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Functional integrity of rostral regions of the immature brainstem is impaired in babies born extremely preterm

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HIGHLIGHTS

- The most important abnormality in brainstem evoked response in babies born at 23–27 weeks of gestation was a significant increase in III–V interval and its click rate-dependent change.
- Babies born extremely preterm have a major impairment in functional integrity in the rostral regions of the immature brainstem.
- The impairment in extremely preterm babies is more significant than in late and very preterm babies.

ABSTRACT

Objective: Babies born extremely preterm are predisposed to brain damage. We test the hypothesis that functional integrity of the auditory brainstem, particularly the rostral regions, is impaired in extremely preterm babies.
Methods: We recruited 68 babies who were born at 23–27 weeks of gestation. At term date, these babies were studied by recording and analysing maximum length sequence brainstem auditory evoked response (MLS BAER) with click rates 91–910/s. Detailed data analysis was performed in 65 babies from whom reliable MLS BAER measurements were obtained.
Results: Compared with normal term controls, the extremely preterm babies showed a significant increase in wave V latency, and I–V interval at all rates 91–910/s ($p < 0.01$–0.001). Of two small intervals, I–III interval showed no apparent abnormality, but III–V interval was significantly increased at all rates, which was supported by a significant increase in III–V/I–III interval ratio (all $p < 0.001$). These abnormalities were more significant at higher than at lower rates. The slopes of wave V latency-, I–V interval- and particularly III–V interval-rate functions were all increased. The same was true for the slope of III–V/I–III interval ratio-rate function.
Conclusions: MLS BAER variables that mainly reflect central neural conduction in the extremely preterm babies were abnormally increased. The most important abnormality was a significant increase in III–V interval and its click rate-dependent change. The abnormalities tended to be more significant than those previously reported in late and very preterm babies.
Significance: Babies born extremely preterm have a major impairment or maturational delay in functional integrity of the rostral regions of the immature brainstem, which is more significant than in less preterm babies.

1. Introduction

It is well known that babies born preterm, particularly extremely preterm, are predisposed to brain damage and neurodevelopmental deficits (Aarnoudse-Moens et al., 2009; Allen, 2008; Anderson and Doyle, 2008; Bolisetty et al., 2014; Fawke, 2007; Folkerth, 2007; Griffiths et al., 2013; Hack and Taylor, 2000; Ishii et al., 2013; Serenius et al., 2013; Xoinis et al., 2007). The damage can involve in various areas of the very immature brain (Dyet et al., 2006; Padilla et al., 2015). Extremely preterm babies also often showed global reductions in cortical and subcortical gray matter, brainstem, and an increased cerebrospinal fluid volume

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(Padilla et al., 2015). When they grow up, these babies often have various degrees of neurodevelopmental deficits, including development delay, sensory and cognitive impairments, behavioral problems, and learning disabilities, etc. Even those who have no obvious major perinatal complications may also have a certain degree of neurodevelopmental deficits (Anderson and Doyle, 2008; Bolisetty et al., 2014; Griffiths et al., 2013; Ishii et al., 2013; Marlow et al., 2005; Payne et al., 2013; Wood et al., 2000). By comparison, whether there is brainstem abnormality remains poorly understood.

Maturational process of the immature human brain and development of sensory and cognitive function can be assessed and monitored using non-invasive neurophysiological techniques, such as evoked potentials and event-related potentials. These techniques can also be used to detect neonatal brain damage, and later neurological impairment and developmental deficits. This is also the case for babies and children born extremely preterm (de Regnier, 2008). Among these neurophysiological techniques, brainstem auditory evoked response (BAER) is a widely used evoked potential to examine functional integrity of the immature brainstem and detect abnormality in clinical conditions that may affect the brainstem auditory pathway (Hall 2007; Jiang 2012, 2013; Wilkinson and Jiang, 2006). More recently, the maximum length sequence (MLS) has been introduced to study the BAER, mainly in neonatal neurology (Jiang, 2012, 2013; Jiang et al., 2000; Jirsa, 2001; Lasky, 1997; Wilkinson et al., 2007). The high-rate stimulation in MLS provides a much stronger temporal/physiological challenge to auditory neurons, enabling us to gain new insights into functional properties of the brainstem and the auditory pathway. This also helps detect some, particularly subtle or occult, brainstem neuropathology that affect the brainstem auditory pathway but may not be detected by conventional BAER (Jiang, 2012, 2013).

