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Increased fetal heart rate variability in periventricular leukomalacia

Hirokazu Kurahashi [a,b], Akihisa Okumura [a,c,*], Tetsuo Kubota [d], Hiroyuki Kidokoro [b,d], Koichi Maruyama [b], Masahiro Hayakawa [b,e], Atsuo Itakura [e,f], Katsuji Matsuzawa [g], Hiroyuki Yamamoto [b], Toru Kato [h], Fumio Hayakawa [h], Kazuyoshi Watanabe [d]

[a] *Department of Pediatrics, Aichi Medical University, Nagakute, Aichi, Japan*
[b] *Department of Pediatrics, Nagoya University Graduate School of Medicine, Nagoya, Japan*
[c] *Department of Pediatrics, Juntendo University Faculty of Medicine, Tokyo, Japan*
[d] *Department of Pediatrics, Anjo Kosei Hospital, Anjo, Aichi, Japan*
[e] *Maternity and Perinatal Care Center, Nagoya University Hospital, Nagoya, Japan*
[f] *Department of Obstetrics and Gynecology, Juntendo University Faculty of Medicine, Tokyo, Japan*
[g] *Department of Gynecology and Obstetrics, Anjo Kosei Hospital, Anjo, Aichi, Japan*
[h] *Department of Pediatrics, Okazaki City Hospital, Okazaki, Aichi, Japan*

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Abstract

Objective: This study used quantitative analysis to determine whether increased variability in fetal heart rate (FHR) is related to the risk of developing periventricular leukomalacia (PVL).

Methods: We analyzed 124 FHR traces of neonates delivered preterm at 27–33 weeks' gestation to 105 mothers. FHR traces 1–3 h before delivery were translated into power-spectrum curves using a fast Fourier transformation. The total power (the area under the curve of 1–10 cycles per minute), segmental power of every cycle per minute, peak power, and frequency edges were calculated, and their relationship with the subsequent development of PVL was examined.

Results: Total power was significantly higher in the PVL group ($n = 9$, median 1813, range 1064–2426) compared to the non-PVL group ($n = 114$, median 1383, range 381–3324, $p = 0.029$). Infants in the PVL group had greater segmental power in segments with 1–2, 2–3, and 9–10 cycles per minute, than those in the non-PVL group. Total power of $\geqslant 1550$ was significantly correlated with the subsequent development of PVL and premature rupture of membranes. Furthermore, the frequency of pregnancy-induced hypertension was significantly reduced in the fetuses with a total power of $\geqslant 1550$.

Conclusion: Our study suggests that a fetus with increased FHR variability is at risk of developing PVL. This study provides additional evidence supporting the contribution of antenatal factors to the subsequent development of PVL.

Keywords: Periventricular leukomalacia; Fetal heart rate; Long-term variability; Fast Fourier transform

1. Introduction

Periventricular leukomalacia (PVL) is one of the most important causes of neurological sequelae in preterm infants, including the development of intellectual and visual deficits, and spastic diplegia. PVL cannot be detected until after the precipitating event. Therefore,

* Corresponding author at: Department of Pediatrics, Aichi Medical University, 1-1 Yazako Karimata, Nagakute, Aichi 480-1195, Japan. Tel.: +81 561 62 3311; fax: +81 561 63 4835.
E-mail address: okumura.akihisa.479@mail.aichi-med-u.ac.jp (A. Okumura).

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it is difficult to determine the timing of brain injury and assess the cause. Regardless of the pathogenesis resulting in the brain injury, electroencephalography (EEG) is a powerful tool for assessing brain damage in preterm infants [1,2]. The severity of acute-stage EEG abnormalities parallels the severity of PVL [3,4]. Furthermore, EEG is more sensitive for detecting PVL than cranial ultrasonography [5]. In addition, the timing of the brain injury can be inferred based on serial EEG recordings beginning immediately after birth. Our previous studies indicated that the timing of brain injury occurs in the antenatal or perinatal period in a large majority of infants with PVL [4,6–8]. Although periventricular vascular anatomical abnormalities, impaired cerebrovascular autoregulation, and vulnerability of cerebral white matter to injury are thought to contribute to the pathogenesis of PVL [9], several studies have indicated that prenatal factors contribute to the development of PVL [10–14]. Of these factors, intrauterine infection, inflammation, and cytokine release have garnered strong attention from researchers [15–17].

