# Activity-based assessment of the sleep behaviors of VLBW preterm infants and full-term infants at around 12 months of age.

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# 博士論文

## Activity-based assessment of the sleep behaviors of VLBW preterm infants and full-term infants at around 12 months of age

（体動データから判定した修正月齢12か月前後の極低出生体重児の睡眠特徴）

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## 1. Introduction

Sleep patterns develop dramatically during childhood and rely on maturity of the central nervous system (CNS). This is one reason that studies on development of sleep-wake behaviors among preterm infants are an important field of interdisciplinary research. One important developmental task is to entrain the innate biologic clock to environmental factors such as the light-dark cycle for development of circadian rhythms during early infancy. Previous studies showed that the sleep-wake circadian rhythm emerges around one corrected month and is established by three to four corrected months in preterm infants, which was the same pattern as observed in full-term infants [1-4]. There are other developmental changes in sleep patterns, such as decreasing sleep duration and increases in the amounts of quiet sleep during early childhood. However, studies reporting on changes in sleep patterns after the establishment of circadian sleep-wake cycle among preterm infants are both few in number and incongruent. Previous studies reported that sleep duration and sleep behaviors within the first ten years of life did not differ between preterm and full-term infants [2,5]. On the other hand, it is pointed out that the sleep quality of preterm infants is lower than that of full-term infants at 20 months' corrected age [6]. It is also reported that mothers of preterm infants showed high levels of anxiety related to raising their infants [7], and that sleep-related issues were of common concern [8,9]. Thus, expression of their anxiety and concern could be related to the characteristics of sleep behaviors among preterm infants.

Furthermore, recently it has been reported that there are some VLBW infants without serious central neurological problems who developed attention deficit/hyperactivity disorder (ADHD) during early school age [10,11]. One cause of ADHD is related to a disorder in the transfusing neurotransmitters, which also have an important role in regulating sleep-wake cycles. In some previous studies which indicated no difference in sleep patterns between preterm and full-term infants, the subjects were born from 24 to 36 gestational weeks, and collected data using sleep logs, which were recorded by infant's mothers. Thus, there is a possibility that the unique course of sleep development of preterm infants, especially very low birth weight (VLBW) infants, could be identified by using objective data correction methods. In this study, the subjects were limited to VLBW preterm infants, and a more objective method was applied. An actigraph is a miniature wristwatch-like acceleration sensor which is able to collect activity data noninvasively and continuously with high reliability, and algorithms are available to estimate sleep status from the activity data. [12,13,14,15]. The purpose of this study was to identify the characteristics of sleep behaviors assessed from activity data among VLBW preterm infants in comparison to full-term infants at the age of around 12 corrected months.

## 2. Subjects and methods

### 2.1. Subjects

The subjects for both groups were recruited from parenting classes which were held by Kobe General Children's Center, Japan. Data collection was done from February 2007 through May 2008 (excluding the summer months). Inclusion criteria were 1) no neurological or developmental problems in preterm and full-term infants 2) birth weight of less than 1500g (very low birth weight) and born less than 32 gestational weeks for the preterm infants 3) born between 37 and 42 gestational weeks for full-term infants. Exclusion criteria were 1) severe illness or congenital abnormality 2) use of infant medication with sedative effects. Age correction was carried out for preterm infants to compare their sleep behaviors with comparable full-term infants. Age correction was done in the following way: the duration between expected birth date and actual birth date was subtracted from the actual age.

2.2. Procedures

The infants' sleep measures were assessed from activity data retrieved by an actigraph (Micro-mini RC, Ambulatory Monitoring Inc., Ardsley, NY). The actigraph consists of a piezoelectric sensor sensitive to accelerations above 0.01g per second and has an internal memory. Each detected activity is counted, digitized, and stored in the memory. In this study, the actigraph collected data using a zero-crossing mode, one-minute epochs, and filter setting mode 18. The recorded activity data was downloaded to a personal computer (Windows-type) using the automatic actigraph interface unit.

