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Diurnal Variation in Febrile Convulsions

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This study sought to determine diurnal variations in febrile convulsions, and to investigate whether such variations influenced the severity of febrile convulsions. The study involved 326 children, between ages 6 months and 6 years, with simple febrile convulsions. Data were collected systematically by interviewing witnesses within the week after febrile convulsions occurred. The frequency of febrile convulsions was approximately 5 times greater in the evening than in early morning. An adaptation curve revealed that the maximum occurrence of febrile convulsions was at 4:00 PM (4:00-4:59 PM), and the minimum, at 4:00 AM (4:00-4:59 AM), similar to the pattern of human body temperature. Temperature and seizure duration did not differ significantly between high-frequency and low-frequency zones (2:00-7:00 PM and 2:00-7:00 AM, respectively) (high-frequency zone vs low-frequency zone, 39.20°C (S.D., 0.68°C) vs 39.22°C (S.D., 0.64°C) and 3.82 minutes (S.D., 5.27 minutes) vs 3.14 minutes (S.D., 3.19 minutes)). These results suggest that the circadian rhythm does not change seizure propensity, but its hourly occurrence is attributable to an elevation in the temperature set point in the 24-hour period. The prevention of recurrent febrile convulsions by rectal administration of anticonvulsants in high-frequency zones would be clinically helpful.

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Introduction

Febrile convulsions affect 2-7% of all children between ages 6 months and 6 years [1,2]. Researchers conducted a review of the literature on febrile convulsions, including those listed in the Medline database. However, only one study from the emergency center of a university hospital contained information on the circadian rhythm of febrile convulsions [3]. We think that patients with more complex febrile convulsions are more likely to be referred to university hospitals than to private clinics. Moreover, private clinics are usually closed at night; therefore, the number of patients with febrile convulsions who consult university hospitals would further increase at night. To eliminate a referral bias, we enrolled patients from different health centers: a private clinic, a university hospital, and a regional central hospital with an affiliated emergency center.

Subjects and Methods

Subjects

This study involved 326 children, between ages 6 months and 6 years, who experienced simple febrile convulsions. Of these, 181 were boys and 145 were girls (male/female ratio = 1.24). The mean age at which patients were examined was 24.2 months. Of 326 patients examined, 136 (41%) had been enrolled in a private clinic, 100 (31%) in the emergency center of a regional central hospital, and the remaining 90 (28%) in Tokyo Medical College Hospital.

The inclusion criteria for classifying simple febrile convulsions comprised: (1) fever (i.e., a body temperature >38°C) at time of seizure; (2) seizure duration of less than 15 minutes; (3) absence of apparent postural asymmetry; and (4) absence of neurologic abnormalities and mental defects before the onset of febrile convulsions. Almost all infants sleep with a caregiver in the same room until they are of elementary school age; they usually nestle with their mother or father. Of the subjects in this study, 68.0% (222/326) had manifested only one seizure; 16.9% (54/326) had manifested two seizures; and 15.1% (50/326) had manifested three or more seizures. Moreover, 36.8% (120/326) had siblings, and among them, 25.1% had experienced febrile convulsions (28/120).

Data Collection

A specialized questionnaire was designed before initiation of the study, and was completed by pediatricians and pediatric neurologists while they interviewed a witness to the patient's seizure. The questionnaire was used to determine the date and time of seizure occurrence, the duration of the seizure, the asleep-or-waking state at the time of the seizure, seizure type, and body temperature. The information provided by the questionnaire

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was reconfirmed when the witness visited the hospital for a second time within a week of the febrile convulsions.

The patient's temperature was measured immediately after the seizure or within 30 minutes after a febrile convulsion upon arrival at the hospital or clinic. Patients' data were accumulated between 1992 and 2006. This study was approved by our institutional review boards.

Statistical Analysis

The time of occurrence of each seizure was recorded over 24-hour periods, and we created a histogram delineating the number of seizures that occurred during each hourly interval. These data were graphically represented in an adaptation curve created using KaleidaGraph, version 4 (Synergy Software, Reading, PA). To determine whether the time of seizure influenced the temperature and duration of febrile convulsions, the *t* test and chi-square test were performed using SPSS, version 10 (SPSS, Inc., Chicago, IL). All tests were two-tailed. $P < 0.05$ was considered significant.