We have previously reported MLS BAER studies in high risk preterm babies who were born at 33–36 week (late preterm) and 28–32 week gestation (very preterm) (Jiang et al., 2012; Jiang and Chen, 2014). These babies showed some MLS BAER abnormalities, suggesting functional impairment in the auditory brainstem. In babies born at 28–32 week gestation, the functional impairment occurs mainly in the rostral regions of the immature brainstem, which tended to be more significant than in those born at 33–36 week gestation. It is presumable that there is also brainstem impairment in babies who are born more prematurely or more preterm (i.e., gestation less than 28 weeks), and the impairment could be more severe than those born less prematurely (28 week or more gestation). In addition, the extremely early exposure to the sound environment *extra utero* could exert certain effect on the peripheral auditory neural pathway. To test the assumption we conducted a detailed study of MLS BAER in babies who were born at 27 week or less gestation to detect any abnormalities in the immature brainstem. The main MLS BAER data in these extremely preterm babies were further compared with those in late and very preterm babies we previously reported to identify any differences (Jiang et al., 2012; Jiang and Chen, 2014).

2. Populations and methods

2.1. Study populations

The study group included 68 babies who were born at 23–27 week (25.7 ± 1.3 week) gestation, birth weight ranging between 559 and 1320 g (831 ± 211 g). There were 28 boys and 40 girls. All were recruited from the Neonatal Unit of John Radcliffe Hospital, University of Oxford. Written informed consent of parents was obtained for each baby before the study entry. These babies had various associated perinatal complications or problems, including apnea, respiratory distress syndrome, bronchopulmonary dysplasia, hyperbilirubinemia, intraventricular haemorrhage, periventricular leukomalacia, metabolic acidosis, hypoglycaemia, patent ductus arteriosus, hypotension, preterm rupture of membranes, necrotizing enterocolitis, sepsis. Significant hearing losses are known to reduce the accuracy in identifying and measuring MLS BAER wave components (Jiang, 2012, 2013). To minimize this adverse peripheral effect, we excluded any babies who had significant peripheral hearing loss (threshold ⩾40 dB normal hearing level — nHL, determined using conventional BAER with 21/s clicks), the same as our previous MLS BAER studies for neurological assessment (Jiang, 2012; Jiang and Chen, 2014; Jiang et al., 2010, 2012; Wilkinson et al., 2007). All babies passed neonatal hearing screening. MLS BAER testing was conducted at term date (37–42 week postconceptional age — PCA) when the babies were in a relatively stable clinical condition, without using supplemental oxygen and ventilation.

The normal term controls were 40 healthy term babies, including 17 boys and 23 girls. Their gestation ranged between 37 and 42 weeks (39.1 ± 1.2 weeks), and birth weight between 2550 and 4525 g (3447 ± 468 g). Monaural hearing threshold was 20 dB nHL or less. None had any major perinatal conditions or problems, listed above. MLS BAER testing was conducted between the 2nd and 5th day after birth.

2.2. Recording of MLS BAER

The testing procedures were approved by the Central Oxford Research Ethics Committee. 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. A Nicolet Spirit 2000 Portable Evoked Potential System (Nicolet Biomedical Inc. Madison, WI, USA) was used to MLS BAER recording and analysis. The study was conducted between May 2008 and February 2012.

Recording of MLS BAER was made in the left ear for all babies to insure that estimates of population statistics were not biased by the ear difference in BAER measurements and to save recording time (Jiang, 2013; Jiang and Chen, 2014; Jiang et al., 2010, 2012, 2014). 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. Sweep duration was set at 24 ms. Acoustic stimuli were rarefaction clicks with a duration 100 μs, delivered monaurally to the left ear through a TDH 39 headphone at 60 dB nHL. No contralateral masking was used.

For neurological assessment, recording of BAER (and measurement and analysis of BAER variables), particularly for MLS BAER, should be made at a hearing level or click intensity of 40 dB or slightly higher above the BAER threshold level of each subject (Jiang, 2012, 2013). This intensity was used in order to compensate for individual differences in hearing sensation and for the influence of sensation level on BAER and MLS BAER interpeak intervals (Jiang, 2012, 2013; Sohmer and Friedman, 1992; Stockard et al., 1979). Thus, in this study although a click intensity 60 dB nHL was used 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 4 extremely preterm babies with a threshold 25 or 30 dB nHL and 80 dB nHL for one babies with a threshold 35 dB nHL). This allowed MLS BAER data in all babies to be collected at a hearing level or click intensity slightly higher than 40 dB above the threshold of each subject. Whereby, any significant effect of threshold elevation and peripheral hearing loss on identification and measurements of MLS BAER wave components was minimized, and MLS BAER data could be compared between different groups of