Received: 23 April 2021 | Revised: 23 June 2021 | Accepted: 12 July 2021

DOI: 10.1111/apa.16029

ACTA PÆDIATRICA NURTURING THE CHILD WILEY

REGULAR ARTICLE

Continuous positive airway pressure treatment may negatively affect auditory maturation in preterm infants

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Funding information
This research received funding from the Arvo and Lea Ylppö Foundation, the Foundation for Pediatric Research, The Finnish Medical Foundation, The Hospital District of South Ostrobothnia and the Turku University Foundation. These funding sources were not involved in any aspect of the study

Abstract

Aim: Nasal continuous positive airway pressure (CPAP) devices generate loud noise, which might harm auditory function and maturation. The function of auditory pathways can be examined by using brainstem auditory evoked potential (BAEP) and brainstem audiometry (BA) recordings. Our objective was to study whether CPAP treatment during the neonatal period is associated with abnormalities in BAEP and BA recordings.

Methods: Included in this retrospective study were preterm infants (birth weight ≤1500 g and/or gestational age ≤32 weeks) born between 2002 and 2006 with a comprehensive clinical background and follow-up data, including the duration of CPAP treatment ($n = 162$). BAEP and BA were recorded near the mean corrected age of one month. The following variables from BAEP and BA examinations were analysed: latencies of BAEP components I, III, V, interpeak intervals (IPI) I-V, I-III, III-V (ms), amplitude I and V (μV), amplitude ratio I/V and BA thresholds.

Results: In the adjusted analysis, a longer CPAP treatment leads to longer latencies of BAEP component III ($p = 0.01$) and V ($p = 0.02$) in the right ear.

Conclusion: CPAP treatment may impair the auditory maturation and processing mediated via the dominant right ear. The hearing and neurodevelopment of the children who are treated with CPAP should be followed.

KEYWORDS
brainstem auditory evoked potentials, continuous positive airway pressure, hearing, noise

1 | INTRODUCTION

Studying risk factors for auditory abnormalities in neonates is important as impaired auditory maturation may predict later delays in language development and an abnormal neurodevelopmental outcome.[1–3] Risk factors for congenital hearing loss include for example neonatal intensive care unit (NICU) treatment longer than 5 days, a family history of permanent childhood hearing loss, assisted ventilation, exposure to ototoxic medications, severe hyperbilirubinemia, congenital infections and neurological disorders.[4]

Abbreviations: BA, brainstem audiometry; BAEP, brainstem auditory evoked potentials; BPD, bronchopulmonary dysplasia; CPAP, nasal continuous positive airway pressure; HFNC, high flow nasal cannulae; IPI, interpeak interval; NEC, necrotising enterocolitis; nHL, normal hearing level; NICU, neonatal intensive care unit; PDA, patent ductus arteriosus; RDS, respiratory distress syndrome; SPL, sound pressure level.

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Specifically, mechanical ventilation is a risk factor for hearing impairment.[5] However, there is a lack of studies investigating whether nasal continuous positive airway pressure (CPAP) treatment could also impair auditory function.

In recent years, CPAP treatment has become more common, and consequently, the length of invasive mechanical ventilation treatment has decreased.[6] In addition, neonates with a lower gestational age require longer CPAP treatment compared with more mature infants.[7] However, CPAP devices can generate high noise intensities of 54–89 dB(A) depending on the airflow level and the device. Infant flow device applied at the time of the present study has been found to create the highest noise intensities.[8] Exposure to noise can potentially damage the maturating auditory system.[9] The developing auditory pathway might be especially vulnerable to a high-frequency noisy NICU environment.[10]

The auditory pathway function of neonates can be evaluated reliably by using brainstem auditory evoked potentials (BAEP), and the hearing thresholds determined by using brainstem audiometry (BA).[11] In a normally hearing infant, BAEP response usually consists of five peaks that are generated in different parts of the auditory pathway from the cochlear nerve to the brainstem. In consequence, BAEP recordings can help to detect and localise possible defects in the auditory pathway. The absolute latencies of each peak and interpeak intervals (IPIs) can be measured in milliseconds, and they decrease gradually with increasing age due to the maturation of the auditory pathway.[12] Reference values can be used to determine the normality of BAEP responses.[13]

