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The development of the circadian heart rate rhythm (CHR) in Asian infants ☆

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ABSTRACT

Objective: To test the hypothesis that term-born Asian infants, at reduced risk to die of Sudden Infant Death Syndrome (SIDS) exhibit a circadian heart rate rhythm (CHR) at a later age than non-Asian term infants.
Method: Repeated overnight heart rate (HR) traces obtained with a battery-operated Polar S810i heart-rate monitor at home in 17 Asian Torajan infants in Indonesia, were compared with those of 52 non-Asian infants monitored as part of the Collaborative Home Infant Monitoring Evaluation (CHIME). HR was determined using a moving window averaging technique. A comparison of median HR during quiet sleep (QS) episodes (identified by minimum HR variability), established the presence of CHR.
Results: Seventy three percent of non-Asian CHIME infants ≤7 weeks exhibited CHR compared to 45% of Asian Torajan infants. Between 8 and 12 weeks, 94% of non-Asian CHIME infants exhibited CHR, compared to 33% of Asian Torajan infants ($p<0.001$). Forty seven and 56% of Asian Torajan infants exhibited the CHR at the age intervals of 16–20 weeks and 21–25 weeks respectively. Active wakefulness percentages as a function of the entire recording and median QS HR were not significantly different in the two groups.
Conclusion: Despite the fact that Asian Torajan infants were on average a week older than non-Asian CHIME babies, between two and three months of age only one in three exhibited the CHR, compared to virtually all non-Asian CHIME infants. We speculate that the cause of this difference rests in the infants' environment rather than their genetic origin.

1. Introduction

Although the human fetus can follow the maternal circadian rhythm, the entrained expression of the circadian clock, based in the suprachiasmatic nucleus (SCN) of the hypothalamus awaits postnatal maturation of the retinal hypothalamic tract, and melatonin neurotransmission [1,2]. After birth, evidence of this maturing nucleus is found in the emergence of a 24-hour sleep wakefulness cycle that supplants the typical poly-phasic sleep wakefulness pattern of the neonate [3]. In less than 10 percent of infants, one finds an intervening brief period of a free-running sleep wakefulness rhythm [4–7] suggesting that the infant brain has not yet learned to synchronize its neural clock mechanism in the SCN with typical *Zeitgebers* such as ambient temperature, light and darkness and human social behavior. The infant will accomplish this synchronization of the clock and its "hands" between one and three months of age, when numerous indicators such as minimum and maximum of heart rates, breathing, body temperature, metabolic rate, salivary melatonin and cortisol can be measured during the typical 24-hour day [8–15]. Further maturation of the circadian rhythm manifests as an increase in amplitude and a shift in most troughs toward the early morning hours [8,9,14].

Wailoo's research team in England noted that Asian infants in their study sample exhibited a delay in the appearance of a circadian temperature modulation [16]. Compared with the 2–3 month appearance of the circadian temperature modulation in Caucasian infants the temperature rhythm of the Asian infants only appeared between

Abbreviations: CHIME, Collaborative Home Infant Monitoring Evaluation; CHR, Circadian Heart Rate Rhythm; HR, Heart Rate; IRB, Institutional Review Board; LIPI, Limbaga Ilmu Penetahuan Indonesia; PSG, Polysomnogram; QS, Quiet sleep; REM, Rapid eye movement sleep; SCN, Suprachiasmatic Nucleus; SD, Standard Deviation; SIDS, Sudden Infant Death Syndrome.

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4 and 5 months. Lodemore et al [17] identified variables that seemed to hasten the appearance of the circadian temperature rhythm: female sex, being firstborn, supine sleeping, affluent families, breastfeeding and older mothers.

The primary objective of this study was to test the hypothesis that the nightly portion of the circadian heart rate rhythm (CHR) in Asian infants in Indonesia appeared later than that of a non-Asian control group. Under the protocol of the Collaborative Home Infant Monitoring Evaluation (CHIME), carried out during the 1990s, a sizable number of subjects underwent an overnight polysomnogram (PSG) that yielded continuous nightly heart rate (HR) values. The available tracings from non-Asian subjects in CHIME were used as controls.

2. Methods

2.1. Participants

Twenty mothers of term born infants between one and two months of age (10 males and 10 females) were recruited for the overnight HR studies in Toraja, Indonesia. These volunteers were drawn from various areas of Toraja consisting of approximately 3000 km^2 of mountainous terrain, inhabited by 446,661 people who live in two provincial towns and 311 villages. The sample included a cross-section of maternal education in Toraja that ranged from two years of elementary school to two years of a vocational school after high school. This variable was chosen as an estimate of socio-economic status. HR studies were carried out in 2007.

