHL. The high pass filter was set to 150 Hz and the low pass filter to 3 kHz. The sensitivity of the amplifier was 10 µV. The sample of 2000 responses were measured and averaged at least twice. If clear BAEP waveforms were not identified, the stimulus level was raised to 95 dB nHL. Each ear was stimulated separately, and ipsilateral and contralateral responses were recorded. An experienced technologist designated the peaks I, II, III, IV and V, and the troughs following the peaks I and V. A specialist in clinical neurophysiology (MD; SKJ) checked the recordings and the reports. Later, the first writer (MD; JA) evaluated all the recordings and identified BAEP components III and V on the contralateral recording.

After a successful BAEP recording, a BA was recorded to determine the click threshold for both ears separately. Initially, the stimulus intensity was 35 dB nHL (33.3 Hz) with a masking white noise of 15 dB nHL in the non-stimulated ear. If no clear waveforms III-V were found, the intensity level was increased in increments of 10 dB nHL up to 65 dB nHL (and masking white noise up to 40 dB nHL) if necessary, until waves III and V were identified.

**Lexical development at the corrected age of one year**

To gather the data of the lexical development at the corrected age of one year, the standardized Finnish version of the MacArthur Communicative Development Inventory (CDI) was used. This data was gathered during a normal clinical follow-up. CDI is a structured parental rating instrument including 380 words presented in 19 semantic
categories. Parents are advised to mark the words their child understands but does not say (receptive lexicon), and the words their child understand and says (expressive lexicon). In this study only the receptive lexicon was utilized. This was done since expressive lexicon is very small at one year of age whereas the mean receptive lexicon size for full-term children is already roughly 80-90 words at this age (10,16,17). The word was acknowledged to be understood if the child repeatedly and clearly responded correctly to the word. These instructions were given in writing to the parents. The total receptive lexicon size was gathered from all children. The data was also divided into two groups according to the total receptive lexicon size: abnormal CDI group (≤ 17 words; the weakest 10th percentile value of the normative data of the Finnish version of the CDI) and normal CDI group (>17 words).

Possible confounding factors
Information on the gestational age, birth weight, small for gestational age status, gender, hearing loss, age at the time of BAEP and BA recordings was gathered from patient files. The age at the time of CDI completion was obtained from the CDI form. The hearing was considered impaired if a hearing loss was diagnosed in the Department of Audiology before 2016. This department is the only unit providing hearing rehabilitation for children in the catchment area of Turku University Hospital.

Statistical analysis
Initially, univariate associations were analyzed between BAEP parameters (latency of BAEP component I, III, V, interpeak interval (IPI) I-V, I-III, III-V (ms), amplitude I and V (µV), amplitude ratio I/V) and BA variables, and the receptive lexicon. The BA results were used in the univariate analysis as continuous variables, category variables and dichotomous variables. Possible BA values were 35, 45, 55, 65, 75, 85 and 95 dB based on the appearance of the BAEP component III and/or V. As dichotomous variable BA was considered normal if the BA threshold was 35 dB in both ears and abnormal if the level
was 45 dB or more in at least one ear. Contralateral BAEP responses were analyzed as dichotomous variables. The contralateral response was considered present if the BAEP wave III and/or V were detectable and absent if neither wave were identified. The receptive lexicon was used in the analyses both as a continuous variable and a dichotomous variable (abnormal ≤ 17 words and normal >17 words). A Pearson correlation, a t-test, a Chi Square Test and Fisher’s Exact Test were used depending on the scale and, in the case of continuous variables, normality of the BAEP and BA variable. Both ears were analyzed separately.

In univariate analysis, the latency of the BAEP component V and the IPI I-V of the right ear ipsilateral response and left contralateral response (with right ear stimulation) showed significant associations with receptive lexicon size and thus, they were chosen for the regression analysis. Only the right ear BAEP variables were included as in the univariate analysis the left ear BAEP variables did not show any significant associations with the receptive lexicon. In addition, the right ear has been found to already be the dominant ear in newborns (18,19). In the univariate analysis, the confounding factors did not show any significant associations. However, gestational age and gender were included in the regression analysis as they can influence auditory function according to the literature (3,20).