The purpose of the present study was to investigate whether CPAP treatment duration in very preterm infants whose birth weight is ≤1500 g and/or gestational age ≤32 weeks is associated with results in neonatal BAEP and BA recordings. Our hypothesis was that long CPAP treatment with protracted noise exposure associates with impaired neural conduction in the auditory pathway seen as prolonged BAEP latencies and interpeak intervals and hearing threshold elevation seen as abnormal BA.

KEY NOTES

- Our study found that auditory function and maturation in preterm infants can be disrupted by nasal continuous positive airway pressure (CPAP) treatment.
- CPAP devices generate noise above the recommended limits, which can damage the developing auditory pathway.
- Preterm infants who required CPAP treatment should be followed as impaired auditory maturation may predict abnormal neurodevelopment.

2 | METHODS

2.1 | Participants

The formation of the study group is shown in Figure 1. In Turku University Hospital, between 2002 and 2006, 242 very preterm infants were born whose birth weight was ≤1500 g and/or gestational age was ≤32 weeks. Of this population, 80 infants were excluded from the study due to the death of the infant, no available BAEP recordings, technically unsuccessful BAEP recordings, corrected age three months or more at the time of the BAEP recording or missing clinical data which was mainly due to the infant being transferred to another city. In order to focus on neonatal BAEP and BA recordings, we only included infants who underwent a BAEP recording under the corrected age of three months which is the age from the expected day of delivery. Consequently, included in the study were 162 preterm infants with available comprehensive clinical data and who underwent BAEP and BA recordings at the Department of Clinical Neurophysiology during the neonatal period. The data were used to investigate the risk factors for delayed auditory maturation and in particular the effects of CPAP treatment on hearing as reflected in BAEP and BA recordings. This retrospective register study was approved by the Hospital District of Southwest Finland Ethics Review Committee in 2016.

2.2 | Data acquisition and equipment

Clinical factors from the neonatal period were gathered from medical records. The characteristics of the study population, the risk factors for hearing loss and outcome factors are presented in Table 1. In Turku University Hospital, the CPAP device used between 2002 and 2006 was an Infant Flow device (Electro Medical Equipment). In 2016, we gathered information about a possible hearing loss from patient files in the Department of Audiology, which is the only unit treating hearing loss in children in Turku University Hospital catchment area.

BAEP and BA recordings were conducted at the Department of Clinical Neurophysiology by experienced evoked potential technologists. Before the recordings, the ear canals of the children were checked and cleaned. The recordings took place in a quiet room, and all the infants were either naturally asleep or peacefully awake. The recordings were conducted using eight-channel Nicolet Viking IV equipment (Nicolet Biomedical Instruments). The recording electrodes were placed on both mastoids, and the reference electrode was placed at the vertex anterior to the fontanel and the ground electrode on the forehead. To deliver the stimuli to the outer auditory canal, we used tubal insert earphones (Nicolet model TIP 300 Ω). Each ear was tested separately.

All the infants first went through a BAEP recording. Broadband rarefaction click stimuli were delivered at the intensity of 85 dB normal hearing level (nHL) (stimulation frequency 10.3 Hz). At the same time, the non-stimulated ear received masking white noise at 45 dB nHL. The low-frequency filter (LFF; high-pass filter) was set to 150 Hz and the high-frequency filter (HFF; low-pass filter)

