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Short-term outcome of functional integrity of the auditory brainstem in term infants who suffer perinatal asphyxia

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ABSTRACT

Objectives: To assess short-term outcome of impaired functional integrity of the auditory brainstem in term infants who suffer perinatal asphyxia.
Methods: Maximum length sequence brainstem auditory evoked response (MLS BAER) was recorded and analyzed at a mean age of 3 months in term infants after perinatal asphyxia. The data were compared with age-matched normal term infants.
Results: The infants after asphyxia showed an increase in the latency of MLS BAER wave III at 91, 455 and 910/s, and wave V at all click rates of 91–910/s. The interpeak intervals in the infants after asphyxia were increased at almost all click rates. The I—V and I–III intervals were increased at all click rates, and the III–V interval was increased at 455 and 910/s. These increases were generally more significant at higher than at lower click rates. The amplitudes of waves I, III and V in the infants after asphyxia were reduced at all click rates. The V/I amplitude ratio was increased at 91–455/s clicks. The slope of III-V interval-rate function was abnormally increased. 17.1% of the infants after asphyxia had an abnormal increase in I—V intervals.
Conclusions: MLS BAER was moderately abnormal at 3 months of age in term infants after perinatal asphyxia, suggesting moderate impairment in the functional integrity of the auditory brainstem. The impairment occurs in 17.1% of the infants. Compared with that found at term, the impairment has improved, but not completely recovered.

1. Introduction

Perinatal asphyxia, or hypoxia-ischemia occurring during the perinatal period, may severely damage the neonatal brain by processes that continue for many hours after the insult [3,16,21,32]. As a result of the damage, infants after perinatal asphyxia may have long-term or permanent neurological impairment and developmental deficits. An increased understanding of the pathophysiological process and outcome of hypoxic-ischaemic brain damage and neurological impairment is important for clinical management of asphyxiated infants to improve neurodevelopmental outcome [2,4,22,23,30,33].

Early in 1980s, abnormality in brainstem auditory evoked response (BAER) was proposed to be an indicator of early brain insult in infants with perinatal problems [17]. A normal BAER requires the integrity of an anatomically diffuse system in the brainstem that is comprised of a set of auditory neurons, their axons, the synapses between them, and the neurons on which each of the BAER components terminate. Disruption of any portion of the system will alter the amplitude and/or the latency of that component [34,35]. With a relatively new technique — the maximum length sequence technique (MLS), we have studied BAER at term date in term infants who suffered perinatal asphyxia [8,11]. During the first few days after birth, these infants showed major MLS BAER abnormalities that suggest functional impairment of the auditory brainstem. The main abnormalities included a significant increase in I—V and III–V intervals and a significant reduction in wave V amplitudes. From the first day after birth through to the end of the first month after birth, these infants demonstrated characteristic dynamic changes in MLS BAER [8,12,13]. By the end of the first month, there were still some abnormalities, although these were relatively less severe in comparison with those seen in the first a few days after birth [12,13].

After the first month of life, whether there are any further changes in the impaired functional integrity of the auditory brainstem remains to be studied. To address this, we studied MLS BAER between 43 and 64 weeks of postconceptional age (PCA), with a mean age of PCA 54 weeks, equivalent to a mean age of 3 month of life, in a group of term infants after perinatal asphyxia. The latencies and amplitudes and interpeak intervals in MLS BAER were compared in detail with age-matched normal term infants to detect any functional abnormality or impairment in the auditory brainstem. The results were further discussed in comparison with those previously reported at term date in term infants who suffered perinatal asphyxia.

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2. Materials and methods

2.1. Patients

We recruited 35 term infants who suffered perinatal asphyxia. Their gestational age ranged between 37 and 42 weeks (39.6 ± 1.5 weeks), and birth weight between 2605 and 4322 g (3503 ± 392 g). Written informed parental consent was obtained for each baby before the study entry. All were studied at a PCA between 43 and 64 weeks (53.7 ± 7.1 weeks).

The diagnostic criteria of perinatal asphyxia were the same as previously reported [11–13]. These were (a) clinical signs of hypoxic-ischemic encephalopathy (hypotonia with reduced or no spontaneous movements, increased threshold for primitive reflexes, lethargy or coma, absence or very weak suck and requirement of tube feeds, and particularly seizure), and other signs of hypoxia, including frequent depression and failure of breathing spontaneously at birth; and (b) depression of the Apgar score (<6 at 5 min), a widely used definition of perinatal asphyxia despite some arguments, and (c) others: meconium staining of the amniotic fluid, umbilical cord blood pH < 7.10, and evidence of hypoxia-ischemia on cranial magnetic resonance imaging and/or ultrasound scan. Of the 35 infants studied, 8 had stage I (mild) hypoxic-ischaemic encephalopathy, 17 stage II (moderate) and 10 stage III (severe), according to Sarnat and Sarnat (1976). Any infants who had congenital malformation, congenital or perinatal infection of the central nervous system, prolonged hyperbilirubinaemia or neonatal meningitis, were excluded to minimize confounding effects. None of the infants received therapeutic hypothermia to exclude any potential cooling effect on the results.

