

Original article

High incidence of status epilepticus and ongoing seizures on arrival to the hospital due to high prevalence of febrile seizures in Izumo, Japan: A questionnaire-based study

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Abstract

Objectives: To determine the incidence of prolonged febrile seizures and status epilepticus in the first three years of life.

Methods: A questionnaire was sent to 1560 families between April 2016 and March 2017 before their child attended a routine health check at three years of age in Izumo, Shimane prefecture, Japan. The questionnaire included an overview of febrile seizures, including the age at which febrile seizures occurred, the duration, and how the condition was managed.

Results: We received 1089 (69.8%) responses and these showed that 134 (12.3%) children had a history of febrile seizures. Fourteen children with febrile seizures (10.4%) had prolonged seizures lasting 10–30 min and six children (4.5%) had status epilepticus. Ongoing febrile seizures that did not terminate on arrival to the hospital were observed in 11 children (8.2%) with febrile seizures. The incidence rates of status epilepticus, prolonged febrile seizures including status epilepticus and ongoing febrile seizures were 184, 612 and 337 per 100,000 children aged 36 months or less, respectively.

Conclusions: There was a greater incidence of status epilepticus than previously thought, possibly due to the high prevalence of febrile seizures in Japan. Eight percent of children with febrile seizures were seizing on arrival to the hospital. These ongoing seizures requiring emergency interventions were almost twice more than status epilepticus. Thus, it is necessary to develop an early intervention for the termination of prolonged febrile seizures.

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Keywords: Prolonged febrile seizure; Status epilepticus; Incidence; Prehospital treatment

1. Introduction

Prolonged febrile seizures and status epilepticus are one of the most common and serious neurological conditions in childhood [1,2]. They are often associated with neurological sequelae and an increased risk of

epilepsy [2]. Prolonged febrile seizures and status epilepticus accounts for 25–30% and 5% of children with febrile seizures, respectively [3]. The prevalence of febrile seizures in Japan (8–10%) is 2–3 times higher than those reported in other countries (2–4%) [4–6]. The incidence rate of status epilepticus per 100,000 children at the age of 14 years or under was calculated as 24 in Rochester, USA, whereas in North London it was 17–23 per 100,000 children at the age of 15 or under [1,7]. In Okayama, Japan, the incidence rate of status epilepticus

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per 100,000 children at the age of 14 or under was 38.8 [8]. In Yachiyo, Japan, it was 41.0 per 100,000 children at the age of 15 or under [9]. The proportion of the febrile status epilepticus for all cases was 24% in Rochester, 32% in London, 46% in Okayama and 63% in Yachiyo. This showed that the incidence rate of status epilepticus was twice as high in Japan and the proportion of febrile status epilepticus was also high.

We made a hypothesis that the high incidence of status epilepticus would be due to the high prevalence of febrile seizures in Japan, as shown by previous epidemiological studies. However, few epidemiological studies of status epilepticus have been carried out in Japan; therefore, we conducted a questionnaire-based survey at the regular health check program for three-year-old children. Moreover, we also examined ongoing seizures on arrival to the hospital, as they were thought to be equivalent to status epilepticus.

2. Methods

2.1. Study design, setting, and selection of participants

We conducted a questionnaire-based survey regarding febrile seizures at a health-check program for three-year-old children from April 2016 to March 2017 in Izumo, Shimane prefecture, Japan. The city had a population of 174,724 in March 2017 and is located in the Shimane prefecture, the western part of Japan. The health-check program was organized by the Department of Health Promotion, Izumo City Office. The health-check program in Izumo was organized for all three-year-old children from Izumo, Hikawa and Hirata; the three locations that covered all the city area of Izumo. We sent questionnaires to participating families before the start of the program. The questionnaire consisted of a brief description of febrile seizure, and questions regarding the date or age of the child (in months) at which each episode of febrile seizures occurred, as well as details of the clinical course, such as a place where the seizure stopped, seizure duration, emergency visit, use of ambulance, whether they were hospitalized or not, number of days they hospitalized, and treatment option for the prevention of febrile seizures. Questions about the causes of fever and history of unprovoked seizures were not included to facilitate caregivers' response and minimize uncertainty (see Appendix). All questionnaires were collected during the child's health-check visit. The study protocol had the approval of the Ethics Committee of Shimane University School of Medicine (No.; 20151020-1).

Febrile seizures were defined as seizures associated with a fever of at least 38.0 °C [10]. Seizures that occurred before the age of 6 months were excluded [11,12]. As mentioned previously, we did not collect

information regarding the causes of fever or inquire about history of unprovoked seizures in this study.

