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Relationship between Eye Movement Period and Micturition in Newborn Infants Differs from that of Human Fetuses at Term

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Aim To investigate the relationship between the onset of eye movement periods and micturition in human fetuses and in neonates with the intention of clarifying the transition in relationship during the perinatal period.

Methods Data were acquired during 1-4 days and/or 1 month (29-33 days) from 6 normal neonates born at term. Eye movements, crying, and eye open periods were observed with a video recorder until micturition occurred. In 29 term fetuses, the time lag between the onset of an eye movement period and micturition was measured by real-time ultrasound instruments.

Results The time lag between the onset of an eye movement period and micturition in neonates (2 minutes; range, 0-57 minutes) was significantly ($P=0.027$) different from the time lag for fetuses (14 minutes; range, 2-32 minutes) and the frequency of micturition occurring within 8 minutes (33%) was significantly lower ($P=0.017$) than that seen for term fetuses (72%).

Conclusion The relationship between the onset of an eye movement period and micturition is different in term human fetuses and neonates of less than 1 month of age. This suggests that the neuronal relationship among brain centers for micturition, rapid-eye-movement sleep, and awakening is dramatically altered perinatally.

Fetal behaviors reflect functional central nervous system (CNS) development *in utero*. In fact, we and other investigators have described the ontogeny of fetal behavior not only through observing the developmental process of each movement during the course of gestation, but also by investigating various movements in relation to or concurrence with one another; over time, the latter process results in gradual integration of movements into more complex forms (1,2). Furthermore, based on these physiological results, the extent and timing of detection and localization of functional brain impairment *in utero* becomes applicable to clinical obstetrics (1,2). In this regard, we can adopt principles of serial observation of movements from fetus to neonate. However, the continuity of behavioral development between the fetal and neonatal states is controversial. Basically, three patterns of change of fetal movements in transition from fetus to newborn have been postulated. Some fetal behaviors, e.g. tremor, startle, twitch, and myoclonus, diminish after delivery (3). In contrast, breathing movement, eye movement, and sucking are seen continuously in transition from fetal to neonatal period. Finally, behaviors such as hand-mouth contact, visual reaching, and kicking movements diminish at birth, but then emerge again several months later. The mechanism of this last transition is still unclear. However, it is considered that synaptic elimination might be involved in this phenomenon (4).

Micturition is a fetal behavioral parameter that develops concurrently with the onset of eye movement periods (5). Eye movement periods correspond with rapid-eye-movement (REM) sleep and state 2F or above (6-8). Some investigators have also suggested that fetal micturition relates to behavioral states (9,10). In infants, micturition rarely occurs during quiet sleep even in the neonatal period, and arousal signs are often noted before micturition occurs (11,12). In this study, we investigated the relationship between the onset of eye movement periods and micturition in human fetuses at term and in neonates to clarify the transition in relationship that occurs during the perinatal period.

Materials and Methods

Study Population

This study evaluated 6 normal infants born between 37 and 41 weeks of gestation. In addition, data on 29 term fetuses reported by Koyanagi et al (5) were used as control. The study was approved by the Ethical Committee of Kyushu University Medical Sciences. All mothers gave written informed consent to participate in the study. Fetuses were found to have no detectable anomaly *in utero*. The women were followed in the Maternity Care Unit of Kyushu University Hospital. They had no medical or obstetric complications and did not use of alcohol, drugs, or medications other than vitamins and/or iron supplements. The period of gestation was calculated from the date of the last menstrual period and was confirmed by serial ultrasonographic measurements of crown-rump length before 11 weeks of gestation. After birth, none of the neonates was found to have any abnormalities. All had birth weight above the tenth percentile.

Procedure and Data Analysis

Data acquisition was performed 1-4 days after delivery in the hospital and/or around 1 month (29-33 days after birth) at home. Infants were placed in the recumbent position on their beds. When each baby started to fall asleep after feeding, the Dri Sleeper™ (Alpha Consultants Ltd., Nelson, New Zealand), which detects moist diapers, was set and the face of the infant was recorded with a digital video recorder (Canon, Tokyo, Japan). The total observation period was divided into one-minute epochs, with monitoring of eye movements, crying, and eye opening until micturition occurred (Fig. 1). Eye opening and crying were defined as arousal signs that corresponded with state 3 or above according to Prechtl et al (3,6).