The normal controls were 36 term infants who had no perinatal problems. Their gestational age ranged between 37 and 42 weeks (39.1 ± 1.3 weeks), and birth weight between 2669 and 4539 g (3468 ± 507 g). The PCA at which the study was carried out was 43–64 weeks (54.1 ± 7.5 weeks). These were all similar to those in the infants after asphyxia, without any significant differences. The Apgar scores in these controls were all ≥ 8 at both 1 and 5 min. Monaural BAER thresholds, determined with conventional BAER, namely the BAER recorded using conventional averaging technique, at the click rate of 21/s, at time of MLS BAER recording were ≤ 20 dB normal nHL in all these controls.

2.2. Recording of MLS BAER

The recording procedures were approved by the Ethics Committee of the Children's Hospital. A Nicolet Spirit 2000 Portable Evoked Potential System (Nicolet Biomedical Inc. Madison, WI, USA) was used to MLS BAER recording and analysis. Recording of MLS BAER was made in the left ear for all infants to ensure that estimates of population statistics were not biased by the ear difference in BAER measurements and to save recording time [11–13,15]. Three gold-plated disk electrodes were placed, respectively, at middle forehead (positive), ipsilateral earlobe (negative) and contralateral earlobe (ground). The impedance between any two electrodes was kept <5 kΩ during MLS BAER recording.

The recording commenced immediately after the baby naturally fell asleep, usually following a feed. No sedatives were used. The baby remained asleep throughout the recording session. Acoustic stimuli were rarefaction clicks with a duration 100 μs, delivered monaurally to the left ear through a TDH 39 headphone. No contralateral masking was used. Conventional BAER was first recorded at 21/s to obtain the threshold, defined as the lowest intensity of clicks that produced visible, replicable wave V. MLS BAER recordings were then started. Sweep duration was set at 24 ms. The sampling rate was 16 kHz. The clicks were presented at 60 dB nHL for all subjects. Higher intensities of the clicks were also used for those who had a BAER threshold > 20 dB nHL (70 dB nHL for two asphyxiated infants with a threshold 25 dB nHL and 80 dB nHL for one with a threshold 40 dB nHL). This allowed MLS BAER data in all infants to be collected at a hearing level or click intensity slightly higher than 40 dB above the threshold of each individual infant, the same as in the normal controls [10,11–13,15]. As a result, the MLS BAER data in the infants after asphyxia could be compared with those in the normal controls at similar hearing levels. Any significant effect of threshold elevation and peripheral hearing loss on the identification and measurements of MLS BAER wave components was minimized.

Two runs of MLS BAER recordings were made for each stimulus condition to assess reproducibility of the recorded waveforms. Presentation of clicks was made at the sequence of 91, 227, 455, and 910/s in the first run, and at a reverse sequence in the second run. Evoked brain responses to 1500 trains of clicks were preamplified, bandpassed at 100–3000 Hz, and then averaged for each run of recording.

2.3. Analysis of data

Measurements of MLS BAER wave components were conducted in the recordings that were obtained at the hearing level or click intensity level of 40 dB or slightly higher above the threshold of each ear tested. Various BAER wave latencies and amplitudes, and interpeak intervals were measured and analyzed. The mean measurements of two replicated MLS BAER recordings to each stimulus condition were used for data analyses. A SPSS package version 20 (Chicago, IL) was used for data analysis.

Comparison of the mean and standard deviation of each MLS BAER variable at each stimulus condition was made between the infants after asphyxia and the normal controls using Student *t*-test. A 2-tailed value of $p < 0.05$ was considered statistically significant. The numbers and percentage rates of major MLS BAER abnormalities in the infants after perinatal asphyxia were obtained for the prevalence of brainstem auditory abnormality in individual infants.

Correlation analysis was conducted to obtain correlation coefficient for the relationship between each MLS BAER variable and click rate (two-tailed test of significance). For those MLS BAER variables that were significantly correlated with click rate, regression analysis was carried out to assess the linear relationship between MLS BAER variables and click rate, and to obtain the latency-, and interval-rate functions. Previous MLS BAER studies in infants have shown that at very high rate of clicks there are characteristic changes in MLS BAER wave latencies and interpeak intervals [15]. For the reasons previously described [15], the regression analysis was conducted between 91 and 455/s, instead of between 91 and 910/s, the same as in our previous studies [15]. The slope for each of the latency-, and interval-rate function was then calculated. For those functions that were significantly greater than zero at the 0.05 level or better in both asphyxiated and control groups, comparison of the slopes were made between the two groups of infants using Student *t*-test to detect any differences between the infants after asphyxia and the normal controls in the changes in MLS BAER components with varying click rate, namely the click rate-dependent changes.

3. Results

Table 1 presents the means and standard deviations (SD) of BAER threshold and MLS BAER wave latencies and interpeak intervals, and Table 2 presents the means and SD of MLS BAER wave amplitude variables. BAER threshold in the infants after perinatal asphyxia was higher than that in the normal controls, but the difference did not reach statistical significance (Table 1). The click intensity level above the thresholds of individual subjects, at which the measurements of MLS BAER recordings were analyzed, in the infants after asphyxia (51.3 ± 5.2 dB nHL) were almost the same as in the normal controls (51.4 ± 4.5 dB nHL). With the increase in click rate, all wave latencies and interpeak intervals were increased and wave amplitude were reduced. This was generally the same in the two groups of infants. The results of the linear