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Original article

The effects of antihistamines on the semiology of febrile seizures

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Abstract

Objective: The aim of this study was to clarify the effects of antihistamines on the semiology of febrile seizures.

Methods: The manifestations of febrile seizures were recorded using a structured questionnaire immediately after patients arrived at the hospital. We focused on events at seizure commencement, including changes in behavior and facial expression, and ocular and oral symptoms. The presence or absence of focal and limbic features was determined for each patient. Drugs taken within 6 h prior to seizure were noted. Seizure manifestations were compared between children who did not take antihistamines and those who took antihistamines.

Results: Seizures lasting ≥5 min were relatively more frequent in children who did not take antihistamines, although the difference was not statistically significant. One or more focal features were present in 60 of 78 children with no antihistamines and 17 of 23 children with antihistamines. One or more limbic features were present in 32 of 78 children with no antihistamines and 9 of 23 children with antihistamines. No significant difference in the numbers of focal or limbic features was apparent between children who did not take antihistamines and those who took antihistamines.

Conclusion: Antihistamines did not significantly affect the semiology of febrile seizures.

Keywords: Antihistamines; Febrile seizures; Focal features; Limbic features; Duration of seizures

1. Introduction

The semiology of febrile seizures (FS) has not been fully understood, although there have been many studies on FS. Neville and Gindner suggested that FS may be of focal origin based on semiology focusing on phenomena evident before the motor events [1]. We also studied FS semiology in terms of manifestations at seizure commencement and showed that symptoms suggestive of focal onset were frequent [2]. These studies indicate that semiology of FS will be more diverse even in "simple" FS than previously considered.

Antihistamines (AH) have been prescribed even to infants and young children with febrile illness in Japan, although their benefits have not been proven objectively and their adverse effects have been repetitively reported [3–5]. Several studies have explored the effects AH on the clinical manifestations of FS and epilepsy. Some authors found that FS duration was longer in children who had taken AH than in those who had not [6–8]. Moreover, epileptic seizures induced by AH have been

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reported [9–11], and some studies have indicated that AH may increase seizure susceptibility in children [12–14]. However, the effects of AH on semiology of FS have not been fully understood.

We hypothesized that FS semiology might be modified by the use of AH prior to onset. We explored the relationship between seizure semiology and prior administration of AH in children with FS to expand our previous work on FS semiology [2]. The aim of this study was to clarify the effects of AH on FS semiology, focusing on focal and limbic features at seizure commencement.

2. Patients and methods

This was a secondary analysis of data obtained in an earlier prospective study on FS semiology [2]. The subjects were children with FS who visited the Departments of Pediatrics of Aichi Medical University Hospital, Anjo Kosei Hospital, and Okazaki City Hospital immediately after their seizures from May 2014 to October 2015. FS were defined as a seizure in children aged 6 months to 5 years associated with a fever >38.0 °C and the absence of central nervous system infection or any acute metabolic derangement. Children with prior evidence of neurological or developmental abnormalities were excluded. The study was approved by the ethics committee of Aichi Medical University Hospital.

FS manifestations were described by the parents using a structured questionnaire as soon as possible after arrival at the hospital (at the latest, within 24 h). The questionnaire has been described elsewhere [2]. Briefly, seizure duration was numerically recorded. We focused on events at seizure commencement. Changes in facial expression were evaluated using a facial action coding system [15]. We also asked whether the child was awake or asleep before seizure onset, and documented the autonomic and motor symptoms during seizure.

Drugs taken within 6 h before FS onset were recorded. We classified cyproheptadine, ketotifen, clemastine, diphenhydramine, and chlorpheniramine as first-generation AH, and cetirizine, levocetirizine, fexofenadine, and olopatadine as second-generation AH.

In line with our previous study [2], the following were classified as focal features:

1) Any change in behavior;
2) Changes in facial expression: fear, sadness, anger, or laughter;
3) Ocular symptoms: lateral deviation or eyelid flutter;
4) Oral symptoms: at least one of the following: drooling, oral automatism, cheek twitching, or mouth deviation;
5) Events during seizure: both specific autonomic symptoms (at least one of the following: pallor, cyanosis, or vomiting) and non-convulsive motor symptoms (atonicity or no obvious movement).