Mothers of study subjects were instructed to keep the actigraph on the infants' ankles continuously for approximately seven days, removing it only during times when it could get wet. They were also asked to complete daily sleep-logs documenting the sleep patterns of the children. The daily log included information about the infants' sleep schedules and sleep quality, for example bedtimes, waking times, and night-wakings, as well as unusual external motions, such as moving in a car or a stroller. Mothers were also asked about demographic and clinical data of the infants and concerns about sleep problems of their infants.

The mothers in both groups of infants were asked to allow their children to participate in this study at the end of each parenting class. The opportunity for a personal interview was set with mothers who indicated a wish to cooperate this study. During this interview, it was confirmed that study candidates met the requirements described above, and they were informed of the details of the study's procedure. Following this, consent from the mothers was obtained. All study procedures adhered to the Helsinki Declarations for Human Investigation, and were approved by the Medical Ethics Committee of Kobe University, Japan.

2.3. Data analysis

Actigraphic data were analyzed using the actigraphic scoring analysis software program, action-w2. "Sadeh for Infants" was chosen as the algorithm for all subjects in this study [14]. Sleep measures included sleep onset time, sleep offset time, nocturnal sleep duration, daytime sleep duration, total sleep duration, number of night-wakings (of more than five minutes), the longest sleep episode, WASO (wake after sleep onset: wake minutes during nocturnal sleeping), sleep efficiency, and activity measures included mean activity score, and ACTX (Activity Index: percentage minutes with more than 0 activity score). Statistical analysis was performed using a chi-square test, a nonparametric U test from Mann and Whitney and a Spearman ('s) rank-correlation coefficient. All statistical procedures were carried out using SPSS Ver16.0 for Windows.

## 3. Results

The subjects were 14 neurologically healthy preterm and 14 neurologically healthy full-term infants with mean ages 13.3±2.1months and 12.3±2.4months, mean gestational weeks of 27.4±2.2 and 39.1±1.1, and average weights of 937.1±202.5g, 2881.4±373.7g, respectively. The demographic and clinical characteristics of the subjects are shown in Table 1. There are five IUGR infants in the preterm group and two IUGR infants in the full-term group. The physical measurements of these IUGR infants are shown in Table 2.

The number of mothers who concerned about sleep problems on their infants was 11 in the preterm group, and five in the full-term group (Table 1). The Chi-square test showed significant difference in the number of mothers who complained of their infant's sleep between the two groups ($\chi^2=7.04$, $p<0.01$). The infant's sleep problems were related to sleep-wake rhythms, including night-wakings, resistance to falling asleep, and irregular sleep-wake rhythms in both groups (Table 3). Only mothers of preterm infants complained that their babies were moving a lot during nighttime and waking up early in the morning.

Comparing the estimated sleep and activity measures of preterm infants with those of full-tem infants, the results showed that 1) sleep onset times and offset times differed significantly, with the preterm infants falling asleep and waking earlier 2) the nocturnal sleep durations of preterm infants were significantly shorter than those of full-term infants 3) the mean activity scores and ACTX during nighttime were significantly higher, but not during daytime 4) the two groups did not differ in any other sleep measures (Table 4). The same tendency was confirmed when the analysis was done with the subjects without IUGR infants in both groups.

The Spearman's rank correlation coefficient was used to test for a relationship between the age in months and nocturnal sleep and activity measures. Significant differences between the ages in months and all nocturnal sleep measures estimated from activity data and mean activity score but ACTX were observed in preterm infants. None of the estimated nocturnal sleep and activity measures among full-term infants had a significant correlation (Table 5). Then, the preterm infants were divided into two groups based on the mean age in months, and the estimated nocturnal sleep and activity parameters were compared between the two groups. There were seven in the group of over 13 months and seven in the group of less than or equal to 13 months, and their mean corrected months were 14.9±0.6, 11.1±1.1 months, respectively. The results showed that five out of eight estimated nocturnal sleep measures (nocturnal sleep duration, number of night-wakings, the longest sleep episode, WASO, sleep efficiency) and mean activity score were significantly different between the two groups: sleep measures estimated from activity data of the group of over 13 months showed improvement (Table 6).

