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Environmental factors influencing biological rhythms in newborns: From neonatal intensive care units to home☆

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ABSTRACT

Photic and non-photic environmental factors are suggested to modulate the development of circadian rhythms in infants. Our aim is to evaluate the development of biological rhythms (circadian or ultradian) in newborns in transition from Neonatal Intensive Care Units (NICU) to home and along the first 6 months of life, to identify masking and entraining environment factors along development.

Ten newborns were evaluated in their last week inside the NICU and in the first week after being delivered home; 6 babies were also followed until 6 months of corrected age. Activity, recorded with actimeters, wrist temperature and observed sleep and feeding behavior were recorded continuously along their last week inside the NICU and in the first week at home and also until 6 months of corrected age for the subjects who remained in the study.

Sleep/wake and activity/rest cycle showed ultradian patterns and the sleep/wake was strongly influenced by the 3 h feeding schedule inside the NICU, while wrist temperature showed a circadian pattern that seemed no to be affected by environmental cycles. A circadian rhythm emerges for sleep/wake behavior in the first week at home, whereas the 3 h period vanishes. Both activity/rest and wrist temperature presented a sudden increase in the contribution of the circadian component immediately after babies were delivered home, also suggesting a masking effect of the NICU environment.

We found a positive correlation of postconceptional age and the increase in the daily component of activity and temperature along the following 6 months, while feeding behavior became arrhythmic.

1. Introduction

The circadian timekeeping system is currently considered as a network composed by multiple oscillators and has the suprachiasmatic nuclei as an important component [1]. Studies with primate models suggest that the suprachiasmatic nuclei are functionally innervated from 25 weeks of gestational age in humans and could be entrained indirectly by light/dark cycles even in prenatal life [2].

Body temperature and sleep/wake rhythms seem to develop according to a sequential pattern, in which a circadian temperature rhythm can be detected earlier in life. Reinforcing this hypothesis, circadian rhythms in rectal and skin temperature have already been detected in preterm newborns inside neonatal care units (NICUs) [3,4], while a circadian rhythm in activity/rest cycle can be identified in term newborns in the first weeks of life [5–7].

Some authors identified a similar ultradian profile of activity/rest cycle in newborns and mothers and also the presence of a circadian component with periods longer than 24 h in the first week of life [7,8]; however only one actigraphy study has been performed in preterm newborns aged less than 40 weeks of corrected age allowing for an earlier detection of a circadian rhythm for this variable [6]. MacMillen et al. [9] demonstrated an earlier emergence of a circadian rhythm of sleep/wake cycle in preterm infants compared to term babies, suggesting that the timekeeping system would be functional as early as 35 weeks of postconceptional age and the apparent delay in the emergence of the circadian rhythm described in other studies would be related to later exposure to a cyclic environment. Recently, Guyer et al. [10], using actigraphy, also demonstrated the earlier emergence of a circadian rhythm in sleep/wake parameters in preterm infants compared to term babies.

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Recently, studies about temperature rhythm have also been improved with the development of a wireless system for continuous measurement of human skin temperature, allowing the longitudinal recording of peripheral temperature. Areas et al. [11] described its use in a chronobiological study, suggesting that wrist temperature measured by the thermistor exhibited a strong circadian rhythm with its acrophase occurring at night, but only one study has been performed in infants [12] and our group investigated its use in newborns [13].

Photic and non-photic environmental factors can influence the emergence of circadian rhythms. Previous studies demonstrated different behaviors, increase in weight gain and, recently, also a circadian melatonin rhythm was described in preterm newborns inside NICUs provided with light/dark cycle [14–16]. Ultradian rhythms have also been demonstrated for preterm neonates in activity, heart rate and temperature, possibly related to feeding schedule and caregiving interventions inside NICUs [17], suggesting a masking effect. Other authors, however, argue in favor of the development of circadian rhythms as a function of postconceptional age and independent of environmental interventions [18,19], as well as, suggesting independent developmental courses for sleep/wake and feeding behavior in infants [6]. Thus there remain controversial points about the development of rhythms in the first year of human life.

The aim of the present study was to evaluate the development of circadian and ultradian rhythms in newborns in transition from intensive neonatal care units to home and along the first six months of life, intending to identify masking and entraining environment factors along development.

