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Diurnal occurrence of complex febrile seizure and their severity in pediatric patients needing hospitalization

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ABSTRACT

Several studies describing the diurnal occurrence of febrile seizures have reported greater seizure frequency early or late in the evening relative to midnight or early morning. However, no articles have reported on the diurnal occurrence of complex febrile seizure. Moreover, no studies have addressed the relationship between seizure severity and diurnal occurrence. We retrospectively evaluated complex febrile seizures in 462 children needing hospitalization, and investigated the relationship between severity and diurnal occurrence according to four categorized time periods (morning, afternoon, evening, and night). Our study showed that complex febrile seizures occurred most often in the evening, peaking around 18:00 (18:00–18:59), and least often at night (02:00–02:59). In addition, the frequency with which patients developed status epilepticus or needed anticonvulsant treatments was also lower during the night. However, the seizure duration and the proportion of the patients who needed anticonvulsant treatment were the same among the four time periods. Furthermore, we compared three subclasses (repeated episodes of convulsions, focal seizures, and prolonged seizures (≧15 min)), two of the complex features (focal seizures and prolonged seizures), and all complex features among the four time periods. However, they were the same among the four time periods. Taken together, our data indicate that although the severity of seizures was stable over a 24-hour period, the occurrence of seizures in our cohort of pediatric patients with complex febrile seizures requiring hospitalization was highest in the evening and lowest at night.

1. Introduction

Febrile seizures (FSs) are the most common type of seizure among children, occurring at a rate of 2–5% [1]. Of the two types of FS, simple FS (SFS) is defined as a primarily generalized seizure that lasts less than 15 min and does not recur within 24 h; a complex FS (CFS) is defined as a focal, prolonged (≧15 min) seizure that may recur within 24 h [2,3]. While SFS does not usually cause lasting neurological sequelae, there is a concern that afebrile seizures may develop after an initial CFS [4,5]. Annegers et al. reported that the risk of afebrile seizures in patients with CFS is high, and risks are 6% to 8% with 1 feature of CFS, 17% to 20% with 2 features (e.g., prolonged and focal), and 49% with 3 features [5]. In addition, development of hippocampal sclerosis after a complex febrile seizure was also reported [6].

A few studies have reported the diurnal occurrence of FS in children, describing that the frequency of FS is greater in the early or late evening than in the middle of the night or in the early morning [7–10]. Although several hypotheses accounting for the diurnal occurrence of FS have been proposed (e.g., circadian rhythm of melatonin secretion or specific body temperature), no conclusion has been reached [7–14]. In addition, no studies have reported on the diurnal occurrence of CFS specifically, nor has there been any discussion of the relationship between severity and diurnal occurrence of CFS.

Because CFS is more likely than SFS to have a harmful etiology, potentially requiring immediate treatment, physicians treating a child with a CFS are more likely to pursue a thorough diagnostic evaluation [15]. Therefore, knowing the occurrence, severity, or specific characteristics of CFS increase at specific times of the day will aid the physicians in treatment.

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The primary goal of this study was to evaluate the diurnal occurrence of CFS in pediatric patients requiring hospitalization. Our secondary goal was to analyze the possible relationships between the diurnal occurrence of CFS and patient characteristics, seizure severity and complex features of CFS, and laboratory data.

2. Materials and methods

2.1. Study design and subjects

This retrospective, clinical observational study was conducted under approval of the Ethics Committee of Hyogo Prefectural Kobe Children's Hospital, with a waiver of informed consent owing to the retrospective nature of the study. Our hospital is a multidisciplinary tertiary care center that handled 281 FS cases over the past year alone. In the current study, we reviewed the medical records of our emergency department (ED) corresponding to a database of 546 consecutive patients (ages 6 months to 60 months) who developed a fever, with a subsequent seizure needing initial hospitalization, between October 1, 2002 and June 30, 2017. Patients with SFS (n = 34), those for whom detailed data or medical records could not be found (n = 3), those with apparent CNS infection (n = 16) such as meningitis (cerebrospinal fluid cells > 8 cells/μL), or those with a history of unprovoked seizure (n = 31: epilepsy (n = 28), West syndrome (n = 1), or Dravet syndrome (n = 2)) were excluded from this study. As a result, 462 individuals with CFS were finally analyzed.

