Early Human Development 103 (2016) 161–165

Contents lists available at ScienceDirect

Early Human Development

journal homepage: www.elsevier.com/locate/earlhumdev

Abnormal findings in brainstem auditory evoked response at 36–37 weeks of postconceptional age in babies with neonatal chronic lung disease

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ARTICLE INFO

Article history:
Received 9 May 2016
Received in revised form 22 July 2016
Accepted 30 August 2016
Available online xxxx

Keywords:
Auditory evoked potentials
Brainstem impairment
Chronic lung disease
Perinatal brain damage
Very preterm infants

ABSTRACT

Aim: To examine brainstem auditory function at 36–37 weeks of postconceptional age in preterm infants who are diagnosed to have neonatal chronic lung disease (CLD).
Study design: Preterm infants, born at 31 and less weeks of gestation, were studied at 36–37 weeks of postconceptional age when they were diagnosed to have neonatal CLD. Brainstem auditory evoked response (BAER) was recorded and analyzed at different click rates.
Results: Compared with healthy controls at the same postconceptional age, the CLD infants showed a slightly increase in BAER wave V latency. However, the I-V, and III–V interpeak intervals in the CLD infants were significantly increased. The III–V/I–III interval ratio was also significantly increased. The amplitudes of BAER waves III and V in the CLD infants tended to be reduced. These BAER findings were similar at all 21, 51 and 91/s clicks, although the abnormalities tended to be more significant at higher than at low click rates.
Conclusion: At 36–37 weeks of postconceptional age, BAER was abnormal in preterm infants who were diagnosed to have neonatal CLD. This suggests that at time when the diagnosis of CLD is made there is functional impairment, reflecting poor myelination, in the brainstem auditory pathway in preterm infants with neonatal CLD.

1. Introduction

The brain damage and neurological impairment in infants who suffer neonatal chronic lung disease (CLD) is known to be due to shared risk factors and causal pathways [6,15]. Among the others, chronic sublethal hypoxia present during the course of CLD may play a major role in the brain damage and neurological impairments in infants with neonatal CLD. The chronic sublethal hypoxia could produce structural, neurochemical and functional alterations in the developing brain, including the brainstem [11,16,20–22]. In experimental rats raised in chronic sublethal hypoxia, we previously observed a marked reduction in staining for myelin basic protein and patchy distribution in the residual myelination in central and upper regions of the brainstem [11]. This was consistent with the abnormal findings in the brainstem auditory evoked response (BAER) in these experimental rats. The BAER has been widely used to assess brainstem auditory function, particularly related to myelination, in infants and children [8,12,26]. In 2006 and 2007, by studying BAER we were the first to report functional impairment in the brainstem auditory pathway at term date in infants who suffer neonatal CLD [11,13,14]. The impairment reflects poor myelination in the pathway at term date in CLD infants. To date, there are no reported studies regarding whether there is also abnormality in brainstem auditory function in CLD infants before term date.

Neonatal CLD occurs predominately in infants who are born at very preterm [10]. Due to the multifactorial nature of the disease process, CLD has long been a challenging neonatal condition for prevention and clinical management [2,9,19,25]. An improved knowledge of the pathogenesis is of great importance for prevention of the disease and improving clinical management of infants with CLD [1,4,5,7]. The diagnosis of neonatal CLD is made at 36–37 weeks of postconceptional age (PCA), i.e. shortly before term age. It is presumable that at time of diagnosis of CLD being made the immature brainstem is already adversely affected by the development of the disease. The understanding is of importance for implementing early neuroprotective intervention shortly after the diagnosis of neonatal CLD is made. We, therefore, examined BAER at 36–37 weeks of PCA in very preterm infants who were diagnosed to have neonatal CLD to uncover if there is any abnormality or impairment in the brainstem auditory pathway.

2. Methods

2.1. Study population

The diagnosis of neonatal CLD was made on the basis of the criteria previously reported [13,14]. The criteria included requirement for supplementary oxygen or ventilatory support beyond 36 weeks of PCA to

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http://dx.doi.org/10.1016/j.earlhumdev.2016.08.015
0378-3782/

maintain PaO2 > 50 mm Hg, clinical signs of chronic lung respiratory disease. To minimize any possible confounding effect of major brain lesions on the BAER, infants who had severe (grade III–IV) intraventricular haemorrhage and periventricular leucomalacia were excluded. Any infants who had major perinatal complications other than neonatal CLD were also excluded. These complications were congenital malformation and congenital or perinatal infection of the central nervous system, hyperbilirubinaemia, hypoxic-ischaemic encephalopathy, neonatal meningitis and persistent pulmonary hypertension, may affect functional integrity of the auditory pathway.

Based on the measurements of main BAER variables (wave V latency and I-V interval) in normal infants to achieve statistical significance for the comparison between groups (probability <0.05), the power calculation ($\alpha = 0.05, \beta = 0.10$), and our previous experience in BAER studies, a minimum 24 infants are needed in each group of infants. Nevertheless, a relatively large number of infants are preferred for a detailed and reliable data analysis to minimize any bias arising from possible variation in individual data obtained. According to the inclusion and exclusion criteria, we recruited 42 very preterm CLD infants, 28 boys and 14 girls, from the Neonatal Unit of the Children's Hospital, Fudan University. Their gestation ranged between 24 and 31 (27.6 ± 2 1.7) weeks and birth weight between 630 and 1555 (1134 ± 229) g. Informed consent was obtained from the parents of each infant. All CLD infants passed the neonatal hearing screening programme with distortion product otoacoustic emission and had a BAER threshold <40 dB nHL to minimize any potential confounding effect of peripheral hearing loss on the recorded BAER waveforms.