Limbic features were defined as seizure symptoms that were very likely of mesial temporal onset. The following items were classified as limbic features [2]:

1) Changes in behavior: crying or screaming;
2) Changes in facial expression: fear or sadness;
3) Oral symptoms: oral automatism.

We compared differences in patient characteristics, and the presence or absence of focal and limbic features by drug usage within 6 h prior to FS onset. The patients were divided into two groups; no AH and use of AH. We used the chi-square and Mann–Whitney U tests, respectively, to compare categorical and numerical variables between the two groups. We additionally compared seizure semiology dividing the patients into three groups; no AH; use of first-generation AH; and use of second-generation AH. We used the chi-square test to compare the rate of each item among the three groups. A p-value <0.05 was considered to reflect statistical significance. All statistical analyses were performed with the aid of EZR ver. 1.33 software (http://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmed.html) [16].

3. Results

Adequate data were available for 101 children with FS. Seventy-eight had taken no AH within 6 h before the onset of FS, 17 had taken first-generation AH, and 6 had taken second-generation AH. No children had taken theophylline in this study. Demographic data are shown in Table 1. We found no significant difference

Table 1
Patients characteristics.

	All (N = 101)	No AH (N = 78)	With AH (N = 23)	
Age (mo)	24 (8–71)	24 (10–71)	24 (8–61)	NS
Sex (M:F)	59:42	43:35	16:7	NS
Past history of FS	40 (40%)	31 (40%)	9 (39%)	NS
Family history of FS	37 (37%)	28 (36%)	9 (39%)	NS
FS duration ≥5 min	34 (34%)	30 (38%)	4 (17%)	NS
FS during sleep	41 (41%)	33 (42%)	8 (35%)	NS

AH: antihistamines, FS: febrile seizures, NS: not significant.

Table 2
Focal features.

Focal features		All (N = 101)	No AH (N = 78)	With AH (N = 23)	
Change in behavior	Any	32 (32%)	24 (31%)	7 (30%)	NS
Change in facial expression	Fear, sadness, anger, or laugh	25 (25%)	19 (24%)	6 (26%)	NS
Ocular symptoms	Lateral deviation or eyelid flutter	11 (11%)	8 (10%)	3 (13%)	NS
Oral symptoms	At least one of following items; Drooling, oral automatism, cheek twitching, or mouth deviation	45 (45%)	32 (41%)	13 (57%)	NS
Both autonomic and motor symptoms listed below Autonomic; at least one of pallor, cyanosis, or vomiting Motor; Atonic or no obvious movement		18 (18%)	13 (17%)	5 (22%)	NS
Number of focal features					
0		24 (24%)	18 (23%)	6 (26%)	NS
1		42 (42%)	36 (46%)	6 (26%)	
2		25 (25%)	17 (22%)	8 (35%)	
3		7 (7%)	5 (6%)	2 (9%)	
4		3 (3%)	2 (3%)	1 (4%)	

AH: antihistamines.

in age, sex, the frequency of earlier FS, or family history of FS between the two groups. FS persisting for ≥5 min were somewhat more frequent in children who did not take AH, although the difference was not statistically significant. The rate of FS during sleep did not differ between the groups.

The presence or absence of focal features by AH use is shown on Table 2. One or more focal features were present in 77 children (60 of 78 children with no AH and 17 of 23 children with AH). We found no significant difference between children with no AH and those with AH in the frequency of any focal features or the total number thereof (Table 2).

The presence or absence of limbic features by AH use is shown in Table 3. One or more limbic features were present in 41 children (32 of 78 children with no AH and 9 of 23 children with AH). We found no significant difference between children with no AH and those with AH in the frequency of any limbic features or the total number thereof (Table 3).

These results were not altered when children with AH were divided into the first- and second-generation AH groups (Supplementary Tables 1 and 2).

