The relationship between quiet sleep and neurobehavioral development in preterm infants.

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Abstract

[Background and aims]

Recent experimental data suggest sleep plays a role in brain development. Behavioral and physiologic assessments of neonatal sleep might lead to more developmentally appropriate state regulation for infants in intensive care and assist in daily medical care and predicting the neurodevelopmental outcome. Analysis of sleep patterns using amplitude-integrated electroencephalography (aEEG) might predict further neurobehavioral developmental states in premature infants. The study aimed to evaluate the relationship between sleep states, investigated by aEEG, and short-term neurobehavioral developments in preterm infants.

[Study design and subjects]

aEEG and neurobehavioral assessments (Neonatal behavioral assessment scale ; NBAS) were performed at 37-39 weeks of post-conceptional age for 10 infants (median gestational age and birth weight were 35 weeks and 2175g. Quiet sleep (QS) data were collected by aEEG over 12 consecutive night hours. QS as the duration of QS intervals and the variation of QS duration periods were analyzed. NBAS were scored by six cluster scores (Habituation, Orientation, Motor, State Range, State Regulation and Autonomic Stability). Correlations analyses examined the relationship between the QS measurement items and NBAS cluster scores.

[Results]

There were significant negative correlations between the variation of QS duration periods and state range (ρ=-0.71, $p<0.05$), and the variation of QS duration periods and state regulation scores (ρ=-0.77, $p<0.05$).

[Conclusions]

Stable QS periods appear to have some short-term effects on neurobehavioral development in premature infants and therefore protected sleep during premature care is potentially advantageous in improving an infant's neurobehavioral status.

【Keywords】 Premature infant, amplitude-integrated EEG (aEEG), neurobehavioral assessment

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INTRODUCTION

In early infancy, the nervous system centering on the brain develops rapidly and many neurons and synaptic connections are actively formed; brainstem, hypothalamus, amygdala and the limbic system are functioning[1)], and show in functional connectivity with the parts of the brain involved in sensory activity (vision, auditory, tactile, etc) and the

frontal lobe[2-6]. For the central nervous system to develop and mature a stable environment during the fetal and newborn period is essential. However, there is mounting evidence that the repeated stress of medical care and from the Neonatal Intensive Care Unit (NICU) environment itself, especially that occurring during the critical early period of infant development, have profound and long-lasting effects on a number of physiological systems, including the central nervous system.

Preterm and/or low birth weight infants are, of necessity, living and developing in an environment that is stressful in multiple ways[7-10]. It is thought that these multiple stressors disturb the stable sleep (rest) state of the preterm infant. Recently the brain during sleep is considered to be active and thus has an important role in the process of reapportioning resources within neurons and the neural systems[11]. Three specific examples of such reapportionment during sleep are suggested : (1) the return of the neurotransmitter, glutamate, to synaptic vesicles at presynaptic sites is most active during waking, (2) the intracellular movement of mitochondria from neuronal processes to the cells soma where mitochondrial replication can occur, and (3) the readjustment of the level and distribution of neurotransmitters within the brainstem modulatory systems and elsewhere that must function in an integrated fashion during waking[12].

These studies suggest that stable sleep contributes to promoting synaptogenesis and maturity of the brain. Furthermore, that active sleep (AS) and quiet sleep (QS) have different roles has only recently become clear. The role of AS is in the forming of the network of whole brain domains such as the cerebral cortex and the diencephalon. Conversely, QS is involved in the connection pattern plasticity of the excitatory and the inhibitory neurons in the thalamocortical and the intracortical, and the remodeling of the synapse. According to a study that investigated the relationship of sleep-wake patterns at 36 weeks gestational age and the cognitive developmental outcome at 6 months in premature infants, the recorded Bayley scales mental development index score and the corresponding night sleep percent were both low values[13]. In addition, it is reported that chronic sleep loss causes damage to neurons[14], and there is the very real fear that sleep loss increases the incidence of pervasive developmental disorders (e.g. autism and Asperger's syndrome), attention defect / hyperactivity disorder and learning disabilities resulting from the low birth weight and/or being preterm[15]. Thus, the need to provide a safe environment within the NICU so that infants, either preterm and/or of low birth weight, are able to maintain a stable sleep state is essential so as to facilitate the maturity of the brain and the neurobehavioral development.

EEG had been one of the most widely used methods in the evaluation of the sleep state, however it is not adequate to measure brain function both continuously and in real time. However, in recent years, amplitude integrated EEG (aEEG) has become the preferred method to measure prolonged brain activity easily and in real time. It is convenient and simple to use for a number of reasons. Firstly, it uses only a single-channel electrode. The recorded wave data (that is rectified and smoothed) is processed by an asymmetric filter, i.e. semilogarithmic amplitude compression, impedance detector and overload detector. The processed data provides a continuous recording of the cerebroelectrical background activity. It is a useful tool to easily, and without physical restrictions, measure an infant's sleep state and the resulting data can be used to assess the development of the central nervous system. This data displays the relative maturity of the sleep pattern. However, there is at present no study that has examined the conduct of the sleep state using both aEEG and neurobehavioral development. The aim of the present study was to evaluate the relationship between sleep states, as identified by aEEG, and short-term neurobehavioral development in infants.