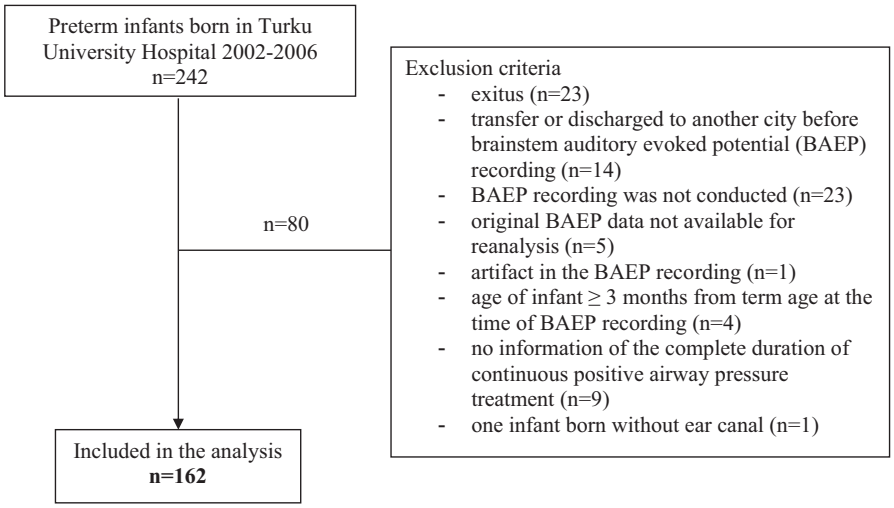

FIGURE 1 The formation of the study group

to 3 kHz. The amplifier sensitivity was 10 μV. We averaged 2000 responses at least twice. If a clear BAEP response was not identified, the stimulus level was raised to 95 dB nHL. After obtaining a BAEP recording with sufficient quality, an experienced technologist marked the peaks I, II, III, IV and V, and the troughs following the peaks I and V. A specialist in clinical neurophysiology (SKJ) analysed the recordings.

After a successful BAEP recording, a BA was done to determine the click threshold of both ears separately. Initially, the intensity of the stimuli was 35 dB nHL (33.3 Hz) with a masking white noise at 15 dB nHL in the non-stimulated ear. If no response was seen, the intensity level was increased at increments of 10 dB nHL. The intensity was raised to 65 dB nHL, if necessary, until waves III and V were visually identified. The interpretation of the BA recordings was based on the presence of waves III and V. BA was considered normal if the threshold was 35 dB nHL in both ears and abnormal if the threshold was 45 dB nHL or higher in at least one ear.

2.3 | Statistical analysis

First, the unadjusted effects of clinical factors (Table 1) on different BAEP variables and BA normality were analysed. The included BAEP variables were as follows: latencies of BAEP components I, III, V, amplitudes of BAEP components I and V, amplitude ratio I/V, interpeak intervals (IPIs) I-III, I-V and III-V. The right and left ears were analysed separately. The associations between continuous, normally distributed clinical factors and BAEP variables were studied by using Pearson's correlation coefficient. To study the associations between dichotomous clinical factors and BAEP variables, a t test for independent samples was used. The associations between clinical category variables and BAEP variables were studied with an analysis of variance. The associations between BA normality and dichotomous clinical factors were studied using a chi-square test, or, in the case of too few observations, with Fisher´s exact test. The associations between continuous clinical factors and BA normality were studied using a binary logistic regression analysis. The associations between brain MRI and ultrasound and BA normality were studied using a chi-square test.