The definitions of a prolonged seizure and status epilepticus were seizures lasting 10 min or more [13], and 30 min or more, respectively. Seizures that did not terminate on arrival to the hospital were called ongoing seizures.

2.2. Outcome measures

The primary outcome of this investigation was the prevalence of febrile seizures at the age of 36 months, and the incidence rate of prolonged febrile seizures, febrile status epilepticus and ongoing seizures in the first three years of life. The prevalence of febrile seizures was calculated separately at the three locations because the response rate of questionnaires was different between the three locations. Secondary outcomes included age of onset, rate of recurrence, and clinical characteristics in febrile seizures, prolonged febrile seizures, status epilepticus and ongoing seizures.

2.3. Analysis

Only febrile seizures occurring at 36 months of age or less were included in our analysis. Descriptive statistical analyses were performed using Microsoft Excel version 14.0 (Microsoft Corporation, Redmond, WA, USA) for averages and medians. The incidence rate of prolonged febrile seizures, febrile status epilepticus and ongoing seizures in the first three years of life per 100,000 population was calculated as follows: each number of children with a history of prolonged febrile seizure, febrile status epilepticus and ongoing seizures / (number of observed children × 3) × 100,000.

3. Results

3.1. Study subjects

During the study period, we identified a total number of 1560 three-year-old children eligible for inclusion in the program. Before the program, we mailed the questionnaires to 1560 families and received 1089 (69.8%) responses at the program sites; the rate of responses was different between the three sites, 710/1097 (64.7%) in Izumo, 216/262 (82.4%) in Hikawa, and 163/201 (81.1%) in Hirata (Table 1).

3.2. Prevalence of febrile seizures

Of the 1089 children, 134 (12.3%) had a history of febrile seizures at 36 months of age; fifty eight (43.3%) of these children were female, though sex was not reported in two cases. The prevalence of febrile seizures

Table 1
Prevalence of febrile seizures.

Program site	Izumo	Hikawa	Hirata	Total
Questionnaire sent n	1097	262	201	1560
Response n (%)	710 (64.7%)	216 (82.4%)	163 (81.1%)	1089 (69.9%)
Febrile seizures n (%)	86 (12.1%)	29 (13.4%)	19 (11.7%)	134 (12.3%)

n: number

was 134/1089 (12.3%) in total, and in each site it was 86/710 (12.1%) in Izumo, 29/216 (13.4%) in Hikawa and 19/163 (11.7%) in Hirata (Table 1).

3.3. Seizure characteristics

In total, 218 seizures were reported in the 134 children with an average of 1.6 seizures per a child; there was one seizure in 89 children (66%), two seizures in 31, three seizures in six, four seizures in two, five seizures in two, six seizures in two children, nine seizures in one child, and ten in another child. The average and median ages at which initial febrile seizures occurred were 18.9 and 17 months, respectively, and a minimum of 6 months. In the total of 218 febrile seizure events, children were transferred by ambulance in 69 episodes (32%) and were admitted in 61 episodes (28%), of which 50 lasted less than one week and in 11 lasted for one week or more. Of the 134 children that experienced seizures, ten children had not visited physicians (Table 2).

From 218 seizures, 130 (59%) seizures lasted less than 3 min and 52 (24%) seizures lasted 3–10 min. In the former, most of the seizures (93%) stopped at home, while in the latter, the seizures stopped at home (37/52, 71%) and during transportation (12/52, 23%) (Table 2).

Prolonged febrile seizures lasting 10–30 min occurred 16 times in 14 children (14/134, 10.4%). The average age at which the initial prolonged febrile seizure occurred was 20.5 months and the median was 18 months. Among the 14 children with prolonged febrile seizures, eight children had a recurrence (57%), of those, two children had a recurrence of prolonged febrile seizures. The first seizures were prolonged febrile seizures in 12

children (12/14, 86%). In 9 out of 16 episodes (56%), children were transferred by ambulance, and admitted in 10 episodes (Table 2).

Status epilepticus occurred 6 times in 6 children (6/134, 4.5%). The average age at which the initial status epilepticus occurred was 21.5 months, and the median 17 months. The first seizures were status epilepticus in 5 children (5/6, 83%). No one experienced a recurrence of status epilepticus by the age of 36 months. Three children (50%) were transferred by ambulance. All children with status epilepticus were undergoing seizure on arrival to the hospital, and they were all hospitalized. Three children were hospitalized for less than one week, and three children for one week or more (Table 2).

