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Review article

New guidelines for management of febrile seizures in Japan

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Abstract

In 2015, the Japanese Society of Child Neurology released new guidelines for the management of febrile seizures, the first update of such guidelines since 1996. In 1988, the Conference on Febrile Convulsions in Japan published "Guidelines for the Treatment of Febrile Seizures." The Task Committee of the Conference proposed a revised version of the guidelines in 1996; that version released in 1996 was used for the next 19 years in Japan for the clinical management of children with febrile seizures. Although the guidelines were very helpful for many clinicians, new guidelines were needed to reflect changes in public health and the dissemination of new medical evidence. The Japanese Society of Child Neurology formed a working group in 2012, and published the new guidelines in March 2015. The guidelines include emergency care, application of electroencephalography, neuroimaging, prophylactic diazepam, antipyretics, drugs needing special attention, and vaccines. While the new guidelines contain updated clinical recommendations, many unsolved questions remain. These questions should be clarified by future clinical research.

Keywords: Lumbar puncture; Electroencephalogram; Status epilepticus; Diazepam; Midazolam; Antipyretics; Antihistamine; Theophylline; Vaccine

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1. Introduction

In 1988, the Conference on Febrile Convulsions in Japan published "Guidelines for the Treatment of Febrile Seizures" in Japanese. The Task Committee of the Conference proposed a revised version of the guidelines in 1996 [1]. The 1996 guidelines were used for the clinical management of children with febrile seizures (FS) for 19 years in Japan. Although the guidelines were very helpful for many clinicians, new guidelines were needed to reflect changes in public health and the dissemination of new medical evidence. For example, the prevention of bacterial meningitis by vaccination has had a strong impact on the application of lumbar puncture in emergency departments.

The Japanese Society of Child Neurology formed a working group of 10 members and three advisors in October 2012. The members of the working group consisted of child neurologists from university hospitals, children's hospitals, a center for handicapped children, and a pediatric clinic. A member of the Medical Information Network Distribution Service (MINDS) joined the working group to give methodological advice.

The new guidelines were not simply a revision of the 1996 guidelines, but started over from the beginning using recent objective methods. The working group formulated clinical questions, selected key words for searching the literature for each question, searched the medical literature systematically, and evaluated the levels of evidence in the literature. The levels of evidence were assessed based on the standards of the Oxford Centre for Evidence-Based Medicine (CEBM) 2011 (http://www.cebm.net/index.aspx?o=5653).

Since the guidelines are aimed mainly at general pediatricians, physicians, and emergency medical staff, the clinical questions focused on the primary care of FS. The working group decided their recommendation for each clinical question by a vote of the members to avoid any biased opinions of a small number of working group members. The grade of recommendation was assessed based on the grading system of the Agency for Health Care Policy and Research (AHCPR, now Agency for Healthcare Research and Quality (AHRQ)). The clinical questions covered the topics of emergency care, application of electroencephalography, neuroimaging, prophylactic diazepam, antipyretics, drugs needing special attention, and vaccines.

The following organizations were asked to review the drafts of the guidelines: Japan Pediatric Society, Japan Pediatric Association, Japanese Society of Child Health, Japanese Society of Pediatric Allergy and Clinical Immunology, Japanese Society for Pediatric Infectious Diseases, Japanese Society of Emergency Pediatrics, and Society of Ambulatory and General Pediatrics of Japan. We also solicited public comments on the website of the Japanese Society of Child Neurology. We asked families of children with FS for opinions from their point of view as patients and families. Finally, we asked a member of MINDS to evaluate the drafts of the guidelines along with an AGREE (advancing the science of practice guidelines, http://www.agreetrust.org/) II assessment. After revision of the drafts from the opinions and comments, the new guidelines were published in March 2015.

In this review article, we discuss several issues that are featured in the new guidelines. Extracts of recommendations in the 2015 guidelines are provided in Table 1. The 2015 guidelines define FS as a seizure accompanied by fever (temperature 38 °C or higher), without central nervous system (CNS) infection, that occurs in infants or children 6–60 months of age [2]. Cases with a history of epilepsy prior to the seizure with fever are excluded from FS. Complex FS is defined as a seizure with focal manifestations, prolonged (15 min or longer) duration, and/or recurrent within 24 h [2]. Simple FS is defined as a seizure without the characteristics of complex FS.