In the adjusted analysis, clinical factors were chosen based on the unadjusted analysis and the literature. Sex, gestational age, age at the time of BAEP recording, administration of gentamicin and/or vancomycin and the duration of mechanical ventilation were chosen based on several significant unadjusted associations with BAEP or BA. Apgar at 5 min age, severe infection, respiratory distress syndrome (RDS), patent ductus arteriosus (PDA) closure, necrotising enterocolitis (NEC), bronchopulmonary dysplasia (BPD) and retinopathy were chosen based on their association with hearing loss in the literature.[14–18] Next, the clinical factors were divided into three different groups based on the nature of the variable. The clinical characteristic group included variables that describe the status of the infant as follows: sex, gestational age, Apgar score at 5 min and the age at the time of BAEP/BA. The risk factor group included variables that are considered risk factors for hearing loss as follows: the duration of ventilation treatment, sepsis and/or meningitis, administration of ototoxic antibiotics (gentamicin and/or vancomycin), RDS, closure of PDA and NEC. The outcome group included conditions that can result from prematurity as follows: BPD, retinopathy and hearing loss. First, each of the three groups was analysed separately for each BAEP variable by using linear regression analysis and for BA normality by using binary logistic regression analysis. The number of children receiving vancomycin was too small for a logistic regression analysis, and thus, it was analysed with linear regression analysis. All significant clinical factors from each of the three groups and the length of the CPAP treatment were then included in the final model. This was done separately for all BAEP variables and for BA normality. Birth weight was not included in the adjusted analysis due to collinearity with gestational age.

In addition, we conducted an additional regression analysis without Apgar at 5 min age, retinopathy, RDS and BPD variables as they did not have significant associations in the initial univariate analysis. RDS and BPD might also induce a multicollinearity problem with the CPAP treatment duration. Administration of gentamicin and/or vancomycin was removed because almost all infants received

TABLE 1 Clinical characteristics of the study sample, Total *n* = 162

Male, *n* (%)	**94 (58)**
At birth	
Gestational age, weeks, mean (SD), range	29.0 (2.7), 23–35
≤32 weeks, *n* (%)	140 (86)
≤1500 g, *n* (%)	136 (84)
≤1500 g and/or ≤32 weeks, *n* (%)	162 (100)
Height, cm, mean (SD)	38.4 (3.6)
Head circumference, cm, mean (SD)	26.9 (2.6)
Apgar score at 1, 5 and 15 min, mean	6/7/7
Corrected age at the time of BAEP recordings, months, mean (range)	0.8 (−1.2–2.8)
Risk factors for hearing loss	
Respiratory distress syndrome, *n* (%)	113 (70)
Duration of mechanical ventilator treatment, days, mean (SD), range	6(11), 0–60
Duration of CPAP treatment, days, mean (SD), range	17(14), 0–60
No CPAP therapy, *n* (%)	11 (7)
Asphyxia, *n* (%)[a]	7 (4)
Fetofetal transfusion, *n* (%)	6 (4)
Patent ductus arteriosus	
Closure with indomethacin, *n* (%)	63 (39)
Closure by surgery, *n* (%)	20 (12)
Necrotising enterocolitis (NEC), *n* (%)[b]	9 (6)
Infections	
Blood culture positive sepsis and/or meningitis, *n* (%)	19 (12)
Maximum CRP concentration, mg/l, mean (SD)	
Age <1 month from birth	15 (26)
Age >1 month from birth	56 (80)
Ototoxic drug administration	
Diuretics, *n* (%)[c]	18 (11)
Gentamicin, *n* (%)	152 (94)
Vancomycin, *n* (%)	32 (20)
Gentamicin, concentration, mg/l, mean (SD)[d]	2.2 (0.5)
Vancomycin, concentration, mg/l, mean (SD)[d]	8.3 (5.2)
Bilirubin	
Maximum concentration, μmol/l, mean (SD)	184 (43)
Maximum concentration in first three days, μmol/l, mean (SD)	141 (34)
Outcome measures	
Retinopathy (diagnosed by an ophthalmologist), *n* (%)	33/101(33)
Bronchopulmonary dysplasia (BPD), *n* (%)	21 (13)
Hearing loss, *n* (%)	6 (4)

Abbreviations: n, Number; SD, Standard deviation; BAEP, Brainstem auditory evoked potentials; CPAP, Continuous positive airway pressure; CRP, c-reactive protein; MRI,Magnetic resonance imaging.

