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Original article

Impaired function of the auditory brainstem in term neonates with hyperbilirubinemia

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Abstract

Objective: We studied maximum length sequence brainstem auditory evoked response in term neonates with hyperbilirubinemia to further our understanding of hyperbilirubinemia on the neonatal auditory brainstem and to determine if maximum length sequence technique improves detection of brainstem auditory impairment due to bilirubin neurotoxicity. *Methods:* Maximum length sequence brainstem auditory evoked response was recorded and analysed shortly after confirming total serum bilirubin levels greater than 15 mg/dL in fifty-seven term neonates with hyperbilirubinemia. *Results:* Most wave latencies and interpeak intervals in maximum length sequence brainstem auditory evoked response in the neonates with hyperbilirubinemia were correlated with the level of total serum bilirubin at some or most click rates used. Compared with age-matched normal term controls, wave V latency in these neonates was increased significantly at all 91–910/s click rates ($p < 0.05$–0.001). The I–V and I–III interpeak intervals were also increased significantly at all these rates, and the III–V interval increased at 227–910/s clicks ($p < 0.05$–0.001). The differences between the neonates with hyperbilirubinemia and the controls were more significant at higher than at lower click rates. The slopes of wave V latency-rate function and I–V and III–V interval-rate functions were all significantly increased. By comparison, the abnormalities in conventional BAER were less significant, with only I–III and I–V intervals were increased (both $p < 0.05$). *Conclusions:* Functional status of the auditory brainstem is impaired in neonatal hyperbilirubinemia. Maximum length sequence technique at high click rates improves detection of bilirubin neurotoxicity to the neonatal auditory brainstem, particularly for the more rostral regions.

Keywords: Hyperbilirubinemia; Bilirubin neurotoxicity; Neonatal auditory brainstem; Auditory evoked response; Term neonate

1. Introduction

A significant increase in serum bilirubin, i.e. hyperbilirubinemia, can result in multiple neurologic impairment and deficits [1–4]. In neonates, hyperbilirubinemia is a most common condition requiring evaluation and treatment [5–10]. An increased understanding of the effect of hyperbilirubinemia on the brain and, in particular, promptly detection of neural impairment due to hyperbilirubinemia are crucial for timing treatment as to reduce the risk of kernicterus occurring, improving the outcome of infants with hyperbilirubinemia [11,12].

The brainstem auditory pathway is known to be sensitive to bilirubin neurotoxicity [4,13]. The functional status of this pathway can be reflected by recording and analysing the brainstem auditory evoked response (BAER), a well-known objective test that particularly suits for infants [14,15]. The response has been previously used as an important tool to assess the effect of

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hyperbilirubinemia on the brain, specifically the auditory brainstem. Most investigators found some abnormalities in infants with hyperbilirubinemia [16–25], while others did not [26,27].

Some previous investigators noticed that conventional BAER, i.e. the BAER that is recorded using conventional averaging techniques, has some limitations in detection of brain damage and neural impairment [15,28–30]. It often fails to demonstrate some early or subtle neural impairment. More recently, the maximum length sequence (MLS) has been introduced to study functional status of the auditory pathway [29–34]. Several lines of recent evidence have documented that the BAER that is recorded and analysed using the MLS technique (MLS BAER) enhances the detection of brain damage and neural impairment in some neonatal problems, typically perinatal hypoxia or hypoxia–ischaemia [29,35–39]. However, there are no reported studies regarding MLS BAER in infants with hyperbilirubinemia. It is unclear whether the MLS technique improves the detectability of BAER for bilirubin neurotoxicity to the neonatal brainstem. Based on the findings in MLS BAER studies in infants with some other perinatal problems, it is plausible that the MLS technique can improve the detection of bilirubin neurotoxicity to the neonatal brainstem. To test this hypothesis and further our understanding of the neurotoxicity of bilirubin to the neonatal brain, we undertook a detailed study of MLS BAER in term neonates who had hyperbilirubinemia.