2. Emergency care

FS is a common disorder encountered in emergency rooms. Although most patients with FS have a benign clinical course, special attention is needed for differentiation of FS from CNS infections. In the 1970s to the 1980s, bacterial meningitis occurred with a higher frequency than in the 2010s [3]. For the differentiation of bacterial meningitis, lumbar puncture was strongly recommended in infants with first episode of FS according to the proposal from the Subcommittee on FS of the American Academy of Pediatrics in 1996 [4]. However, there were critical reports regarding the recommendation of lumbar puncture in children with FS in 2009 and 2010 [5–7]. Kimia et al. reported an extremely low incidence of bacterial meningitis in children with features of first simple or complex FS [6,7]. Given the reduction in the incidence of bacterial meningitis, the Subcommittee of the American Academy of Pediatrics revised the practice guidelines for simple FS in 2011, and recommended lumbar puncture only in children who presented with a seizure and a fever and had meningeal signs and symptoms [2]. In Japan, *Haemophilus influenzae* type b and pneumococcal vaccines were introduced around 2010, and the incidence of bacterial meningitis has been dramatically reduced [8]. After the reduction in the incidence of bacterial meningitis in children in Japan, we made recommendations in the 2015 guidelines as follows: "(1) lumbar puncture is not routinely needed for children with FS; (2) lumbar puncture should be considered for children with FS and signs of CNS infections, such as meningeal signs, altered consciousness longer than 30 min, or bulging anterior fontanel".

The role of blood examination in children with FS is still controversial. While blood examination is

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Table 1
Extracts of recommendations from the 2015 guidelines in Japan for the management of febrile seizures (FS).

CQ1-1. Is lumbar puncture needed in children with FS?
1) Lumbar puncture is not routinely needed for children with FS. (Grade C)
2) Lumbar puncture should be considered for children with FS and signs of CNS infections, such as meningeal signs, altered consciousness longer than 30 min, or bulging anterior fontanel. (Grade A)

CQ2-1. What is the first-line treatment of febrile status epilepticus?
1) Intravenous diazepam or midazolam are recommended as the first-line treatment of febrile status epilepticus. (Grade A)
2) Attention to respiratory depression is needed. (Grade B)

CQ3-1. Should EEG be performed in children with a history of FS?
1) EEG is not routinely needed for children with simple FS. (Grade C)
2) The clinical significance of EEG for children with complex FS is not established, although some reports have suggested a correlation between epileptiform discharges on EEG and development of epilepsy. (Grade C)

CQ4-1. What are the criteria for the use of prophylactic diazepam?
1) Prophylactic diazepam is not routinely needed in children with a history of FS. (Grade C)
2) Prophylactic diazepam can be used in children with the following criteria: (Grade B)
   1. Children with a history of a prolonged febrile seizure lasting 15 min or longer.or
   2. Children with repeated FS and two of the following risk factors:
      (1) focal or repeated seizures within 24 h
      (2) preexisting neurological abnormality or developmental delay
      (3) family history of FS or epilepsy
      (4) age younger than 12 months
      (5) seizure within 1 h after onset of fever
      (6) seizure occurring with body temperature less than 38 °C

CQ5-1. Should children with a history of FS take antiepileptic drugs regularly?
1) Regular use of antiepileptic drugs is not recommended in children with a history of FS. (Grade C)
2) In children with prolonged or repeated FS in spite of the use of prophylactic diazepam, regular use of antiepileptic drugs can be considered. (Grade B)

CQ6-1. Do antipyretics affect the incidence of FS?
1) The use of antipyretics does not affect the incidence of FS. Prophylactic use of antipyretics for FS is not recommended. (Grade C)
2) There is no evidence for induction of FS by antipyretics. (Grade C)

CQ7-1. What are drugs that need special attention for children with a history of FS?
1) Use of sedative antihistamine agents or xanthines in children with a history of FS is not recommended, because these drugs possibly prolong seizure duration. (Grade C)

CQ8-1. Are children with a history of FS able to receive any vaccines?
1) Children with a history of FS can receive all currently available vaccines if the caregiver understands both the benefits and risks of the vaccines. (Grade A)

FS, febrile seizure; EEG, electroencephalogram.

supposed to be performed for children with first simple FS in hospital emergency departments, in actuality, blood examination might not be routinely performed for these children in small clinics. In a review of the literature regarding blood examination for children with FS, bacteremia was reported to be found in 1–4% of patients with FS, but none of them had bacterial meningitis [9–12]. It was also reported that examination of serum electrolytes and glucose level did not have a strong impact on the differential diagnosis of FS [2]. From these observations, we made the following recommendations in the 2015 guidelines: "(1) blood examination is not routinely needed for children with FS; (2) blood examination should be considered in cases of poor general condition, prolonged altered consciousness, or signs of dehydration".

In preparing the 2015 guidelines, we also discussed the application of cranial computed tomography (CT) or magnetic resonance imaging (MRI) in children with FS. In the literature, cranial neuroimaging is not generally recommended in patients with FS [13]. However, lumbar puncture in children with prolonged altered consciousness or other neurological abnormalities and possible intracranial space-occupying lesions may lead to cerebral herniation [14,15]. In the 2015 guideline, due to the risk of cerebral herniation, we recommend CT or MRI before lumbar puncture in children with FS.