[a]Asphyxia criteria were Apgar score ≤7 at the age of 1 min combined with breathing difficulty and asphyxia symptoms[30]

[b]NEC was categorised according to Vermont Oxford Network definitions

[c]Diuretics were furosemide and/or hydrochlorothiazide and/or spironolactone

[d]Gentamicin and vancomycin concentrations were measured according to the treatment protocol before the second dose

gentamicin (94%). The dependent variables (BAEP latencies, amplitudes and IPIs) and other explaining variables (clinical factors) were the same as in the initial regression analysis.

Statistical analyses were done using SAS for Windows version 9.4 (SAS Institute Inc). *p*-values below 0.05 were considered statistically significant.

3 | RESULTS

The characteristics of the subjects and data are presented in Table 1. The mean duration of CPAP treatment was 17 days (median 15 days, range 0–60 days). Of the 162 infants, only 11 did not receive any CPAP therapy (0 days). Of these 11 infants, two were on a ventilator during their stay in the NICU. A normal BA was found in 122 infants and an abnormal BA in 32 infants. A hearing loss was diagnosed in six children at the ages of six months to eight years, and they all use a hearing aid.

The main results are presented in Table 2. After controlling for the confounding factors, in the adjusted analysis, a longer CPAP treatment duration associated with a longer latency of BAEP component III ($p = 0.01$) and V ($p = 0.02$) in the right ear. In addition, boys had a significantly longer latency than girls of BAEP component III (left ear $p = 0.0009$), interpeak interval (IPI) I-V (left ear $p = 0.03$) and IPI I-III (right ear $p = 0.02$; left ear $p = 0.0006$). A lower gestational age associated with a longer IPI III-V (left ear $p = 0.04$). A younger corrected age at the time of the BAEP recording was associated with a longer latency of BAEP component V (right ear $p = 0.0006$; left ear $p<0.0001$), IPI I-V (right ear $p = 0.01$; left ear $p = 0.0004$) and IPI III-V (right ear $p = 0.007$; left ear $p = 0.009$). Infants who received gentamicin and/or vancomycin had a longer IPI I-V (right ear $p = 0.006$, left ear $p = 0.007$) and IPI I-III (right ear $p = 0.01$) than infants who did not receive any antibiotics. Children diagnosed with hearing loss had significantly longer latency than normal hearing children of BAEP component V in the left ear ($p = 0.0002$). The duration of mechanical ventilation, RDS, BPD, NEC, sepsis and/or meningitis and retinopathy did not associate with the BAEP variables in the adjusted analysis. (Table 2).

The length of CPAP treatment did not increase the risk of an abnormal BA in our study. Abnormal BA was more often found in babies with later hearing loss (OR 16.9; 95% CI 1.5–184.9; $p = 0.02$).

In the additional regression analysis, the results did not change greatly. However, in addition to the latency of BAEP component V (right ear $p = 0.002$), a longer IPI I-V now associated weakly with a longer duration of CPAP treatment (right ear $p = 0.048$).

4 | DISCUSSION

In the present study, a longer CPAP treatment duration associated, independently from other risk factors, with longer latencies of BAEP components III and V as well as an interpeak interval I-V in the right

TABLE 2 Clinical factors associating with BAEP latencies and interpeak intervals (IPI) in right (R) and left (L) ear according to the adjusted linear regression analysis

BAEP variable	Ear	Clinical factor	B	SE	*p*-value
Latency III	R	Duration of CPAP treatment	0.005	0.002	0.01
	L	Male sex	0.14	0.04	0.0009
	R	PDA closure with indomethacin or operatively	−0.17	0.06	0.005
Latency V	R	Duration of CPAP treatment	0.004	0.002	0.02
	R	Age at the time of BAEP recording	−0.13	0.04	0.0006
	L	Age at the time of BAEP recording	−0.17	0.03	<0.0001
	L	Hearing loss	0.54	0.14	0.0002
IPI I-V	L	Male sex	0.11	0.05	0.03
	R	Age at the time of BAEP recording	−0.09	0.04	0.01
	L	Age at the time of BAEP recording	−0.12	0.03	0.0004
	R	Administration of gentamicin and/or vancomycin	0.32	0.11	0.006
	L	Administration of gentamicin and/or vancomycin	0.32	0.12	0.007
IPI I-III	R	Male sex	0.10	0.04	0.02
	L	Male sex	0.14	0.04	0.0006
	R	Apgar at 5 min age	0.03	0.01	0.02
	R	Administration of gentamicin and/or vancomycin	0.24	0.09	0.01
IPI III-V	L	Gestational age	−0.003	0.002	0.04
	R	Age at the time of BAEP recording	−0.08	0.03	0.007
	L	Age at the time of BAEP recording	−0.07	0.03	0.009
	R	PDA closure with indomethacin or operatively	0.11	0.05	0.02