The ongoing seizures on arrival to the hospital were 11 times in 11 children (11/134, 8.2%). The average age at the ongoing seizure was 19.7 months, and the median was 18 months. Among the 11 ongoing seizures, it was reported that there were three seizures lasting three to ten minutes, two prolonged seizures lasting 10–30 min, and six seizures of status epilepticus. The number of ambulance call-outs was six times (55%) and hospitalization was nine times (82%), of which five lasted less than one week, and four lasted one week and more (Table 3).

3.4. Incidence of status epileptics, prolonged febrile seizures and ongoing seizures

Incidence rates of status epilepticus, prolonged febrile seizures including status epilepticus and ongoing seizures were 184, 612 and 337 per 100,000 children aged 36 months and less, respectively.

Table 2
Clinical characteristics according to seizure duration.

Seizure duration	n	Where did the seizure stop?			Transported by ambulance	Admission		
		Seizing on arrival to the hospital	During transportation	At home		admitted	<7 days	≥7 days
Status epilepticus seizures	6	6 (100%)			3 (50%)	6 (100%)	3	3
Seizures lasting 10–30 min	16	2 (12%)	6 (38%)	8 (50%)	9 (56%)	10 (63%)	9	1
Seizures lasting 3–10 min	52	3 (6%)	12 (23%)	37 (71%)	23 (44%)	16 (31%)	13	3
Seizures <3 min	130		9 (7%)	121 (93%)	34 (26%)	29 (22%)	25	4
Seizure descriptions not detailed	14	NA	NA	NA	NA	NA		
total	218	11 (5%)	27 (12%)	166 (76%)	69 (32%)	61 (28%)	50	11

NA: not available.

Table 3
Clinical characteristics of ongoing seizures on arrival to the hospital.

Duration of seizure	n	Transported by ambulance	Admission required	<7 days	≥7 days
Status epilepticus	6	3 (50%)	6 (100%)	3	3
Prolonged Seizures (10–30 min)	2	2 (100%)	2 (100%)	2	
Seizures lasting 3–10 min	3	1 (30%)	1 (33%)		1
Total	11	6 (55%)	9 (82%)	5	4

4. Discussion

We reported the findings from a cross-sectional survey of three-year-old children with a history of febrile seizures who took part in a health-check program. This study confirmed a high prevalence of febrile seizures and high incidence rate of status epilepticus in Japan [4,8,9].

The prevalence of febrile seizures in this study was even higher than those previously reported in Japan. In previous studies of three-year-old children that also participated in a health-check program for in Japan, a questionnaire revealed the prevalence of febrile seizures was 6.5–8.4% [14–16], and an interview revealed that it was 8.3%–9.9% [4]. Our study showed a prevalence of 12.3%, which is high in comparison to previous studies. The majority of the children (124/134, 93%) had been taken to the hospital for the febrile seizures. Moreover, the prevalence of febrile seizures at each site of the program, 11.7%, 12.1% and 13.4%, was consistently high, although the questionnaire recovery rates, 64.5–82.4%, varied between the three sites.

We re-calculated data from previous studies in order to compare them with our data of children up to the age of three. The incidence rate of status epilepticus per 100,000 children under 5 years of age was 57.2 for all cases and 16.9 for febrile status epilepticus in Rochester, USA [7] and 33.5, 13.8 in North London, UK [1], respectively. In Okayama, Japan, the incidence rate of status epilepticus per 100,000 children in the first three years of life was 93.0 for all cases and 46.4 for febrile status epilepticus [8]. In our study, the incidence rate of febrile status epilepticus per 100,000 children in the first three years of life was 184, which is three to five times higher than those of previous studies in Rochester and London, and two times higher than the incidence rate in Okayama, Japan. However, this could be due to a difference in case ascertainment. Retrospective record reviewing in the Okayama study was possibly insufficient for including all patients.

In a previous study, the proportion of prolonged febrile seizures including status epilepticus and status epilepticus in febrile seizures was 13.1% and 5.1%, respectively [3] and 14.9% and 4.5%, respectively, in our study. The proportions were almost similar in the two studies. Therefore, the high incidence of prolonged febrile seizures and status epilepticus was apparently related to the high prevalence of febrile seizures.