The healthy controls were 29 preterm infants who did not had CLD or any other perinatal complications or problems, 19 boys and 10 girls. Since there were rarely healthy infants who were born at 30 or less weeks of gestation, the controls were recruited with a gestation between 31 and 36 (34.4 ± 1.6) weeks. Their birth weight ranged between 1185 and 2640 (2089 ± 385) g. The BAER thresholds at time of BAER recording were all within normal range (20 or less dB nHL).

2.2. BAER recording

The recording in the CLD infants was carried out at PCA 36–37 weeks at which the diagnosis of CLD was made. Similarly, the recording in the healthy controls was also carried out at 36–37 weeks of PCA. The procedures of study were approved by the Children's Hospital Ethics Committee of Fudan University. The recording was performed using a Spirit 2000 Evoked Potential System (Nicolet Biomedical Inc. Madison, WI, USA).

The left ear was tested in all infants to keep consistency in recording conditions and save recording time, the same as in our previous BAER studies [13,14]. The infants lay supine in a baby cot, without using any sedatives. Prior to BAER recording, the auditory meatus was inspected and cleaned of any vernix or wax. After skin preparation, three gold-plated disk electrodes were placed, respectively, at the middle forehead (positive), the left (ipsilateral) earlobe (negative) and the right (contralateral) earlobe (ground). Interelectrode impedances were maintained below 5 kΩ. A TDH 39 earphone, supplied by Nicolet Biomedical Inc. Madison, WI, was comfortably placed over the ear with great care to avoid collapsing ear canals. After the infant fell asleep naturally, often after a feed, the recording was started with a sweep duration of 12 ms on the recording screen of the monitor.

Rarefaction clicks of 100 μs were delivered to the left ear through the earphone. The intensity of the clicks was 60 dB nHL for all infants. For those CLD infants who had a BAER threshold >20 dB nHL and a prolonged wave I latency, suggesting a conductive hearing loss, higher intensities were also used in order to obtain reliable BAER waveform with clearly identifiable waves I, III and V. The clicks were presented at three repetition rates with an order of 21, 51 and 91/s in the first run, and a reverse order in the second run. Brain responses evoked by the clicks were amplified, bandpass filtered between 100 and 3000 Hz, and inputted to the averager. Any data that exceeded 91% of the sensitivity parameter setting (51 μV) were automatically rejected by the system. Sampling was discontinued whenever there were excessive muscle artefacts on the monitoring oscilloscope. Each run, or recording, included the averaged responses to 2048 clicks. To examine reproducibility of the recorded BAER waveforms, duplicate recordings were made in response to each stimulus condition.

After the first BAER testing, some of the CLD infants were re-tested once or twice every one or two days before 37 weeks of PCA, depending on baby's clinical conditions and the availability of testing personnel. In total, 68 test occasions were obtained from the CLD infants.

2.3. BAER analysis

The wave components in BAER were analyzed blind to the medical history and clinical data of each infants. The threshold of BAER was determined by establishing the lowest intensity of the clicks. Measurement of latency and amplitude was made for each of BAER waves I, III and V. Interpeak intervals (I-V, I–III and III–V) were then calculated. The III–V/I–III interval ratio was calculated to assess the relative changes between the III–V and I–III intervals, and the amplitude ratio of waves V and I and III (i.e. V/I and V/III amplitude ratios) were also calculated for relative changes between different wave amplitudes.

For the CLD infants who had a normal BAER threshold (≤20 dB nHL), analysis of BAER data were based on the data collected with the clicks at 60 dB nHL. For those with a BAER threshold >20–30 dB nHL the analysis was based on the data collected at 70 dB nHL (4 test occasions), and for those >30–40 dB nHL the analysis was based on the data collected at 80 dB nHL (1 test occasion). This allowed to obtain reliable and clear BAER waveforms in all CLD infants and to analyse BAER data at a level ≥ 40 dB above the threshold of each infant, the same as in the healthy controls. Measurements of two replicated BAER recordings to each stimulus condition were averaged for data analyses. Comparison of mean and standard deviation of each BAER variable at each stimulus condition was made between the CLD infants and healthy controls using Student's *t*-test. Correlation and regression were made between BAER variables and the repetition rate of clicks. These statistical analyses were conducted using a version 21 SPSS package.

3. Results

3.1. BAER at 21/s clicks

The PCA at which the BAER testing was carried out was similar in the CLD infants (36.5 ± 0.42) and the healthy controls (36.3 ± 0.51). At time of the testing, the BAER thresholds obtained were 13.9 ± 6.3 dB nHL in the CLD infants, which did not differ significantly from that in the healthy controls (13.3 ± 3.8 dB nHL). There was no significant difference in the hearing level at which BAER data were analyzed between the CLD infants (52.1 ± 8.9 dB) and the controls (50.9 ± 9.2 dB). Therefore, the measurements of BAER variables obtained were comparable between the two groups of infants. Means and standard deviations (SD) of BAER wave latencies interpeak intervals (>40 dB above BAER threshold in the CLD infants (68 testing occasions) and healthy controls (29 testing occasions) are given in Table 1, and those of BAER wave amplitudes in Table 2.

At the conventionally used 21/s clicks, the latencies of BAER waves I and III in the CLD infants were slightly, with no statistical significance, shorter than in the healthy controls. On the other hand, wave V latency was slightly longer than that in the healthy controls, without any statistical significance, either. However, the I-V interpeak interval in the CLD infants was significantly longer than that in the healthy controls ($P < 0.05$, Table 1). Of the two smaller components of the I-V interval, the I–III interval in the CLD infants was slightly longer than that in the controls, but III–V interval was significantly longer than that in the