Monitoring of fetal heart rate (FHR) is commonly performed during labor and delivery for assessing the well-being of the fetus. Traditionally, the interpretation of FHR monitoring has emphasized markers of fetal distress which suggest fetal hypoxia or acidosis. Loss of variability, and the presence and severity of deceleration suggest a poor fetal prognosis [18,19]. However, few studies have examined the relationship between FHR monitoring and brain injury in preterm infants [20,21]. Presently, there is no established FHR pattern that predicts the subsequent development of PVL in preterm infants. Okamura et al. reported that increased FHR variability is related to an intrauterine environment which contributes to PVL formation. An oscillatory trace with increased baseline variability and tachycardia with superimposed deceleration were significantly associated with the incidence of PVL [22]. Together, these data might provide a clue for establishing a method for distinguishing fetuses at high risk for developing PVL. The work performed by Okamura et al. was based on a visual inspection of FHR traces. In the present study, we quantitatively evaluated the waveform of FHR traces using a fast Fourier transform algorithm to assess whether it is possible to identify fetuses at risk of developing PVL, and to explore the obstetric factors affecting FHR patterns.

2. Methods

We reviewed the FHR traces of preterm infants delivered at 27–33 weeks gestation at Nagoya University Hospital and Anjo Kosei Hospital between 1998 and 2004. Infants were excluded if we could not obtain sufficient follow-up information after discharge from the neonatal intensive care unit, or if they had congenital or chromosomal anomalies. We also excluded infants who had postnatal episodes, such as severe, prolonged hypotension and renal failure, potentially resulting in brain insult, because we clarified the relationship between PVL and the antenatal fetal state represented by the FHR traces. We also excluded certain cases of multiple births when it was difficult to distinguish the FHR trace of the infant(s) who developed PVL from that of the normal infant(s). This study was approved by the ethics committee of Nagoya University Graduate School of Medicine.

This study analyzed FHR recordings made immediately before labor onset. The FHR was analyzed as follows. We focused on FHR traces during the steady state before the onset of delivery. FHR traces with deceleration were excluded, and FHR segments recorded 1–3 h before the onset of delivery with no strong uterine contractions were selected from the FHR recordings of each infant. A 10 min FHR trace for each infant was selected from the FHR records immediately before labor onset. The FHR traces were printed on paper, and the printed FHR segments were scanned using an image scanner (EPSON GT-F600, Tokyo, Japan) and saved as JPEG files (Fig. 1). The resolution of the images scanned was set at 300 dots per inch. The image data were translated into numerical data using Graphcel (free software, available from http://www.vector.co.jp/soft/dl/win95/business/se247204.html), and saved as Excel files (Fig. 1). The 10 min FHR trace was translated into 1024 numerical values. For all cases of multiple gestation, the FHR trace of each fetus had to be clearly distinguished from other fetuses in the uterus. The numerical data were transformed into power-spectrum curves (Fig. 1) using a fast Fourier transformation in a published template [23] for Microsoft Excel 2007. Fast Fourier transformations decompose a sequence of values into components at different frequencies, and these components are expressed as a graph, called a power-spectrum curve. The area under the curve for a given frequency band reflects the number of components of the corresponding frequency in the original sequence. An increase in the number of components is synonymous with increased FHR variability. The minimum resolution of the power-spectrum curve in our method was 0.1 cycles per minute (cpm). FHR analyses were performed by two of the authors, who were blind to the presence or absence of PVL diagnosis.

We calculated the following variables; total power (TP), area under the curves between 1 cpm and 10 cpm; the segmental power (SP), the area under the curve for every 1 cpm from 1 cpm to 10 cpm; the peak power, the maximum power value between 1 cpm and 10 cpm; and the frequency edge, the frequency at which the area constitutes 50%, 75%, or 90% of the TP. The power calculated as an area under the curve was expressed as a unitless number. Furthermore, we calculated the average FHR during the analyzed segment.