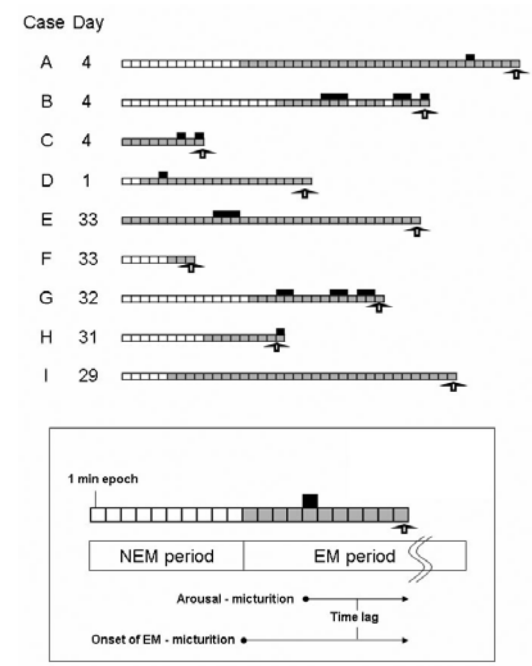
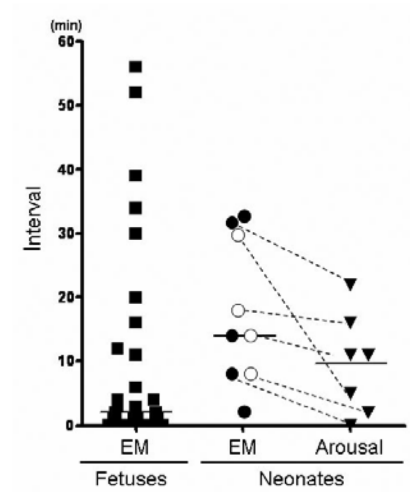


Figure 1. Schematic diagram of occurrence of eye movement (EM), arousal signs, and micturition in human neonates. Total observation time was divided into one-minute epochs, and eye movement, arousal signs, and micturition were recorded. The neonatal age (days) is indicated on the left side. Schema of measurement for interval time between the onsets of EM/arousal signs is indicated in lower diagram. Black box – arousal signs; gray box – epoch in which any eye movement was observed; arrow – micturition; NEM – no eye movement.

Fetal data sampling has been described elsewhere (5). In brief, the time lag between the onset of an eye movement period and the first subsequent micturition was measured in 29 fetuses at 37 to 41 weeks of gestation. Each fetus was examined only once, with the mother in a semi-recumbent position, using real-time ultrasound instruments (ALOKA SSD-280 and/or TOSHIBA SAC 12A with a linear array transducer of 3.5 MHz) (Toshiba, Tokyo, Japan).

Definition of Eye Movement/No Eye Movement Period

The neonatal eyelid and/or eye were continuously observed using the video recorder. A single eye movement could be observed through the eyelid even when closed. With the total observation period divided into one-minute epochs, a


(min)
60
50
40
30
20
10
0
Interval
EM
EM
Arousal
Fetuses
Neonates

states in neonates are performed by direct electronic methods. In contrast, because of the limitation of these methods, observations of behavioral parameters and their coordination are used for the human fetus. In the human fetus, micturition is seen more frequently during the active phase of fetal heart rate (FHR) variation than during the quiet phase of FHR variation (15,16). These two FHR phases, state 1F (S1F (''quiet sleep'') in comparison with S2F (''active'' or REM sleep), corresponded with the no eye movement and eye movement periods, respectively (6,17-19).

Synaptic transmission is often incomplete and the neuronal axons and/or synapses may grow either to the wrong target or to an inappropriate region (20). It has been assumed (21) that micturition associated with REM sleep indicates neuronal development of descending control of fetal micturition. The control center of REM sleep, the locus coeruleus and peri-alpha (22), and micturition, the dorsolateral tegmentum (23,24), are located very closely.

The finding that there is a relationship between the onset of the eye movement period and first micturition during 37-41 weeks of gestation, but not at 33-36 weeks, suggests a similar underlying mechanism whereby such a phenomenon in the pons becomes manifest in the human fetus at term (5). The relationship between REM sleep and penile erection occurs due to spread of activation or an overflow phenomenon between controlling neural centers that are in the close proximity (25,26). The neural control for awakening has not yet been clarified; however, the locus coeruleus is considered to be involved in this process, as well as the pedunculopontine nucleus and brain stem reticular formation (27,28). Therefore, weakening of this relationship might indicate a dramatic alteration of the neuronal relationship among centers for micturition, REM sleep, and awakening around the time of birth, although it is unclear whether the awaking center has already started to work in human fetuses. We previously documented that two conditions exist at 35 weeks of gestation or greater: short-duration pupil dilatation and long-duration constriction, with the former significantly occurring during eye movement periods (29). In human adults, pupillary diameter change is proportional to the range of states from sleep to alertness (30). Therefore, among these fetal behavioral parameters, pupillary changes, as well as micturition, may play crucial roles in assignment of awakening in the late human fetus. Further studies are required to examine these parameters, including the use of electronic methods for animal models to define fetal states that indicate not only behavioral development but also anatomical alternation within the CNS.

The other issue is that this alteration in the CNS occurs very rapidly after birth. Our results showed that concurrence of micturition with onset of the eye movement period was not significant even at 1-4 days after birth. We expected gradual transition in concurrence from the onset of the eye movement period to signs of arousal and micturition. However, even before 4 days after birth, no neonate showed concurrence between the onset of eye movement period and micturition. Thus, it is controversial that this alteration can be elucidated only by synaptic elimination. Recent evidence suggests that rapid alteration in action of neurotransmitters also occurs during the perinatal period (31). It has been suggested that human fetuses at term can learn and their learning ability has a significant relationship not only to gestational age but also to behavioral development (32). Other factors including molecular dynamics of neurotransmitters and their receptors or extrinsic factors, e.g. light, might also be taken into consideration.

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