The protocol was approved by the Institutional Review Board (IRB) of Childrens Hospital Los Angeles, with a waiver of written informed consent, based on the culture in which the study was to be carried out. Instead, an explanation of the study preceded each HR monitoring session followed by an oral consent. Lembaga Ilmu Pengetahuan Indonesia (LIPI), the official agency that oversees research by foreigners in Indonesia, gave permission for the study and directed the search for a complete set of approvals from national and local agencies in Indonesia. These permissions guaranteed collaboration from health professionals in the field.

In addition, HR derived from PSGs of 64 term born non-Asian infants from the CHIME study (34 boys and 30 girls) were available for comparison with Torajan tracings. In the early 1990s, IRBs at clinical centers in Cleveland, Chicago, Toledo, Honolulu and our own University, in Los Angeles had approved these CHIME PSG studies and informed consent was obtained from all parents or caregivers.

2.2. Instrumentation

Some of the infants in Indonesia lived in remote areas where electricity was unavailable. A team of biomedical engineering students at Michigan Technological University adapted a battery-powered Polar HR Monitor (S810i) designed for runners, to work with infants. A band around the chest holds a transmitter that sends the HR data to a storage watch, placed in the vicinity of the baby. This data was subsequently downloaded to a laptop computer via an infrared USB interface port and stored using specially designed software.

For the CHIME protocol in the US, the ALICE 3 data acquisition and analysis system was used to obtain overnight PSGs in the various sleep laboratories [18]. This system included a 486/33 IBM computer, a 20-inch monitor and optical disk storage (Healthdyne, Marietta, GA).

2.3. Procedures

In Toraja, three trained research assistants visited mothers and infants at home between 5 and 7 PM for application of the transmitter bands around the chest, just under the arms. Mothers were instructed to follow their usual routines including changing clothes and breastfeeding as long as they kept the watch in the vicinity of the infant (at a distance of no more than one meter). These units were removed in the morning between 6:00 and 8:00 AM by one of the three research assistants who visited the home again for that purpose. This procedure was initiated in all infants between three and seven weeks of age and repeated either two or three times (Table 1). This was thus a longitudinal CHR study.

As part of a different study, a systematic in-home interview with mothers by two of the authors (TH, SS; 19) revealed that in Toraja most infants are wrapped in a sarong (long cotton cloth) or a blanket, including their heads. They are placed supine on a hard kapok mattress on the floor where they sleep with their mother and often the father and other siblings. These mothers do not smoke, and they tend to recline with their infants and report going to sleep before 9:00 PM. Feeding information was also obtained during this interview and classified as either exclusive breastfeeding or breastfeeding with some addition of solids. Formula feeding is rare in rural Toraja [19,20].

In the US, CHIME PSG's were gathered in a cross-sectional manner. In the five laboratories, personnel were trained in a standardized protocol for obtaining PSG data [21] to ensure comparability of the results. Monitoring onset could be as early as 6:00 PM or as late as 9:00 PM and the monitoring would continue for at least eight hours. Throughout the night a demand-feeding schedule was followed with opportunity for breastfeeding. In some laboratories mothers were offered a recliner in the room with the instruction to be as quiet as possible; in others, the mother or caretaker was offered a separate room to rest.

The youngest infants were typically wrapped in a blanket while arm movements of older infants were limited with gauze bands secured with safety pins to the diaper. Infants were placed in a supine or side-lying position, and, in most laboratories they were observed with the help of a low-illumination or infrared video camera and

Table 1
Monitoring age and exclusive breast feeding.

		N	Mean (SD)	Range	# (%) Exclusive breast feeding
Non-Asian CHIME*	≤7 weeks	30	39** (7.6) 5 weeks + 4 days	27–49 weeks	13 (43%)‡‡
	8–12 weeks‡	17	64 (9.0) 9 weeks + 1 day	53–84 weeks	3 (18%)§
Asian Torajan infants	≤7 weeks	11	39 (7.3) 5 weeks + 4 days	29–49	10 (91%)‡‡
	8–12 weeks‡	15	76 (11.4) 10 weeks + 6 days	57–86	14 (93%)§
	16–20 weeks	15	127 (10.5) 18 weeks + 1 day	112–139	14 ((93%)
	21–25 weeks	9	165 (7.0) 23 weeks + 4 days	153–170	8 (89%)

*5 infants were older than 14 weeks and excluded from group comparisons; one was exlusively breastfed, two formula-fed and two received both.
**Days. ‡ Asian Torajan infants were on average 1 week and 5 days older than non-Asian CHIME infants ($t = 3.3$ df 30, $P<0.003$). ‡‡ $P<0.02$; § $P<0.0001$.