2. Material and methods

Preterm newborns (ages ranging from 28 weeks to 36 weeks of gestational age at birth) and term babies were recruited in the Neonatal Care Unit (NICU) of the Hospital Universitário of the Universidade de São Paulo. The project was approved by the ethical committees of both the Hospital Universitário and of the Instituto de Ciências Biomédicas, according to the Declaration of Helsinki, and written informed consent was signed by parents. They were all healthy newborns, with normal Apgar scores, no evidence of perinatal asphyxia or neurological disease and not treated with sedative drugs.

Nine preterm babies and one term newborn were evaluated inside the NICU, with overall data inside the NICU previously published [13]. These subjects were followed in the first week after being delivered home and five preterm and one term infant remained in the study and were also followed until six months of corrected age for preterm babies and 6 months of postnatal age for the term infant. Corrected age refers to the age of a preterm child from the expected date of delivery, while postnatal age means the time elapsed after birth; postmenstrual age, otherwise refers to the gestational age at birth plus the postnatal age. In the present study, data of the last week inside the NICU were evaluated for comparisons with the rhythmic pattern at home.

All infants had their activity, wrist temperature and observed sleep and feeding behavior recorded continuously along their last week inside the NICU. The same parameters were recorded along the first week after being delivered home and, for the subjects who remained in the study, for fifteen consecutive days every month until six months of corrected or postnatal age.

Sleep, activities, staff interventions and feeding diaries were filled every day by hospital staff inside the NICU and by parents at home. Babies had their activity monitored by actimeters Micro-Mini-Motionlogger® – Ambulatory Monitoring Inc. (Ardsley, New York, USA), attached to their right ankle with a soft sleeve bandage and data were recorded every minute. Wrist skin temperature was recorded every 10 min with a thermistor with a data logger, Thermochron iButton® – Maxim Dallas (Dallas, Texas, USA), attached to the left wrist with Micropore 3 M®.

Activity, sleep/wake behavior (according to data extracted from diaries), feeding and wrist temperature data were grouped in 10 min blocks and divided in time series of seven days each, according to postmenstrual age, for each subject. Actograms-like graphics were constructed for all variables. The rhythmic analysis was performed using the chronobiological statistic package "El Temps" [20].

The rhythmic patterns of all variables were evaluated with the Lomb Scargle algorithm [21], scanning for all significant periodic signals in the range from 1 h to 28 h. This is a periodogram technique which fits sinusoidal curves of different periods to time series, resulting in a Periodogram value (LSP), representing the relative contribution of each periodicity for the overall oscillations, with a significance level ($p < 0,05$). Activity and wrist temperature acrophases were investigated through the Cosinor algorithm [22], a method based on the least square fitting of a specified period of cosine function to data series. Acrophase stabilities were tested with the Rayleigh method, an index of interdaily stability, which provides an r vector, with a length proportional to the degree of phase homogeneity for the analyzed period [12,23,24].

Wilcoxon paired test was used to compare the daily rhythm potency of activity, wrist temperature and sleep/wake behavior inside the NICU and immediately after being delivered home, using the LSP as dependent variable and the environment (NICU or home) as independent variable. The Spearman correlation test was performed to evaluate the relation of postconceptional age and the potency of the circadian rhythm for activity, wrist temperature and sleep/wake.

3. Results

Anthropometrical measurements, gestational age, Apgar score and delivery mode for all newborns are presented in Table 1.

Wrist temperature presented clearly a dominant circadian rhythm for 7 subjects in their last week inside the NICU (the other 3 subjects showed a 12 h rhythm as the most robust), while activity/rest cycle presented a circadian rhythm for 5 subjects, but dominant for only 3 babies; a 3 h rhythm (the 180 min component of Lomb Scargle

Table 1
Subject´s gestational and anthropometrical data.

ID	Sex	GA (weeks)	Delivery mode	Weight at birth (g)	Apgar 5th min	PM when delivered home (weeks)	Subjects followed until 6 months (PCA)
1	F	39 3/7	V	3450	10	41	X
2	M	34 2/7	V	2705	9	37 1/7	X
3	M	32 3/7	V	1310	9	38 3/7	
4	M	33 6/7	V	2012	9	35	X
5	M	32 6/7	CS	1625	7	39 6/7	X
6	F	30	V	1235	9	38	X
7	M	31 5/7	V	1830	9	40 4/7	
8	M	30 3/7	V	1330	7	37	
9	F	28 3/7	CS	1110	9	42 3/7	X
10	M	28	V	920	8	40 6/7	

F: female; M: male; GA: gestational age at birth; V: vaginal delivery, CS: cesarean section; PM: postmenstrual age. Subject 1 (in grey) was the only term newborn.