## 4. Discussion

### 4.1. The characteristics of activity-based assessment of sleep behaviors of VLBW

The actigraph is capable of collecting activity data continuously and of estimating sleep measures through the use of algorisms. These sleep measures were highly correlated with polysomnography and observation method [13,14,15]. Thus, it could be possible to assess the sleep behavior from the sleep measures using the activity data. The results showed that estimated nocturnal sleep durations of preterm infants were significantly shorter than those of full-term infants. Since the subjects were limited to VLBW preterm infants, born at less than 32 gestational weeks, the difference in sleep behaviors between the two groups was shown clearly in this study. The developmental course of sleep patterns in healthy infants showed increases in nocturnal sleep durations, while the number and durations of waking episodes at night decreased in the first year of life [16], and decreasing daytime and total sleep durations in the two years of life [17]. Also, comparing the estimated sleep measures of preterm infants by ages in months, the sleep measures showed improvement with advancing age in this research. Therefore, the results suggested that nocturnal sleep durations of preterm infants estimated from activity data do not reach the same level as those of full-term infants in their normal developmental courses, though sleep measures improved with age.

Prenatal factors, such as Intrauterine Growth Retardation (IUGR) is thought to be a factor which affects infants' sleep behaviors [18]. There are five IUGR infants in the preterm group and two IUGR infants in the full-term group. It is possible that the sleep measures of IUGR infants lead to shorter nocturnal sleep time and high activity rates at night in the preterm group. Therefore, we compared the estimated sleep measures of the subjects without IUGR infants in both groups and the results showed same tendency as in the original analysis. We need to increase the number of IUGR infants to confirm the characteristics of IUGR infants born prematurity in a future study.

Another factor which might affect the sleep measures in our subjects was the light-dark cycled environment in the NICU [19]. The subjects were treated in five different NICUs, and these facilities provided developmental care in different ways. Consequently, it was difficult to compare the sleep measures due to the care they were received different facilities. However, this is another essential element in determining how the environment in NICUs affects the developmental course of sleep behaviors among preterm infants during early childhood.

The mean activity scores and ACTX of preterm infants were significantly higher than those of full-term infants. The activity score is one of important measures for showing the degree of brain maturation, and the score decreased with age in healthy infants [17,20]. Therefore, the difference in the activity scores and ACTX between the two groups suggested that the development of the sleep patterns in preterm infants is immature in comparison with full-term infants. Recently, VLBW infants without serious neurological problems have been reported as being more likely to be diagnosed with ADHD [10,11]. Moreover, Gossel-Symank [6] suggested that less restful night sleep duration is one characteristic of preterm infants aged 20 corrected months, and this is also observed in infants with ADHD. Thus, further research is needed to understand the developmental course of physical activity during nighttime, because it could possibly lead to the early detection of ADHD among preterm infants.

Mothers of preterm infants were far more concerned about the sleep problems of their children than the mothers of full-term infants. Short nocturnal sleep duration estimated from activity data and restlessness during nighttime could be related to be these concerns. It is necessary to provide care to improve their sleep patterns and confirm the changes in sleep measures.

4.2. Limitation of this study

There is concern over the issue of choosing an algorithm to distinguish sleep-wake status of our subjects, since a validated algorithm which can be applied from infancy through young childhood has not yet been developed. Previous study reported that the data for sleep schedules derived from sleep logs had a high correlation with the data from actigraphs [12]. Thus, we calculated actigraphic sleep measures using previously developed algorithms, compared them with the sleep schedules derived from parental sleep logs and decided to use "Sadeh for infants" for all subjects.

Another concern is that the male-female ratio was different in the groups, which may have affected the results of this study. However, previous studies indicated that the development of sleep patterns does not differ with sex [17,21]. Thus, it is speculated that the disproportionate male-female ratio of the two groups has not affected the results of this study.