Abbreviations: B, Beeta, Parameter estimate; BAEP, brainstem auditory evoked potentials; CPAP, continuous positive airway pressure; IPI, interpeak interval; PDA, Patent ductus arteriosus; SE, Standard error.

ear. This prolongation of latencies indicates that CPAP treatment may adversely affect the central auditory conduction, as other potential factors did not contribute to this association. The loud noise created by CPAP devices could have damaged the auditory pathway as the function of the auditory pathway depends on myelination and the synaptic efficacy within the pathway,[12] and both can be impeded by noise.[19,20]

In literature, a conclusion has been made that early noise exposure may damage the developing auditory system.[9,10] However, this conclusion is mostly based on animal studies that have shown that noise can cause dysmyelination of the auditory nerve[20] and damage the synapses in the cochlea.[19] In humans, exposure to noise during pregnancy did not increase hearing screening failure in newborns.[21] In utero, the child is protected from loud noise by amniotic fluid and maternal tissues. In the NICU, this protection is missing. However, increasing attention is paid to noise levels in the NICU.

Our results indicate that particularly the central parts of the auditory pathway are affected by noise because the association was found between CPAP and BAEP components III and V and possibly IPI I-V; these components arise within the lower pons and midbrain, reflecting functional integrity and synaptic efficacy within the more central brainstem pathways.[12] Thus, our results could demonstrate that in preterm infants, prolonged CPAP treatment may interfere with the maturation of the auditory pathways, possibly by impairing myelination or synaptogenesis and synaptic efficacy. This phenomenon is found in the central brainstem structures, rather than the peripheral parts of the pathway, the auditory nerve, and the cochlea.

CPAP devices are a common source of noise in NICUs. Preterm infants especially require long CPAP treatments.[7] CPAP devices have been reported to generate noise with intensities up to 54–89 dB(A). Noise intensities increase with an increasing CPAP flow rate. In addition, the intensities are found to vary between different CPAP devices. At 12 l/min airflow level, the CPAP device applied at the time of the present study (Infant Flow) has been found to generate a noise level of 89 dB(A). [8] This is clearly above the recommendations, suggesting that the noise level in the NICU should not exceed 45 dB.[22]

The number of previous studies investigating the association between CPAP treatment and hearing is limited. Rastogi et al[23] suggested that preterm infants treated with CPAP are not at an increased risk for hearing screening failure or hearing loss compared with infants treated with mechanical ventilation. However, they used simple, not optimally accurate, automated auditory brainstem responses for hearing screening which only give a pass or failure result; furthermore, the duration of CPAP treatment was not taken into consideration. In our study, a longer duration of CPAP treatment associated with longer latencies of components III and V and possibly IPI I-V, which indicates a slower central auditory conduction and maturation. These changes may be too subtle to be detected by routine neonate hearing screening methods.