In the regression analyses, the latency of the BAEP component V, the IPI I-V and the contralateral response were grouped one at a time together with gestational age and gender. In addition, latency of the BAEP component V, IPI I-V and the contralateral BAEP response were analyzed in one group and gestational age and gender in one group. Linear regression analysis was used with the continuous receptive lexicon variable and logistic regression analysis with the dichotomous lexicon variable.

RESULTS
Clinical characteristics are presented in Table 1. The data included 93 boys (60%) and 62 girls (40%). Mean birth weight was 1245 g and mean gestational age at birth was 29 weeks. BAEP and BA recordings were conducted at the mean corrected age of 1.1 months and a CDI form was completed at the mean corrected age of 12.1 months. On average, preterm children in the present study understood 71 words ranging from zero to 311 words at the corrected age of one year. (Table 1)

The results of the regression analyses are presented in Tables 2a and 2b. Infants with longer interpeak interval (IPI) I-V in the right ear in neonatal BAEP recording had smaller receptive lexicon at one year (p=0.043) after controlling for gestational age and gender. When BAEP variables were analyzed separately, infants with longer IPI I-V were more likely to have abnormal receptive lexicon size (OR=29.9; CI 95 %.=1.3-683.7; p=0.033). With right ear stimulation the absence of contralateral response increased the risk for abnormal lexicon size (OR=0.2; CI 95 %.=0.02-0.99; p=0.049). Long IPI I-V increased the risk for an abnormal receptive lexicon at one year by up to 29-fold and a visible contralateral response reduced the risk for a poor receptive lexicon by 80 %.

BA results did not have any significant associations with the receptive lexicon in the univariate analyses.

DISCUSSION

The results of the present study suggest that abnormalities in the neonatal BAEP recording at the corrected age of one month associate with weak receptive lexicon size at the corrected age of one year in preterm infants. Thus, BAEP recordings can provide important information about auditory processing in the neonatal period, and poor performance in this recording may predict impaired language development. It is known that especially congenital permanent childhood hearing loss increases the risk for language development problems (21). Even unilateral hearing loss has been found to
adversely affect language development (22). BAEP and BA are reliable methods and they give detailed information on both ears separately. In our data there were only two children who were diagnosed with hearing loss later in childhood (both until the age of two years). Most of the children in our study had normal hearing. This could indicate that milder defects in auditory function, such as impaired neural conduction and processing of auditory pathways reflected for example in absent contralateral responses, could also have an adverse impact on language development.

Impaired auditory processing was identified in our study in the form of prolongation of BAEP latencies in the right ear and absent contralateral responses with right ear stimulation in BAEP recordings. Prolongation of latencies can be explained by delayed myelination and poorer synaptic efficacy in the auditory pathways. The absence of a contralateral response in the present study especially supports the conclusion that poorer synaptic efficacy interferes with the auditory processing. Damage in the auditory pathway can be caused by prematurity and related co-morbidities as well as treatments and noise in the NICU (3,7,23).

Our finding that neonatal BAEP associates with later lexical development, is in line with two previous studies (14,15). Amin et al. (14) found that both the worse ear and the better ear IPI I-V (BAEP performed at 35 week postmenstrual age) associated with auditory comprehension and expressive communication at the age of three years in 80 premature infants (birth ≤33 gestational weeks). In addition, another study found that early BAEP (done before hospital discharge) of very low birth weight children may predict intelligence quotient, language development and academic achievement at the age of eight years (15). In these previous studies, however, the study groups were smaller compared to the present study and children at very different stages of language development were included. In the present study, the language assessment was done already at the corrected age of one year compared to previous studies where language development
was evaluated at the ages of three and eight years (14,15). In addition, in the study by Amin et al. (14), the BAEP was performed at the postmenstrual age of 35 weeks when the BAEP may be more unreliable due to very small ear canals and fluid in the ears. In the present study, BAEP was conducted at the corrected age of one month, when the children were clinically stable and there were no acute conditions.