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Table 1. Demographic and clinical characteristics of preterm and full-term Infants

| | | Pretem infant(N=14) | Full-tem infant(N=14) | |
|---|---|---|---|---|
| Sex | | | | |
| | No. of male | 9 | 2 | |
| | No. of female | 5 | 12 | |
| Birth order | | | | |
| | No. of first born | 12 | 10 | |
| | No. of subsequent born | 2 | 4 | |
| Gestational age at birth (week) | | | | |
| | Mean (SD) | 27.4 (2.2) | 39.1 (1.1) | *** |
| | Range | 24-32 | 37-40 | |
| Apgar score | | | | |
| 1min | Mean (SD) | 5.5 (2.5) | 9 (1.4) | |
| | Range | 1-9 | 5-10 | |
| 5min | Mean (SD) | 7.3 (1.5) | 9.8 (0.4) | |
| | Range | 5-10 | 9-10 | |
| Delivery mode | | | | |
| | No. of Vaginally born | 0 | 11 | |
| | No. of Cesarean section | 14 | 3 | ** |
| | Unknown | 0 | 1 | |
| Physical measurement at the time of birth | | | | |
| Weight (g) | | | | |
| | Mean (SD) | 937 (202) | 2881 (374) | *** |
| | Range | 666-1430 | 2164-3690 | |
| Hight (cm) | | | | |
| | Mean (SD) | 34.7 (3.7) | 48.7 (2.1) | *** |
| | Range | 29.6-44.0 | 45.0-53.0 | |
| Head Circumustance (cm) | | | | |
| | Mean (SD) | 25.7 (3.2) | 31.9 (1.7) | *** |
| | Range | 21.0-33.0 | 29.0-34.5 | |
| No. of IUGR infant | | 5 | 2 | |
| Physical measurement at the time of study | | | | |
| Weight (g) | | | | |
| | Mean (SD) | 7893 (2588) | 8544 (1151) | n.s. |
| | Range | 5600-11580 | 6580-10958 | |
| Hight (cm) | | | | |
| | Mean (SD) | 73.9 (4.7) | 71.5 (5.5) | n.s. |
| | Range | 66.6-81.1 | 66.6-84.9 | |
| Head Circumustance (cm) | | | | |
| | Mean (SD) | 46.1 (2.3) | 44.1 (2.0) | * |
| | Range | 44.0-48.6 | 41.0-47.6 | |
| No. mother who complained of sleep problems on their children | | 11 | 5 | ** |

* P< .05, ** p< .01, *** p< .00, n.s. ,non significant

Table 2. Profile of IUGR infants

| | ID | Sex | Week of Birth (week) | Corrected age of month at the time of study (month) | AP (1min) | AP (5min) | Physical measurements | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | at time of birth | | | at time of study | | |
| | | | | | | | Weight (g) | Height (cm) | Head circumference (cm) | Weight (g) | Height (cm) | Head circumference (cm) |
| Preterm Infant | A | M | 32 | 15 | 8 | 9 | 1174 | 37.5 | 26.5 | 7405 | 71.7 | 45.5 |
| | B | M | 27 | 14 | 8 | 8 | 662 | 29.6 | 23.8 | 8590 | 74.5 | 45.8 |
| | C | M | 30 | 14 | 9 | 9 | 1092 | 37.5 | 26.7 | 9470 | 75.4 | 48.0 |
| | D | M | 26 | 12 | 5 | 8 | 698 | 32.0 | 23.4 | 7520 | 72.4 | 46.6 |
| | E | M | 29 | 15 | NA | NA | 944 | 35.5 | 25.2 | 9055 | 85.5 | 48.0 |
| Full-term Infant | F | F | 39 | 11 | 5 | 9 | 2164 | 45.0 | 29.0 | 7260 | 66.7 | 43.0 |
| | G | F | 40 | 16 | 10 | 10 | 2440 | 47.0 | 30.5 | 8650 | 73.0 | 41.0 |

These are the physical measurements of IUGR infants in of preterm and full-term group. Infant A and F were assessed symmetrical IUGR, other infants were assessed asymmetrical IUGR.

