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Developmental change of amplitude-integrated electroencephalographic activity in preterm infants with intraventricular hemorrhage

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ABSTRACT

Background: Amplitude-integrated electroencephalography (aEEG) allows continuous brain function monitoring at bedside.
Objectives: This prospective cohort study was designed to longitudinally evaluate aEEG tracings at increased postmenstrual age (PMA) in preterm infants with intraventricular hemorrhage (IVH).
Methods: Biweekly aEEG recordings were performed on preterm infants <32 weeks gestational age from 24 to 36 weeks PMA. The tracings were evaluated according to a scoring system adapted from Burdjalov et al.
Results: We analyzed 496 aEEG recordings in 105 preterm infants. The control group consisted of 42 infants with no IVH, whereas the IVH grade I, II, III, and IV groups consisted of 38, 8, 3, and 14 infants, respectively. There were significant differences in the cycling and total maturation scores among the IVH groups at 36 weeks PMA ($p = 0.010$ and $p = 0.006$, respectively). The IVH-IV patients maintained low scores in their cycling as their PMA increased, in contrast to their continuity and amplitude scores. The risk factors affecting the aEEG maturation scores at 36 weeks PMA in the IVH-IV patients included seizure events with the administration of antiepileptic drugs and the insertion of external ventricular drains ($\beta = -0.679$ and $\beta = -0.418$, respectively; $p = 0.003$).
Conclusions: The low cycling scores persisted until 36 weeks PMA in the IVH-IV group.

1. Introduction

Cerebral function monitoring (CFM) using amplitude-integrated electroencephalography (aEEG) has become an important part of the clinical surveillance of sick newborn or premature infants in neonatal intensive care units (NICUs). In fact, aEEG is one of the most accurate bedside methods to establish neurologic prognosis in full-term asphyxiated infants [1–3]. Comparative studies of aEEG versus conventional EEG have been performed to assess the sensitivity of the two techniques for neonatal seizure detection [4,5]. In addition, aEEG appears to reflect brain function status in infants with various diseases, such as congenital heart disease [6], bronchopulmonary dysplasia [7], sepsis [8], and periventricular leukomalacia (PVL) [9].

Intraventricular hemorrhage (IVH) is one of the major morbidities in preterm infants. Although the methods of evaluating neurologic status are still lacking for such neurological morbidities, several aEEG studies on IVH patients have been recently reported. Olischar et al. [10] collected standardized data on the influence of IVH on aEEG activity and certain parameters, such as the maximum number of bursts per hour, continuity, and low-voltage burst suppression, could be used to predict neurologic outcomes [11–13]. However, these studies were performed over a relatively short period of time during the acute stage of IVH events, and there have been no reports on the effect of IVH on the progressive maturation of aEEG activity over time. The developmental changes in aEEG maturation in normal preterm infants have been studied using various scoring systems [14–16], and the factors that affect the maturation of aEEG have recently been reported [16]. The purpose of this study was to evaluate the aEEG maturation patterns in preterm infants who had experienced the major neurological morbidity, IVH.

2. Patients and methods

2.1. Subjects

Inborn preterm infants <32 weeks gestational age (GA) who were admitted to the NICU of Seoul National University Children's Hospital from November 2009 to October 2011 were enrolled, and aEEG recordings were examined prospectively. The exclusion criteria included the following: 1) chromosomal anomalies, 2) congenital brain anomalies, 3) hypoxic ischemic encephalopathy (HIE), 4) isolated PVL not associated with IVH, 5) fetal hydrops, 6) acute stage of severe sepsis, and 7) administration of sedative drugs for ventilator use or imaging studies, except for antiepileptic drugs (AEDs) for seizure control.

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Table 1
Demographic and clinical characteristics of the study groups.