METHODS

1.Participants;

The study included 10 infants (7 boys and 3 girls). Participant characteristics are shown in Table 1. The inclusion criteria were the absence of congenital heart disease, abnormal central nervous system manifestations, chromosomal aberrations and lung malformations.

The infants were cared for in the NICU of the Hamamatsu medical center, Shizuoka, Japan. Their parents gave written informed consent, and the Ethics Committees of Seirei Christopher University (approval No.12020) approved the study.

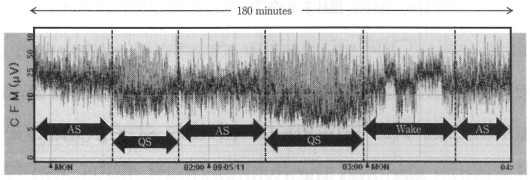
Table 1. Characteristics of study participants

No. of subjects	10
Sex (Male / Female)	7 / 3
gestational age (week)	35 (29-39)
Birth weight (g)	2175 (1529-2948)
Apgar score	
1min	8(5-9)
5min	9(8-10)
PCA at experimental day (week)	38 (37-39)
weight at experimental day (g)	2582 (2322-2864)

PCA: post-conceptional age — median (range)

2. Procedure;

The sleep patterns were measured by an EEG instrument (CFM-6000, Atom Medical Corporation, Tokyo, Japan). All EEGs were recorded at the infant's bedside with two surface electrodes (Fp1 and Fp2) according to the international 10-20 system. Measurement was performed between 37 and 39 weeks of post-conceptional age (median 38 weeks) and measurements were collected during 12 consecutive night hours (i.e. PM6:00-AM6:00). In addition, we listed the time, content and the context in which medical care was carried out during the measurement and excluded it from the later analysis. The recorded data from the EEG were then analyzed using the algorithm proposed by Tao et al[16], and we then judged the time-dependent changes of sleep states. From the time-dependent changes of sleep states data, we examined the following; the duration of QS intervals and variation of QS duration. Figure 1 shows about a discrimination method of AS and QS.



The narrower bandwidth corresponds to the continuous activity during active sleep(AS)and wakefulness(Wake), and the broader bandwidth represents discontinuous background activity during quite sleep (QS). We observed eye movements, and judged AS / Wake or QS state. Then, wevisuallydiscriminatedsleepstatebyEEGpattern

Figure 1. The methods of discrimination of sleep EEG state.

This research examined infant's neurobehavior using the Brazelton Neonatal Behavioral Assessment Scale (NBAS)[17]. The NBAS was used for the infant's behavioral assessment so as to standardize the examination procedure between individual children and also other research carried out. The NBAS has been the most consistently used assessment criteria of neonatal neurobehavior in clinical practice and research[18]. The NBAS contains 28 behavioral items and 18 reflex items which are administered in a particular sequence and can be grouped into "packages" (Habituation, Motor-Oral, Trunk, Vestibular and Social-Interactive) which follow an established order. The order of items is organized according to their level of intensity or the degree of stimulation. The initial items do not involve any handling of the baby, but as the examination progresses the items become more stimulating, beginning with minimally intrusive tactile items and ending with the more massive vestibular items. The NBAS was administered by a pediatric physical therapist so as to guarantee the validity and reliability of the examination. The NBAS examination was performed in the same week, as determined by post-conceptional age, as the aEEG measurement. The NBAS scores were reduced to six clusters: (1) habituation, (2) orientation, (3) motor performance, (4) range of state, (5) state regulation, and (6) autonomic stability. We used the Statistical Packages for the Social Sciences software, version 19 (SPSS; IBM Japan Inc., Tokyo, Japan) for statistical analysis. Correlation analyses were conducted to examine the relationship between QS scores and NBAS cluster scores.

RESULTS

The result of QS scores and NBAS cluster scores are presented in Table 2. The correlation between QS scores and NBAS cluster scores are shown in table 3. There were significant negative correlations between the variation of QS duration periods and state range (ρ=-0.71, $p<0.05$), and the variation of QS duration periods and state regulation scores (ρ=-0.77, $p<0.05$). There was no significant correlation in others. Figure 2 shows the scatter diagram of variation of QS duration and NBAS cluster scores (range of state and state regulation).

