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Impaired neural conduction in the auditory brainstem of high-risk very preterm infants

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HIGHLIGHTS

- High-risk very preterm infants showed significantly abnormalities in maximum length sequence brainstem auditory evoked response, particularly the components that reflect central neural function.
- The abnormalities were more significant when compared with normal term infants than with low-risk very preterm infants.
- The impaired neural conduction along the auditory brainstem, mainly the more central regions, in high-risk very preterm infants is mainly attributed to the associated perinatal problems and partly related to very preterm birth.

ABSTRACT

Objective: To test the hypothesis that neural conduction in the auditory brainstem is impaired in high-risk very preterm infants.
Methods: Eighty-two very preterm infants (gestation 28–32 weeks) with various perinatal problems or complications were studied at term using maximum length sequence (MLS) brainstem auditory evoked response (BAER) with click rates 91–910/s. The data were compared with those in 31 age-matched low-risk very preterm infants and 44 normal gestation (term) infants.
Results: High-risk very preterm infants showed a general increase in MLS BAER wave latencies and interpeak intervals. Wave V latency, and III–V and I–V intervals in high-risk very preterm infants were significantly longer than in normal term infants at all click rates, particularly higher rates. I–III interval was significantly longer, and III–V/I–III interval ratio was significantly greater at higher rates. These latency and intervals in high-risk very preterm infants were also longer, though relatively less significantly, than in low-risk very preterm infants. Click rate-related changes in major MLS BAER variables in high-risk infants were more significant than in the two groups of controls.
Conclusions: There were major abnormalities in MLS BAER variables that mainly reflect central neural conduction in high-risk very preterm infants. The abnormalities were relatively less significant when compared with low-risk very preterm infants than with normal term infants.
Significance: Neural conduction in the auditory brainstem, mainly the more central regions, is impaired in high-risk very preterm infants. The impairment is largely attributed to the associated perinatal problems, and partially related to very preterm birth.

1. Introduction

Infants who are born at very preterm (gestation < and = 33 weeks) are often associated with various perinatal problems or complications. Many of these problems may directly or indirectly damage the very immature brain. A large body of research shows evidence that high-risk preterm, particularly very preterm, infants, i.e., those who have perinatal problems or complications, are at an increased risk of brain damage, neurological impairment and developmental deficits late in life, e.g., significant development delay, sensory and cognitive impairments, learning disabilities, and behavioral and emotional problems (e.g., Aarnoudse-Moens et al.,

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2009; Allen, 2008; Fawke, 2007; Folkerth, 2007; Hack and Taylor, 2000; Lawrence et al., 2010; Saigal and Doyle 2008; Schafer et al., 2009; Stewart et al., 1999; Vohr et al., 2005). Very preterm infants are also predisposed to auditory problems (Newton, 2001; Wilkinson and Jiang, 2006). Those who have perinatal problems are more prone to developing auditory impairment and at a significantly higher risk for auditory neuropathy and sensorineural hearing loss (Marlow et al., 2005; Wilkinson and Jiang, 2006; Xoinis et al., 2007). Nevertheless, our knowledge of the functional integrity of the auditory system in high-risk very preterm infants remains very limited.

Previous studies of auditory function in preterm infants were mainly using the brainstem auditory evoked response (BAER), with varied results (Amin et al., 1999; Eggermont and Salamy, 1988; Hall, 2007; Lasky et al., 2012; Volpe, 2001; Wilkinson and Jiang, 2006). More recently, the maximum length sequence (MLS) has been used to study the BAER in infants and children (Jiang, 2008, 2012; Jiang and Wilkinson, 2012; Jiang et al., 2000; Jirsa, 2001; Lasky, 1997; Wilkinson et al., 2007). This relatively new technique uses patterned stimulus presentation rather than the uniformly spaced stimuli used in conventional BAER. The nature of the stimulus, along with the relatively new processing technique, allows presentation of stimuli at much higher rates (up to 1000/s or even higher) than is possible with conventional averaging methods, because it permits the overlap of responses to successive stimuli (Jiang, 2012; Picton et al., 1992). The higher rates provide a much stronger temporal/physiological challenge to auditory neurons, and permit a more exhaustive sampling of physiological recovery or "fatigue" than is possible with conventional stimulation. This enables us to gain new insights into functional properties of the brainstem and the auditory pathway, and provides some novel information about neural processing that cannot be offered by conventional BAER. Clinically, this enables this technique to have a potential to detect some early or subtle brainstem auditory neuropathology that may not be shown by conventional BAER, improving the sensitivity of the BAER in detection of neuropathology that affects the brainstem auditory pathway (Jiang, 2012).