4. Discussion

FS semiology did not differ by the use of AH in our study. The frequencies of focal and limbic features and the total numbers thereof were not affected by the use of AH. No significant differences were observed in the clinical variables or the frequency of FS persisting for ≥5 min. Thus, AH did not seem to affect FS semiology.

The brain histaminergic system has been intensely studied and is known to be important in the context of

Table 3
Limbic features.

Limbic features		All (N = 101)	No AH (N = 78)	With AH (N = 23)	
Change in Behavior	Cry or scream	17 (17%)	13 (17%)	4 (17%)	NS
Change in facial expression	Fear or sadness	19 (19%)	15 (19%)	4 (17%)	NS
Oral symptoms	Oral automatism	14 (14%)	11 (14%)	3 (13%)	NS
Number of limbic features					
0		60 (59%)	46 (59%)	14 (71%)	NS
1		33 (33%)	26 (33%)	7 (18%)	
2		7 (7%)	5 (6%)	2 (12%)	
3		1 (1%)	1 (1%)	0	

AH: antihistamines.

behavioral and brain disorders. Changes in this system have been reported in patients with Alzheimer's disease [17], narcolepsy [18], and schizophrenia [19]. Near-infrared spectroscopy revealed impaired behavioral performance and cortical activation in the lateral prefrontal cortex during selective attention, verbal fluency, and working memory tasks in children taking first-generation AH [20–22]. Moreover, several studies found that histamine raised the seizure threshold and reduced seizure susceptibility [23,24]. First-generation AH such as ketotifen and chlorpheniramine elicit epileptiform activity [25]. Thus, we hypothesized that FS semiology might be affected by AH. However, AH did not modulate the focal or limbic features of seizures in our cohort, suggesting that FS semiology may not be affected by AH, although AH may increase seizure susceptibility.

Several studies found that FS duration was greater in children taking AH, especially first-generation AH, than in those not taking AH. Takano et al. reported that the FS duration was 39.3 ± 14.2 min in an AH group and 28.1 ± 15.6 min in a no-AH group [7]. Zolaly et al. reported that FS duration was 9.3 ± 14.2 min in a first-generation AH group, 6.0 ± 6.1 min in a second-generation AH group, and 4.5 ± 4.3 min in a no-AH group [6]. In contrast, Haruyama et al. found that the FS duration in children taking AH was no longer than that in children not taking AH, provided theophylline was not also prescribed [8]. An experimental study of maximal electroshock seizures in rats found that first-generation AH caused dose-dependent prolongation of electroencephalographic and tonic extensor seizures [13]. However, the pathogenesis of maximal electroshock seizures may not be the same as that of FS. In our study, the frequency of FS persisting for $\geq$5 min did not vary by AH use status, suggesting that effects of AH on FS duration may not be strong.

Our study has several limitations. First, the number of children taking AH was small, compromising statistical power. A larger number of children with FS should be investigated to obtain more definitive results. We could not explore the effects of AH on susceptibility to FS; this requires a well-designed prospective study on a large number of children. Our questionnaire has not been validated and may have been somewhat inappropriate. Our definitions of focal and limbic features are tentative. The questionnaire needs revision, and careful definitions of focal and limbic features are required. In this study, only information on drugs taken within 6 h before FS was collected, because we were afraid that correct information of drugs >6 h before FS may not be easily obtained. It is unknown whether or not children in no AH group had had AH >6 h before. The half-life of most AH is estimated to be 8 h or longer according to the information from pharmaceutical companies. There is a possibility that children in no AH group may have been affected by AH.

In summary, AH did not affect the semiology of FS. However, we consider that unnecessary AH use should be avoided; there is no evidence that AH effectively treat the common cold [26], and adverse events such as sedation have been commonly reported, associated especially with first-generation AH [3]. Further studies are necessary to clarify the effects of AH on FS manifestations.

Disclosure

None of the authors has any conflict of interest to disclose.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.braindev.2018.07.005.

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