Significant associations between CPAP treatment and BAEP were found only in the right ear which is the dominant ear in newborns.[24] Studies have shown that the right ear and left auditory cortex are more eligible for processing rapidly changing broadband stimuli, for example, speech,[25] and a right ear advantage can already be seen in newborns.[24] In the present study, boys tended to have significantly longer latencies of BAEP components and IPIs than girls; this is supported by previous studies.[13,26] Infants who received gentamicin and/or vancomycin also had longer IPIs. Both of these antibiotics are considered to be ototoxic.[27]

Studies utilising BAEP and BA recordings have shown that impaired auditory pathway function in the neonatal period can predict developmental problems. BAEP and BA recordings have been found to associate with language development and neurological outcome later in childhood.[1–3] For example, in our previous study, we found that longer IPI I-V in the right ear in neonatal BAEP recordings of preterm infants associated with weak receptive language abilities at the age of one year.[2]

4.1 | Strengths and limitations of the study

The present study included a large cohort of clinically well-documented neonates at increased risk for hearing deficit. Both BAEP and BA were employed as these are considered to be the most sensitive and accurate diagnostic tools for assessing hearing and function of the auditory pathways in neonates.[11] In addition, in Turku University Hospital we have our own large reference value database[13] that allows sensitive and accurate diagnostics. In the present study, neonates were usually tested after discharge at the corrected age of one month when they did not have any acute conditions such as infection or hyperbilirubinemia, which could have influenced the results. However, it is possible that the occurrence of prolonged BAEP components could have been transitory because the BAEP latencies and IPIs decrease with increasing age.[12] In addition, fluid in the ears can temporarily cause prolonged latencies. As we did not conduct any follow-up recordings or examinations of later auditory function, these factors could have influenced our results.

As this was a register study, the blood pressure values, durations of apneas or oxygen levels of individual infants during CPAP treatment were not obtainable. Hyperoxia can disrupt brain development,[28] and thus, it is possible that oxygen administration related to CPAP treatment may influence auditory function. In addition, information about the intensities and flow rates of the Infant Flow CPAP device was not available. Information concerning the distance between the CPAP device and the infant or whether the child was in an incubator or in a crib was also not obtainable. However, the CPAP device itself, located outside of the crib or incubator, is probably not the origin of the loudest noise. The loudest noise is considered to be generated in the nasal prongs leading to the high noise levels reported in the literature.[8]

According to the results of the present study, BA thresholds were not elevated in preterm infants who were treated with CPAP. It could be that the intensity of the device is not great enough to

cause elevation in BA thresholds measured with rough click stimuli at a rather high intensity (35 dB). The typical high-frequency hearing loss caused by noise may not change the thresholds measured with click stimuli, although it might have been identified by frequency specific BA. However, noise generated by CPAP devices may cause disturbances in auditory processing reflected in BAEP as prolonged latencies.

In the future, more research on this subject is needed: studies that would include more modern CPAP devices with sound pressure measurements. In the new, more modern CPAP devices, alarm noise levels might be lower but the sound produced by the airflow has not changed. High-flow nasal cannulae (HFNC) are now also being increasingly used for infants. However, the average noise levels in HFNC and CPAP devices are the same and they both exceed the recommended 45 dB limit.[29] During the years of the present study, HFNC was not yet used in the NICU. It would also be beneficial to investigate the associations between the duration of CPAP treatment and psychoacoustic and neurophysiological findings later in childhood.

5 | CONCLUSIONS

The present study found that CPAP treatment increases the risk for prolonged latencies in BAEP recording, but without a rough hearing threshold elevation in the dominant right ear in preterm infants. The results suggest that the loud noise generated by CPAP devices may damage the developing central auditory pathway in preterm infants. Another explanation for prolonged latencies could also be the ongoing maturation of the auditory pathway during the time of BAEP recording. Thus, more research on the association of CPAP treatment and auditory maturation is needed. From a practical point of view, it would be beneficial to follow the hearing and neurodevelopment of children who have been treated with CPAP in the NICU, paying particular attention to the noise levels of CPAP devices and the length of CPAP treatment.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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How to cite this article: Antinmaa J, Salonen J, Jääskeläinen SK, Kaljonen A, Lapinleimu H. Continuous positive airway pressure treatment may negatively affect auditory maturation in preterm infants. Acta Paediatr. 2021;00:1–8. https://doi.org/10.1111/apa.16029