Using the MLS technique, we have previously studied the BAER in infants with a range of perinatal conditions or problems. The results have documented that this relatively new technique improves the detection of auditory abnormality and brain damage or neuropathology in some perinatal problems that affect the brainstem auditory pathway, typically perinatal hypoxia–ischemia (Jiang, 2008, 2012; Jiang and Wilkinson, 2012; Jiang et al., 2000,2003,2007,2009a,b,2010,2012; Li et al., 2011; Wilkinson et al., 2007). We have recently found that high-risk infants born at late preterm, i.e., high-risk late preterm infants, are at risk of brainstem auditor impairment (Jiang et al., 2012). It is conceivable that high-risk infants born at very preterm, i.e., high-risk very preterm infants, are also at risk of brainstem auditor impairment. We hypothesize that very preterm birth and, in particular, the associated perinatal problems affect or damage axonal myelination and synaptic function, which determine neural conduction, in the auditory brainstem, leading to impaired neural conduction.

To test the hypothesis, we carried out a detailed study of MLS BAER in high-risk very preterm infants, except for those who had neonatal chronic lung disease or bronchopulmonary dysplasia that is known to have a major detrimental effect on the very immature auditory brainstem (Jiang and Wilkinson, 2012; Jiang et al., 2010; Wilkinson et al., 2007). The data obtained were compared with those in normal term infants to detect any abnormalities in the auditory brainstem. Comparison of MLS BAER data was also made between high-risk very preterm infants and age-matched low-risk very preterm infants to exclude or minimize any potential confounding effect of very preterm birth on the results.

2. Materials and methods

2.1. Subjects

There were one study group (high-risk very preterm infants) and two control groups (normal term infants, and low-risk very preterm infants who were matched in gestation with the study group). Informed consent of parents was obtained for each subject before the study entry. These infants were all examined at term age (37–42 weeks postconceptional age – PCA). There were significant differences in the PCA between these groups (PCA 39.3 ± 1.8, 39.4 ± 1.4, and 39.6 ± 1.7 weeks, respectively, for the high-risk very preterm infants, normal term controls, and low-risk very preterm controls).

High-risk very preterm group—82 infants who were born between 28 and 32 weeks (29.8 ± 1.3 weeks) of gestation and had one or more major perinatal complications or problems (e.g. respiratory distress syndrome, apnea, hyperbilirubinemia, intraventricular haemorrhage, periventricular leukomalacia, metabolic acidosis, sepsis, hypoglycaemia, patent ductus arteriosus, hypotension, preterm rupture of membranes). None had neonatal chronic lung disease or bronchopulmonary dysplasia to exclude the known major effect on the MLS BAER (Jiang, 2012; Wilkinson et al., 2007), as that we could have a better understanding of the effect of other perinatal problems on the auditory brainstem. Birth weight ranged between 986 and 2200 g (1457 ± 311 g). As in our previous MLS BAER studies (Jiang, 2012; Jiang et al., 2010, 2012; Wilkinson et al., 2007), any infants who had significant peripheral hearing loss (threshold ⩾40 dB normal hearing level—nHL, tested with conventional BAER) were excluded to minimize any significant effect of peripheral hearing loss on the measurements of MLS BAER components.

Normal term control group—44 infants who were born between 37 and 42 weeks (39.0 ± 1.2 weeks) of gestation and did not have any major perinatal problems. Birth weight ranged between 2543 and 4496 g (3451 ± 467 g). Monaural hearing threshold was 20 dB nHL or better, determined by conventional BAER, i.e., the BAER that obtained using conventional averaging techniques, with clicks delivered at a repetition rate 21/s.

Low-risk very preterm control group—31 infants who were born between 28 and 32 weeks of gestation but did not have any major associated perinatal problems. The gestation (30.1 ± 1.3 weeks) did not differ significantly from the high-risk very preterm group. Birth weight ranged between 1210 and 1950 g (1,519 ± 158 g), which was slightly higher than, but did not differ significantly from, that in the high-risk very preterm infants. Monaural hearing threshold was 20 dB nHL or better.

2.2. Recording of MLS BAER

The recording was carried out using a Nicolet Spirit 2000 Portable Evoked Potential System (Nicolet Biomedical Inc. Madison, WI, USA). The procedures of MLS BAER recording and analysis were reviewed and approved by the Children's Hospital Ethics Committee of Fudan University. The left ear was tested in all infants to keep consistency in recording conditions and save recording time, the same as in our previous MLS BAER studies (Jiang et al., 2010, 2012; Wilkinson et al., 2007). 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. Sweep duration was set at 24 ms. Acoustic stimuli were rarefaction clicks with a duration 100 μs, delivered monaurally through a TDH 39 headphone to the left ear.