Results

Diurnal Variation in Febrile Convulsions

The number of febrile convulsions, as represented in the histogram and adaptation curve (Fig 1), revealed that the maximum number of seizures occurred at 4:00 PM (from 4:00-4:59 PM), and the minimum number of seizures at 4:00 AM (from 4:00-4:59 AM). Thus, the frequency of febrile convulsions was approximately 5 times higher in the evening than in early morning ($P < 0.005$).

Comparison of Body Temperature and Seizure Duration Between Febrile Convulsions Occurring in Early Morning and Those Occurring in Late Evening

To determine whether the seizure duration of febrile convulsions was related to diurnal variation, we compared seizure durations in the ''low-frequency zone'' (2:00-7:00 AM) with those in the ''high-frequency zone'' (2:00-7:00 PM). Their mean duration (with standard deviation [S.D.]) was 3.14 minutes (S.D., 3.19 minutes) in the low-frequency zone (n = 28), and 3.82 minutes (S.D., 5.27 minutes) in the high-frequency zone (n = 132). The difference in durations between the two zones was not significant, according to *t* test and chi-square test. The average temperature (with S.D.) during an febrile convulsion was 39.22°C (S.D., 0.64°C) in the low-frequency zone, and 39.20°C (S.D., 0.68°C) in the high-frequency zone. This difference was also not significant.

During febrile convulsions, 54% of patients were awake, 28% were asleep, and 10% were drowsy. The asleep-or-awake state in 8% of patients was undetermined.

Discussion

The circadian rhythm of core temperature indicates that, in adults, the lowest temperature was recorded in the early morning (~36.5°C), and the highest temperature was recorded in the early evening (37.5°C) [4]. With regard to infants, from about 4 weeks of age, circadian rhythms begin

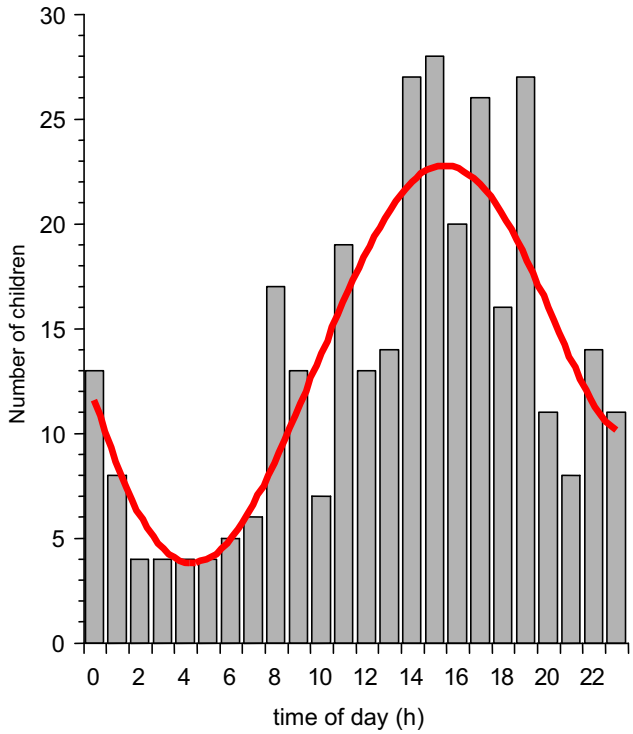

Figure 1. Diurnal variation in febrile convulsions in 326 patients. The histogram demonstrates the number of children with febrile convulsions at each hourly interval in a day. The frequency of febrile convulsions was lowest at 4:00 AM, and the highest at 4:00 PM. The adaptation curve is represented by $Y = 15.327 - 3.897X + 0.143X^2 + 0.054X^3 - 0.004X^4 + 0.001X^5$.

to emerge, as evidenced by a nadir in core temperature in the early morning [5]. By age 3 months, the infant's brain begins the circadian release of melatonin. By age 6 months, the period, amplitude, and phase activity of infants are the same as those of adults, although infants exhibit a different sleep pattern (i.e., ''multimodal'') from that of adults [6]. By approximately 1.5 years of age, toddlers give up their morning nap, and by age 6 years, children experience only nocturnal sleep [5,6]. Febrile convulsions occur only to a limited extent between age 6 months and preschool age, during which period the circadian rhythm of body temperature seems to be robust [5,6].