MacArthur Communicative Development Inventory was used to assess language performance at the corrected age of one year. The CDI method is widely used and it has been shown to be a valid method to assess early language and communicative development (16,17). Studies have shown that a small early receptive lexicon size is an early sign of weak lexical and language development in preterm children (10–12). A very small early receptive lexicon size especially (at corrected age of 12 and 15 months) has been found to associate with weak language performance at the age of 24 months (10,12). The present findings provide information on the possible background factors for the weak receptive lexicon growth in preterm infants, and imply that accurate hearing testing with BAEP and BA recordings in the neonatal period could be used to reliably detect infants who require a closer follow-up of language development.

In the present study the evaluated confounding factors did not associate with the receptive lexicon in the univariate analyses. However, other studies have found that a smaller gestational age (GA) increases the risk for delayed language development (24) and that boys have a higher risk for language delay (11). Thus, we included GA and gender in the regression analysis although in the univariate analyses these factors did not associate with the receptive lexicon. The lack of association between GA and the receptive lexicon in the present univariate analyses might be due to the fact that all the children in our study were preterm and thus, the GA range was quite small.
The present study suggests that preterm infants at risk for early delayed language development can already be found in the neonatal period based on an abnormal BAEP recording. This opens an opportunity for even earlier language rehabilitation. Preterm infants have been found to benefit from postnatal auditory experience (25) and they have also shown better cognitive and language outcomes at the corrected age of 7 and 18 months in relation to the amount of parental talk exposure in the NICU period (26). However, there are contradictory findings showing that preterm infants do not gain any advantage by a longer exposure to speech than full term infants (27). Nevertheless, evidence exists that the quality of the early language environment provided by caregivers is considered an important factor in language development (28). Early rehabilitation of infants at risk for language problems could include information to parents on how to enrich the language environment of the child. Based on the results of the present study, the infants at risk can already be distinguished in the neonatal period by using a BAEP recording.

Limitations of the study
This was a retrospective study where all the tests (BAEP, BA and CDI) were part of the normal clinical follow-up routine in Turku University Hospital. Consequently, some information is lacking. For example, we did not have information about maternal educational status or socioeconomic status.

Conclusions
In the present study, right-ear auditory pathway abnormalities in the neonatal period of premature infants associated with early language development. This finding suggests that at the corrected age of one month preterm infants, who are at increased risk for language development, could already be identified. Neonatal BAEP recording is thus a useful method for diagnosing not only brainstem abnormalities and hearing loss but also delayed auditory maturation that can impair early language development. The use of BAEP can
help with the early identification of children at risk for language problems, thus enabling prompt rehabilitation in the neonatal period.
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>BA</td>
<td>brainstem audiometry</td>
</tr>
<tr>
<td>BAEP</td>
<td>brainstem auditory evoked potentials</td>
</tr>
<tr>
<td>CDI</td>
<td>the MacArthur Communicative Development Inventory</td>
</tr>
<tr>
<td>GA</td>
<td>gestational age</td>
</tr>
<tr>
<td>IPI</td>
<td>interpeak interval</td>
</tr>
<tr>
<td>NICU</td>
<td>neonatal intensive care unit</td>
</tr>
<tr>
<td>VLBW</td>
<td>very low birth weight</td>
</tr>
</tbody>
</table>
CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

FUNDING

This research received funding from the Arvo and Lea Ylppö Foundation, the Foundation for Pediatric Research, The Finnish Medical Foundation, the Turku University Foundation and The Hospital District of South Ostrobothnia. These funding sources were not involved in the study. They did not participate in the study design, the data collection, the analysis, interpretation of the results or the writing of the manuscript.
REFERENCES