NA, no answer

Table 3. Mother's concerning of sleep problems (multiple answers)

| | Preterm infant | Full-term infant |
|---|---|---|
| Night-wakings | 3 | 3 |
| Resistance to falling asleep | 3 | 1 |
| Short night-time sleep duration | 0 | 1 |
| Irregular sleep-wake rhythms | 6 | 2 |
| Moving a lot during night-time sleeping | 1 | 0 |
| Waking up early in the morning | 2 | 0 |
| **Total** | 15 | 7 |

Table 4. Estimated sleep and activity measures of preterm and full-term infants

| | Preterm infant (N=14) | Full-term infant (N=14) | p value |
|---|---|---|---|
| | Mean (SD) | Mean (SD) | |
| Nighttime | | | |
| Sleeo onset time, PM | 9:26 (1:13) | 9:50 (1:08) | * |
| Sleep offset time, AM | 6:55 (0:50) | 7:37 (1:13) | ** |
| Nocturnal sleep duration (min) | 529.1 (63.5) | 548.1 (73.5) | * |
| Number of night-wakings (more than 5 min) | 2.4 (2.1) | 2.4 (1.7) | |
| Longest sleep episode (min) | 204.6 (91.3) | 202.7 (101.4) | |
| WASO (min) | 40.9 (35.0) | 36.0 (36.1) | |
| Sleep efficiency (%) | 93.1 (5.7) | 93.9 (5.7) | |
| ACTX (%) | 58.7 (9.7) | 54.3 (9.2) | ** |
| Mean activity score (counts / min) | 24.2 (10.1) | 21.5 (11.0) | * |
| Daytime | | | |
| Daytime sleep duration (min) | 124.7 (63.2) | 111.6 (66.6) | |
| ACTX (%) | 89.1 (8.7) | 89.2 (6.0) | |
| Mean activity score (counts / min) | 207.6 (24.6) | 207.3 (26.6) | |
| 24 hours | | | |
| Total sleep duration (min) | 651.8 (85.2) | 655.8 (95.1) | |
| Longest waking episode (min) | 367.9 (141.8) | 354.0 (149.3) | |
| Longest sleep espisode (min) | 182.8 (80.1) | 194.4 (94.9) | |

* $p < .05$, ** $p < .001$

Table 5. Relationships between estimated nocturnal sleep and activity measures and age in months (Spearman('s) rank-correlations)

| | Preterm infant | | Full-term infant |
|---|---|---|---|
| | Age in months | | Age in months |
| Nocturnal sleep duration (min) | 0.39 | ** | -0.2 |
| Number of night-wakings (more than 5 min) | -0.29 | ** | -0.01 |
| Longest sleep episode (min) | 0.33 | ** | -0.2 |
| WASO (min) | -0.28 | * | -0.09 |
| Sleep efficiency (%) | 0.32 | ** | 0.04 |
| Mean activity score (counts / min) | -0.3 | ** | 0.06 |
| ACTX (%) | -0.06 | | 0.21 |

* p< .05, ** p< .001

Table 6. Estimated nocturnal sleep and activity measures of preterm infants

| | Less than or equal to 13 monts (N=7) Mean (SD) | Over 13 months (N=7) Mean (SD) | p value |
|---|---|---|---|
| Sleeo onset time, PM | 9:36 (1:11) | 9:23 (1:16) | |
| Sleep offset time, AM | 6:49 (0:46) | 6:58 (0:53) | |
| Nocturnal sleep duration (min) | 497.9 (53.3) | 543.2 (66.7) | ** |
| Number of night-wakings (more than 5 min) | 3.1 (2.5) | 2.1 (1.7) | * |
| Longest sleep episode (min) | 117.3 (95.5) | 217.8 (86.5) | ** |
| WASO (min) | 53.1 (42.8) | 33.7 (28.0) | * |
| Sleep efficiency (%) | 90.7 (7.0) | 94.4 (4.3) | ** |
| ACTX (%) | 59.4 (12.4) | 58.5 (8.2) | |
| Mean activity score (counts / min) | 28.5 (12.6) | 21.8 (7.7) | ** |

* p< .05, ** p< .001