Table 2. Median and range of QS scores and NBAS cluster scores

duration of QS intervals (min)	19.2 (15.2-30.7)
variation of QS duration (min)	4.4 (2.1-6.8)
habituation	7.5(6.4-8)
orientation	6.8(4.4-7.5)
motor performance	6.2 (3.3-6.8)
range of sta	5.2(2.8-5.6)
state regulation	5.6 (2.3-6.3)
autonomic stability	7.2 (5.8-7.7)

median (range)

Table 3. Correlation coefficients between QS scores and NBAS cluster scores

	duration of QS intervals	variation of QS duration
habituatio	0.31	-0.45
orientation	-0.21	-0.37
motor performance	0.28	-0.33
range of state	0.17	-0.71*
state regulation	0.02	-0.77*
autonomic stability	0.23	-0.39

Spearman's ρ *$p<0.05$

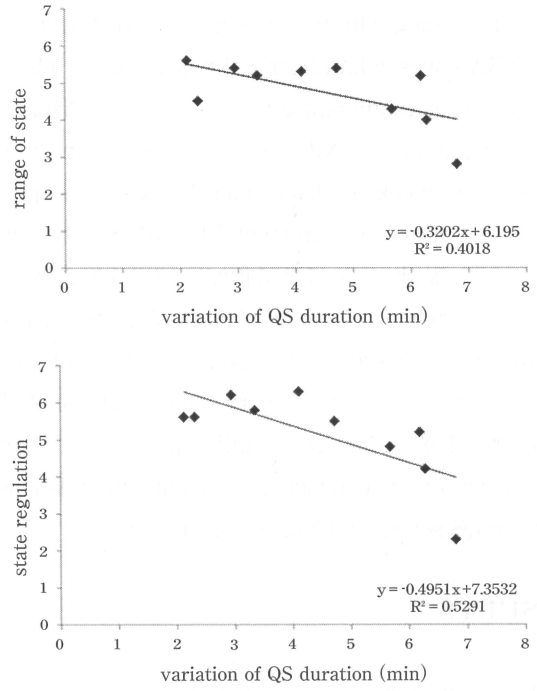


Figure 2. The scatter diagram of variation of QS duration and range of state / state regulation)

DISCUSSION

In the present study we evaluated the relationship between sleep states, as investigated and recorded using aEEG, and short-term neurobehavioral development, assessed using NBAS, in 10 infants. The characteristics of the duration of QS intervals and the variation in QS duration periods are in agreement with the earlier studies on the sleep state of the fetus and preterm infants using ultrasonotomography and EEG[19].

There were significant negative correlations between the variation of QS duration periods and state range, and the variation of QS duration periods and state regulation scores. It suggested that there was a positive relationship between the ability to state control during waking and the ability to maintain QS. Previous research has suggested that QS corresponds to non-REM sleep in adults, and it was generated through the synchronized nerve actions of ipsilateral and contralateral cerebral cortex, the corpus callosum, and the thalamus[20-22]. The information in the brain is organized and integrated by these synchronized nerve actions. Halassa et al. gives more details on the role of non-REM sleep; (a) to facilitate the connection and integration of function between the cortex and the thalamus, (b) to remove any unnecessary synapse, and (c) to improve the stability of synapse strength within the whole brain[23]. The QS in preterm infants has the same functional role as that of non-REM sleep in adults, and it is an important factor to advance the maturation of the brain. The "state range" and "state regulation" scores in NBAS represent the degree of an infant's arousal and state stability and the ability to regulate his/her state in the face of increasing levels of stimulation.

In fact, they give an indication of the level of maturity, the ability of self-regulation and the ability to adapt to the external environment and the physiological condition. Newman suggests evidence of the anterior cingulate gyrus being involved in the cry production, and this structure along with the amygdala and other forebrain areas are active in responding to cries, and is present in mammals such as macaca mulatta[24]; it is inferred that this is a key region for self-regulation. Infants that could maintain stable QS were considered to have an appropriate level of development in the area of the cerebral cortex, corpus callosum, thalamus, and synapse optimization based remodeling by connection of cortex-thalamus. Especially, the optimization of perceptual information processing in the cortex-thalamus encourages the function of the cingulate gyrus, and this leads to a higher ability to state regulate.

We acknowledge that the present study has a number of limitations. The limitations of this study include the small sample size and the evaluation of aEEG and NBAS at only one point in time. Because of the latter limitation, we cannot make inferences about the infant's developmental course. Future investigations with this methodology should include more subjects and repeated measurements over time to monitor the course of the developmental process. Additionally, evaluating infants' development with polysomnography and actigraph in future studies would give great insights into the development process as well as the characteristics of sleep and behavior.

To conclude, the results from our current study indicate that there is a relationship between stable QS and the

ability of state regulation in premature infants. Stable QS periods appear to have some short-term effects on neurobehavioral development in premature infants and thus protected sleep during premature care has potential beneficial effects for improving an infant's neurobehavioral status.

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