2.2. Definitions

Patients were diagnosed with FS by physicians in our ED, based on an interview of the parents describing jerking movements and impaired consciousness that met the criteria of FS detailed below. Identification of FS was made in accordance with guidelines established by the ILAE and American Academy of Pediatrics [2,3]. Namely, SFS is defined as primarily generalized seizures that last less than 15 min and do not recur within 24 h. The CFS was defined as a focal, prolonged (≧15 min), and/or recurrent seizure occurring within 24 h of the first seizure onset in children with no history of neonatal or unprovoked seizures and apparent CNS infection. We defined the condition as “febrile” if a patient had a temperature of more than 38 °C within 24 h before or after convulsion. Seizure onset was defined as the beginning of any neurological symptoms, such as convulsion, eye deviation, or impaired consciousness. In addition, in this study, status epilepticus (SE) was defined using newly established criteria; namely, a convulsive seizure or a sequence of intermittent seizures lasting 5 min or longer and with the patient not fully regaining consciousness [2,16]. This definition deviates from the academic definition of SE, which is defined as seizure activity lasting more than 30 min [2,17–19]. Admission criteria for our institution include all patients with CFS and with parental consent. All patients were 6–60 months of age. Neurological performance at baseline was assessed by the pediatric neurologist using the Pediatric Cerebral Performance Category (PCPC) scale, with a score of 1 representing normal performance; 2, mild disability; 3, moderate disability; 4, severe disability; 5, persistent vegetative state; and 6, death [20]. Time of day was categorized into four 6-hour periods (night: 24:00–05:59, morning: 06:00–11:59, afternoon: 12:00–17:59, evening: 18:00–23:59).

2.3. Clinical data

We retrospectively reviewed the medical databases and charts of Hyogo Prefectural Kobe Children's Hospital. Data regarding demographics, clinical presentation, treatment, and laboratory tests were obtained. Body temperature, PCPC, and laboratory data were measured at patient presentation. If patients were transferred from another hospital, all data from the hospital at presentation were included. The following data were collected for the corresponding number of patients: seizure duration (n = 462), white blood cell count (n = 460), hemoglobin (n = 460), platelet count (n = 459), aspartate aminotransferase (n = 459), alanine aminotransferase (n = 458), sodium (n = 458), glucose (n = 456), and C-reactive protein (n = 460).

2.4. General clinical protocol

An antiepileptic drug (AED) for febrile status epilepticus was administered on an individual basis according to hospital protocols. In general, we begin a regimen with intravenous benzodiazepine administration (diazepam and/or midazolam), followed by fos-phenytoin or phenobarbital as second line treatment. If the response to these AEDs was poor, this condition was defined as refractory SE and intravenous anesthesia such as thiamylal or intravenous drip midazolam is used.

2.5. Outcome measures

The primary outcome of this study was to reveal the diurnal frequency of CFS cases in hospitalized pediatric patients. Secondary outcomes included the relationship between the diurnal occurrence of CFS and the characteristics of patients, severity and complex features of CFS, and laboratory data.

2.6. Statistics

Results are expressed as number (%) or median (1st quartile, 3rd quartile). One-way analysis of variance (ANOVA) or the chi-square test was used when appropriate for statistical analysis of the results. These were obtained as nominal P-values without Bonferroni correction (P = 0.05). To perform a Bonferroni correction, the P-value threshold of 0.05 was divided by 8 (number of separate tests) to yield a corrected threshold P-value of 0.0083 (see Table 3). Analyses were performed using GraphPad Prism 5.0 (GraphPad Software, San Diego, CA, USA).

3. Results

3.1. Population demographics

We enrolled 462 patients (249 male and 213 female) with a median age of 21.6 months (range, 6.2–59.6 months). The median body temperature was 38.8 °C at presentation, and 405, 23, 16, and 18 patients had a PCPC score of 1, 2, 3, and 4, respectively. The median seizure duration was 44 min, and the number of patients with SE was 385 (83.3%). Intravenous diazepam (n = 237) and/or midazolam (n = 176) were used for first line treatment, and intravenous phenobarbital (n = 22) and/or fos-phenytoin (n = 67) were used for second line treatment. Intravenous drip midazolam (n = 4) or thiamylal (n = 73) was used for third line treatment.

3.2. Diurnal variation of CFS

The diurnal variation in the occurrence of CFS in patients requiring hospitalization is shown in Fig. 1. The CFS frequency increased during the day and in the evening, with the maximum number of CFS cases reported at 18:00 (from 18:00–18:59), and the lowest number at night (02:00 (from 02:00–2:59)). The frequency of CFS was about five times higher at 18:00 than at 02:00. No differences were found in terms of sex, age, body temperature, or in any laboratory data (Data not shown). To compare across longer periods of time, the data were subdivided into four six-hour-long periods as shown in Table 1. Even when subdivided by time period, there were no significant differences in age, sex, body temperature, and laboratory data.

We also evaluated the severity of CFS in terms of seizure duration and SE, and noted in detail the treatment provided for the seizures occurring in each of the 6-hour blocks (Table 2). Although SE appeared