2. Methods

2.1. Subjects

Included were 57 term neonates who were diagnosed as hyperbilirubinemia during the first 10 days after birth. Gestation ranged between 37 and 42 weeks (39.2 ± 1.3 weeks), and birthweight between 2265 and 5305 g (3422 ± 537 g). Total serum bilirubin (TSB) levels were all greater than 15 mg/dL, ranging in 15.3–36.6 mg/dL (19.9 ± 3.5 mg/dL) and required phototherapy and/or exchange transfusion during the first 10 days of life. Twenty-two of these neonates had evidence of hemolysis (rhesus hemolytic disease, anaemia, a positive direct antiglobulin test, reticulocytosis, or a peripheral blood smear compatible with hemolysis), 6 had an associated infection (pneumonia or sepsis), 13 had Apgar scores of 4–7 at 1 and 5 min, and the remaining 16 did not have any major perinatal problems except for hyperbilirubinemia.

Neonates who had any major perinatal problems or complications that can affect the neonatal BAER had been excluded to minimize any confounding effects. These included congenital malformations, in utero infection, a family history of hearing loss, low birthweight, severe intrauterine growth retardation, bacterial meningitis, seizures, hypoxia–ischemia, persistent pulmonary hypertension, and ototoxic medication [15]. Significant peripheral hearing problems can affect MLS BAER waveforms and the measurements of MLS BAER wave components [29]. To minimize such an effect 2 neonates who had a BAER threshold >40 dB normal hearing level (nHL) had been excluded from the study entry. Those who failed our neonatal hearing screening programme with distortion product otoacoustic emission were also excluded.

Normal controls were 43 healthy term neonates, with a gestation 37–41 weeks (38.9 ± 1.2 weeks), and birthweight 2569–4539 g (3460 ± 459 g). All had a monaural hearing threshold less than 20 dB normal hearing level (nHL). None had any major perinatal conditions and any evidence of hyperbilirubinemia.

2.2. MLS BAER recording procedures

This study was approved by the Central Oxford Research Ethics Committee. The informed consent of parents was obtained for all subjects. Recording of MLS BAER was conducted during the first 10 days after birth when there were clinical signs of jaundice and a TSB level greater than 15 mg/dL. At time of MLS BAER testing, postconceptional age was 37–42 weeks for both study and control groups; 39.4 ± 1.3 weeks for the study group and 39.1 ± 1.4 weeks for the control group, which did not differ significantly.

Shortly (within 30 min) after obtaining blood sample and confirming TSB level greater than 15 mg/dL, the subjects were prepared for MLS BAER recording. The subjects lay supine in a cot in a quiet room. The auditory meatus was inspected and cleaned of any vernix or wax. Three gold-plated disc electrodes were placed, respectively, at the middle forehead (positive), the left (ipsilateral) earlobe (negative) and the right (contralateral) earlobe (ground). Recording of MLS BAER was made using a Spirit 2000 Evoked Potential System (Nicolet Biomedical Inc. Madison, WI, USA). Interelectrode impedances were maintained at 5 kΩ or below. Rarefaction clicks of 100 μs were delivered to the ear through a TDH 39 earphone (supplied by Nicolet Biomedical Inc. Madison, WI), which was comfortably placed over the ear with great care to avoid pressing the ear canal. Only the left ear was tested in all subjects to save the time of recording, the same as our previous MLS BAER studies [35–39].

After the subject fell asleep naturally, often after a feed, conventional BAER was recorded at 21/s clicks to determine BAER threshold (the lowest intensity at which wave V can be reliably recognised) and obtain BAER data for comparison with MLS BAER data at the same click intensity levels. Thereafter, recording of MLS BAER commenced at 60 dB nHL of clicks. Higher intensities were also used in those who had an increased BAER threshold (>20 dB nHL). The clicks were