Table 1. Clinical characteristics of the study sample (n=155)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/Female, n (%)</td>
<td>93 (60)/62 (40)</td>
</tr>
<tr>
<td>Weight, g, mean (SD), range</td>
<td>1245 (366), 535-2180</td>
</tr>
<tr>
<td>≤1500 g, n (%)</td>
<td>115 (74)</td>
</tr>
<tr>
<td>Gestational age, weeks, mean (SD), range</td>
<td>29 (2.4), 24-35</td>
</tr>
<tr>
<td>≤32 weeks, n (%)</td>
<td>137 (88)</td>
</tr>
<tr>
<td>≤1500 g or ≤32 weeks, n (%)</td>
<td>155 (100)</td>
</tr>
<tr>
<td>Small for gestational age, n (%)</td>
<td>49 (32)</td>
</tr>
<tr>
<td>Corrected age (months) at the time of BAEP recordings, mean (SD), range</td>
<td>1.1 (0.3), 0.3-2.2</td>
</tr>
<tr>
<td>Corrected age (months) at the time of CDI completion, mean (SD), range*</td>
<td>12.1 (0.6), 10.0-15.5</td>
</tr>
<tr>
<td>Hearing loss diagnosis**, n (%)</td>
<td>2 (1.3)</td>
</tr>
<tr>
<td>Receptive lexicon (number of words) at the age of one year, mean (SD), range</td>
<td>71 (67), 0-311</td>
</tr>
</tbody>
</table>

*n=133 (22 missing values)

**Hearing loss was diagnosed until the age of 2 years by an audiologist in the Department of Otorhinolaryngology in Turku University Hospital

BAEP: brainstem auditory evoked potentials
CDI: the MacArthur Communicative Development Inventory
SD: standard deviation
Table 2a. BAEP variables associating with weak receptive lexicon according to the adjusted linear regression analysis

<table>
<thead>
<tr>
<th>BAEP variable</th>
<th>CDI variable</th>
<th>B</th>
<th>SE</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPI I-V (right ear)</td>
<td>receptive lexicon</td>
<td>-40.1</td>
<td>19.6</td>
<td>0.043</td>
</tr>
</tbody>
</table>

Table 2b. BAEP variables associating with weak receptive lexicon according to the adjusted logistic regression analysis

<table>
<thead>
<tr>
<th>BAEP variable</th>
<th>CDI variable</th>
<th>OR (95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPI I-V (right ear)</td>
<td>CDI abnormal</td>
<td>29.9 (1.3-683.7)</td>
<td>0.033</td>
</tr>
<tr>
<td></td>
<td>(&lt;17 words)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contralateral response</td>
<td>CDI abnormal</td>
<td>0.2 (0.02-0.99)</td>
<td>0.049</td>
</tr>
<tr>
<td>(right ear stimulation)</td>
<td>(&lt;17 words)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

B  Beeta, Parameter estimate  
BAEP  brainstem auditory evoked potentials  
CDI  the Finnish version of the MacArthur Communicative Development Inventory  
IPI  interpeak interval  
SE  Standard error
Preterm infants
(birth weight ≤1500 g and/or birth ≤32 gestational weeks) born in Turku University hospital 2007-2012
n=378

Excluded due to absent pediatric follow-up
- Death of a child (n=36)
- Lost to follow-up (n=128)
  o Follow-up was arranged outside the pediatric follow-up policlinic in Turku University Hospital
  o Living outside the catchment area of Turku University Hospital

Children who attended routine follow-up n=214

Excluded due to absence of CDI form
- CDI form was not completed by parents (n=24)
- Bilingual or non-Finnish speaking family (n=23)
- Hearing loss of the parents (n=2)

Included in the analysis n=155

Excluded due to absent/unreliable BAEP recording
- Not obtainable recording (n=7)
- Otitis media during BAEP recording (n=1)
- Corrected age >2.5 months at the time of BAEP recording (n=2)

BAEP brainstem auditory evoked potentials
CDI the MacArthur Communicative Development Inventory