Unfortunately, our questionnaire does not seek information on subjects' napping habits. Little research has been conducted concerning the effects of napping on the circadian rhythm of temperature in children. Campbell et al. reported that in young adults, napping does not seem to change the night-sleep pattern, but instead shortens the circadian rhythm of both asleep-awake states and temperature, so that it is closer to 24 hours [7].

As illustrated in Figure 1, the frequency of febrile convulsions was highest at 4:00 PM and lowest at 4:00 AM, and unexpectedly, this trend closely coincides with the circadian rhythm of human body temperature [4,5]. If, for example, an infant with febrile convulsions routinely exhibits a core temperature of 36.5°C in the early morning and 37.5°C in the late evening, and the threshold of febrile convulsions is assumed to be 38.5°C, then an increase of

2°C in the early morning, but 1°C in the late evening, would be required to attain the critical temperature of 38.5°C. Accordingly, the diurnal variation in febrile convulsions is thought to be based on a change in the thermoregulatory set point.

Body temperature is known to decrease during sleep. Moreover, body temperature has its own endogenous circadian rhythm, and during a sleep episode, the body temperature decreases further [8]. These temperature-decreasing effects are brought about via decreased oxygen consumption, dilatation of the peripheral vessels, and increased sweating, which elevates thermal emission [9]. Furthermore, arginine vasopressin, which is secreted at night, exerts a strong, endogenous antipyretic effect [10-12]. Reduced sympathetic-nerve activity during sleep is also known to induce a decrease in body temperature [9].

To the best of our knowledge, only Manfredini et al. investigated diurnal variation in febrile convulsions [3]. They studied 188 patients referred to the emergency room of an Italian university hospital, and demonstrated that febrile convulsions were most frequent at 6:31 PM. Our results are consistent with theirs, but with a slight discrepancy with respect to the time. This discrepancy can be attributed to the ''advanced phase,'' which differs across cultures and sleep habits [8].

In this study, we also demonstrated that no significant difference existed in the duration of seizures during febrile convulsions between low-frequency and high-frequency zones. These results suggest that the circadian rhythm itself does not alter seizure intensity or brain excitability. In other words, sleep, the autonomic nerve system, and arginine vasopressin hardly affect the severity of convulsions. However, these factors play a role in the regulation of body temperature, which in turn affects the frequency of convulsions. Furthermore, temperatures at the time of febrile convulsions did not differ between early morning (low-frequency zone) and late evening (the high-frequency zone). These temperatures were 39.22°C (S.D., 0.64°C) and 39.20°C (S.D., 0.68°C) for the low-frequency and high-frequency zones, respectively. According to some researchers, the rate of increase in temperature, rather than the critical temperature, plays an important role in the development of febrile convulsions. Nevertheless, as Aicardi commented, this contention has not been proven by definite evidence [1]. Our data suggest that temperature itself is more important than the steepness of temperature rise, because two groups (high-frequency and low-frequency zones) with different temperature set points exhibited almost the same temperature at the time of occurrence of febrile convulsions.

Recently patients with febrile convulsions were reported to exhibit significantly higher temperatures than age-matched control subjects [13,14]. From an immunologic perspective, interleukin-1β, a proinflammatory cytokine, was implicated in the generation of febrile convulsions [15,16], and polymorphisms in the interleukin gene may be used as markers of susceptibility to febrile convulsions [17]. These reports promote the hypothesis that febrile convulsions occur when temperature reaches a certain level in children who have a genetic tendency to develop higher temperatures during infections.

Our study has certain limitations. The circadian rhythms of each child were not examined, and localized and non-random samples were used. Moreover, other factors that influence body temperature, such as a history of sleeping poorly at night, sleep onset time, napping, and household environment, must be taken into consideration in future studies.

Febrile convulsions constitute the most common convulsive disorder, with a good prognosis. The seizures last for only a few minutes and cease before the child reaches the hospital or clinic. However, for parents or caregivers, a seizure is an emotionally traumatic event, and parents are constantly worried about fever or recurrence of seizures [3,18]. Therefore, it is important to inform them that febrile convulsions have a benign prognosis, and that anticonvulsants, such as oral or rectal diazepam, are effective in preventing febrile convulsions, especially when treatment is given in the late evening.

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