	Normal (n = 42)	IVH-I (n = 38)	IVH-II (n = 8)	IVH-III (n = 3)	IVH-IV (n = 14)	*p*-value
Gestational age (wk)	27^{+6} (23^{+3}, 31^{+6})	29^{+2} (24^{+1}, 31^{+5})	26^{+1} (23^{+5}, 30^{+3})	27^{+0} (26^{+5}, 30^{+1})	26^{+2} (24^{+6}, 31^{+4})	0.005*
Birth weight (g)	875 (420, 1460)	975 (370, 1910)	845 (520, 1070)	780 (670, 1160)	755 (660, 1590)	0.118*
SGA:AGA (% SGA)	15:27 (35.7)	15:23 (39.5)	1:7 (12.5)	2:1 (66.7)	2:12 (14.3)	0.192†
Birth length (cm)	34.0 (26.5, 39.5)	36.0 (26.5, 45.0)	34.5 (29.0, 37.5)	35.5 (30.0, 37.0)	33.8 (27.0, 42.5)	0.102*
Birth head circumference (cm)	24.5 (19.8, 29.0)	25.2 (19.5, 29.0)	23.5 (20.3, 25.0)	25.5 (22.5, 27.0)	23.5 (21.3, 29.0)	0.063*
Male:female (% male)	24:18 (57.1)	23:15 (60.5)	4:4 (50.0)	2:1 (66.7)	9:5 (64.3)	0.963†
Singleton:twins:triplets:quadruplets (% multiple births)	19:16:7:0 (54.8)	19:15:2:2 (50.0)	4:1:2:1 (50.0)	0:2:1:0 (100.0)	5:6:1:2 (64.3)	0.275†
VD:CS (% CS)	18:24 (57.1)	14:24 (63.2)	3:5 (62.5)	1:2 (66.7)	6:8 (57.1)	0.980†
Apgar score, 1 min	4 (1,7)	3 (1,7)	2 (0, 5)	5 (3,7)	2 (0, 7)	0.037*
Apgar score, 5 min	7 (2,8)	6 (1,8)	5 (0, 7)	6 (5,8)	5 (0, 8)	0.184*
Cord blood pH	7.28 (7.09, 7.43)	7.28 (6.90, 7.40)	7.32 (7.09, 7.40)	7.23 (7.02, 7.36)	7.35 (6.98, 7.40)	0.255*
RDS, surfactant (%)	13 (31.0)	15 (39.5)	6 (75.0)	1 (33.3)	10 (71.4)	0.029†
PDA, treated (%)	31 (73.8)	25 (65.8)	7 (87.5)	3 (100.0)	13 (92.9)	0.212†
BPD, ≥ moderate (%)	15 (35.7)	13 (34.2)	4 (50.0)	0 (0.0)	9 (64.3)	0.156†
Postnatal dexamethasone (%)	1 (2.4)	2 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)	0.816†
ROP, operation (%)	6 (14.3)	3 (7.9)	4 (50.0)	0 (0.0)	6 (42.9)	0.005†
NEC, ≥ stage II (%)	3 (7.1)	4 (10.5)	2 (25.0)	1 (33.3)	3 (21.4)	0.328†
Sepsis, culture-proven (%)	6 (14.3)	5 (13.2)	4 (50.0)	0 (0.0)	3 (21.4)	0.110†
Hypotension, inotropics (%)	17 (40.5)	16 (42.1)	4 (50.0)	2 (66.7)	11 (78.6)	0.128†
IVH detection (PMA, wk)		30^{+2} (27^{+0}, 34^{+2})	27^{+3} (25^{+6}, 30^{+3})	28^{+0} (27^{+1}, 30^{+4})	27^{+1} (25^{+0}, 32^{+3})	<0.001* 0.669*
(PNA, d)		4.5 (1, 66)	8.5 (1. 27)	4.0 (2,10)	3.5 (0, 28)	
Antiepileptic drug at 36 wk PMA (%)	1 (2.4)	0 (0)	0 (0)	0 (0)	5 (35.7)	<0.001†
External ventricular drain (%)	0 (0)	0 (0)	0 (0)	1 (33.3)	2 (14.3)	0.001†
Theophylline at 36 wk PMA (%)	12 (28.6)	2 (5.3)	2 (25.0)	1 (33.3)	7 (50.0)	0.009†

The data are shown as medians with (ranges) or numbers with (percentages).
The *p*-values reflect differences among the five groups.
IVH, intraventricular hemorrhage; SGA, small for gestational age; AGA, appropriate for gestational age; VD, vaginal delivery; CS, cesarean section; RDS, respiratory distress syndrome; PDA, patent ductus arteriosus; BPD, bronchopulmonary dysplasia; ROP, retinopathy of prematurity; NEC, necrotizing enterocolitis; PMA, postmenstrual age; PNA, postnatal age.
* Kruskal–Wallis test.
† Chi-square test.

This study was approved by the Institutional Review Board of Seoul National University Hospital (IRB No. H-0711-025-225), and informed consent was obtained from the parents of all patients enrolled in this study.

2.2. aEEG monitoring

The aEEG recordings were performed using the Cerebral Function Monitor (CFM6000, Olympic Medical, Seattle, WA, USA) for at least 6 h biweekly from 24 to 36 weeks postmenstrual age (PMA). The initial aEEG was obtained at least 48 h after birth. Three gold disk electrodes were attached to the scalp over the mid- and bi-frontal areas to obtain a single-channel aEEG. Instances of patient handling or routine nursing care were recorded directly on the tracings. The quality of the recordings was monitored by simultaneously measuring the impedance, and aEEG tracings with an impedance ≥15 kΩ were discarded.

2.3. Brain imaging study

Brain ultrasonography (US) was performed routinely on days 1, 3, and 7 after birth or whenever the possibility of intracranial hemorrhage was suspected. After 7 days, brain USs were regularly performed at 1-to-4-week intervals, depending on the clinical course of the patient, until discharge. A Vivid 7 Dimension ultrasound machine (GE Vingmed Ultrasound AS N-1390 Horten, Norway) with an 8.0-MHz transducer was used for all the USs. Brain US scans were performed and assessed by pediatric radiology specialists. IVH was classified as grades I though IV according to Papile et al. [17].

According to our institute's protocol, extremely low birth weight infants and all preterm infants with IVH-III and -IV were assessed with brain magnetic resonance imaging (MRI) after 36 weeks PMA before discharge with parent's consents.

2.4. Interpretation of aEEG

The aEEGs recorded from each infant were interpreted by two independent neonatologists (J.S. and H.K.) with extensive experience in neonatal aEEG interpretation. To control for general interpretation bias, both aEEG interpreters were unaware of the patient's identity and medical history. Overall, good agreement was found between the neonatologists' interpretations (kappa = 0.810, $p < 0.001$). Any discordance in the aEEG scoring was resolved by a conference between the neonatologists, and a final score was agreed upon and considered for statistical analysis.

The most stable, uninterrupted recording period for each patient was chosen for aEEG analysis, and the tracings were visually evaluated and graded according to a scoring system adapted from Burdjalov et al. [14]. The following component variables of the aEEG recordings were evaluated: continuity (0–2), cycling (0–5), amplitude of lower border (0–2), and bandwidth span and amplitude of lower border (0–4). The individual component scores were added to determine the total maturation score (0–13).