In this study, we also focused on ongoing seizures that continued on arrival to the hospital. In previous studies, ongoing seizures were seen in 52% and 85% patients with prolonged febrile seizures or status epilepticus [17,18], where in the former, the seizures were stopped by ambulance treatment in 25% of the patients. We think that this type of seizures is clinically important, because it requires prompt intervention by antiepileptic drugs and is equivalent to status epilepticus, considering the transfer time to the hospital. It is often hard to estimate seizure duration in a clinical setting; however, ongoing seizures are relatively easy to count because of independence from the time. Therefore, the incidence rate of ongoing seizures can be a practical number of the patients with emergency. In Japan, from calling an ambulance to be taken to the hospital takes on average 48 min, where it takes 8.5 min from ambulance call to the arrival at the requested site and 39.3 min from the site to the hospital [19]. In case of transfer by ambulance, the seizure duration of ongoing seizure must be over 30 min, i.e., that of status epilepticus.

Febrile status epilepticus is less likely to terminate spontaneously [20] and early treatment is essential for the outcome in status epilepticus [21]. It is recommended that first line therapy is applied within five to ten minutes of seizure onset [22], therefore, it is necessary that medical staff provide prehospital treatment with antiepileptic drug. Studies of prehospital treatment for status epilepticus, which used intravenous or rectal diazepam [23], intravenous lorazepam and diazepam [24], as well as intramuscular midazolam [25], showed an early seizure termination. In prolonged febrile seizures, prehospital antiepileptic drug therapy was successful for seizure termination before arrival to the hospital in half of the patients [17]. However, even in the countries where prehospital treatment for prolonged seizures is instituted, delay of treatment still occurs [26].

Although the incidence rate of status epilepticus in Japan, reported by the study of Okayama and our study is twice or more as high than that in other countries, prehospital treatment using antiepileptic drugs is currently prohibited in Japan. Moreover, our study showed a lower number of ambulance call-outs as only 6 out of 11 children (55%) with ongoing seizures, although the call-outs were 77% and 90% in the previous studies [17,18]. This low ambulance activation may

affect the prehospital treatment. In a study in Tokyo, ambulances were called out for 75% children with febrile seizures, which was higher than that of our study, however, the authors mainly discussed issues surrounding unnecessary ambulance call-outs [27]. If drug treatment in ambulance for seizure disorders were allowed in Japan, the role of ambulance transfers would change.

There is also another valid reason why prehospital treatment should be introduced. In our study, 17 out of 20 children (85%) with either prolonged febrile seizures or status epilepticus did not have a prior febrile seizure. This was almost the same as the FEBSTAT study [20], in which 86% of patients did not have a prior febrile seizure. Therefore, the caregivers could not help to prevent a seizure by administering preventive antiepileptic drugs, such as diazepam suppository [11,12].

This study had several limitations. First, since questionnaires were used for data collection, the accuracy of febrile seizure diagnosis is uncertain. Most children (124/134, 93%) were seen by doctors, as we previously mentioned. However, the causes of fever were not specified in this study; therefore, central nervous infections were not excluded. Moreover, some children may have exhibited a type of encephalopathy rather than febrile status epilepticus. Second, because the questionnaire did not ask about afebrile seizures, some children with febrile seizures could have also experienced unprovoked seizures or epilepsy. Among three-year-old children in Fuchu, Tokyo, the prevalence of afebrile seizures were 0.9% [4]. Therefore, the number of children with both febrile and afebrile seizures appeared relatively small. Third, seizure duration estimates may not be accurate, and could be either over-estimated or under-estimated. Caregivers may feel as if a seizure lasted longer than it actually did. Moreover, a child may have been already seizing prior to being noticed by a caregiver. Therefore, the recorded seizure durations may be inaccurate, especially seizures lasting 3–10 min and those lasting more than 10 min. The categorization of status epilepticus in our study appeared accurate because children with status epilepticus were all seizing on arrival to the hospital. However, status epilepticus and ongoing seizures can be associated with diagnostic uncertainty, as some children with febrile seizures show mimicking prolonged seizures without epileptiform discharges [28,29]. Therefore, we may have overestimated the incidence of both status epilepticus and ongoing seizures. Fourth, caregivers of children with febrile seizures may be more likely to respond to the questionnaire than those of unaffected children, possibly overestimated. Data from the three sites were analyzed separately and the prevalence was consistently high, though the response rates of questionnaires varied.

5. Conclusion

Our data indicated that there was a greater incidence of status epilepticus than previously thought, possibly due to the high prevalence of febrile seizures in Japan. The ongoing seizures on arrival to the hospital can be important practical and statistical indicators as they possibly represent status epilepticus. Moreover, our data shows the need to further promote prehospital treatment in Japan.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.braindev.2019.07.009>.

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