3. Febrile status epilepticus

The 2015 guidelines cover febrile status epilepticus (SE) in a different chapter from emergency care of common FS. First, the definition of SE is discussed. In

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epidemiological studies, SE has been defined as a single epileptic seizure of >30 min duration or a series of epileptic seizures during which function is not regained between ictal events in a >30-min period [16]. This definition has been applied to the studies of febrile SE [17]. However, a new definition with shorter seizure duration has been proposed as an operational definition [18]. Recently the Task Force of the International League Against Epilepsy proposed a new definition of SE including definitions with short and long seizure durations [19]. The new definition has two operational dimensions: the time point (t1) beyond which the seizure should be regarded as "continuous seizure activity" and a second time point (t2) after which there is a risk of long-term consequences. The time points are different in each seizure type [19]. Although there is not enough evidence to define the first time point in FS, the 2015 guidelines define the first time point for starting first-line medication as 5 min. More studies are needed to determine the time course of FS for the definition of the appropriate time point to start treatment.

The 2015 guidelines address the choice for the first-line medication for febrile SE. Traditionally, intravenous diazepam has been used as the first-line medication for SE. Lorazepam is not available in Japan. Midazolam has been used for the treatment of SE in children in Japan, although midazolam was approved only for anesthesia, not for the treatment of SE until 2014 [20]. In December 2014 midazolam was approved as a treatment for SE in Japan. We recommended intravenous diazepam or midazolam as the first-line treatment of febrile SE in the 2015 guideline. In Japan, the non-intravenous (nasal, buccal or intramuscular) formulation of midazolam for SE is not available at the time of writing of this article. In other countries, studies have reported that non-intravenous midazolam is as effective as intravenous diazepam, and produces seizure cessation in a shorter time period if the time required to place a venous line is included [21,22]. Early approval of non-intravenous midazolam is needed in Japan.

The 2015 guidelines discuss the application of neuroimaging, electroencephalography, and lumbar puncture in children with febrile SE. These examinations have two purposes: (1) differentiation of acute encephalitis, encephalopathy and meningitis, and (2) prediction of long-term prognosis after febrile SE, especially mesial temporal lobe epilepsy. There are many children in Japan who experience a peculiar form of acute encephalopathy with febrile SE, and it is important to distinguish this encephalopathy from FS [23]. Cranial MRI is usually normal at the onset in patients with this form of acute encephalopathy, but a second MRI a few days later shows edema in widespread cerebral white matter on diffusion-weighted imaging. MRI re-examination should be reconsidered in children who do not have full recovery of consciousness after febrile SE. Regarding bacterial meningitis, Chin et al. studied the CSF in nine of 24 children with convulsive SE and fever, and found four children with bacterial meningitis [24]. Three of the four patients with bacterial meningitis were previously neurologically normal. Indications for lumbar puncture should be considered in children with febrile SE, while lumbar puncture is not needed in children with simple FS without other neurological symptoms.

The roles of MRI and EEG in children with febrile SE for prediction of subsequent mesial temporal lobe epilepsy are still unknown. Many MRI studies performed within several days after febrile SE have revealed abnormality of the hippocampus [25–29]. The incidence of hippocampal abnormality in these reports has varied from 2%-64%. The variability of the incidence of hippocampal abnormality may depend on the timing of the scans, patient population and type of MRI sequence (T2-weighted or diffusion-weighted images). In children with febrile SE, performance of EEG within 3 days after the occurrence of febrile SE shows focal slowing, attenuation or epileptiform discharges [30]. Long-term follow-up studies are needed to clarify whether the findings of MRI and EEG performed during the acute period have value in predicting the onset of mesial temporal lobe epilepsy.

4. Application of EEG

There are longstanding debates on the usefulness of EEG in children with FS. The usefulness of EEG has two aspects. The first is the application of EEG in predicting long-term outcome, especially the subsequent development of epilepsy. In our literature review, some observational studies suggested a correlation between EEG abnormalities and subsequent epilepsy, while other studies did not reveal such a correlation. In 1968 Frantzen et al. reported that the recurrence rate of FS was not influenced by initial EEG abnormalities and that EEG was of no prognostic value for the development of epilepsy [31]. Recently Pavlidou et al. prospectively studied 560 children with first FS, and reported no correlation between EEG findings and development of epilepsy [32]. On the other hand, three studies of children with complex or simple FS showed a correlation between EEG abnormalities and development of epilepsy [33–35]. The variability of the results regarding correlation of EEG abnormalities and subsequent epilepsy may be related to differences in study population, timing of EEG, or EEG recording conditions. While the predictive value of EEG for subsequent epilepsy is controversial, it should be noted that the development of epilepsy cannot be prevented by knowledge of EEG findings. From these observations in preparing the 2015 guidelines, we concluded that EEG examination is not indicated for children with simple FS. The clinical

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significance of EEG for children with complex FS is also not established, although some reports have suggested a correlation between epileptiform discharges on EEG and development of epilepsy.

The second aspect of the usefulness of EEG is the differential diagnosis of acute encephalopathy from FS. Although the usefulness of EEG is recognized for the differential diagnosis of acute encephalopathy in many clinical situations, few peer-reviewed reports have appeared in the literature validating the utility of EEG for such differentiation. Multicenter studies with standardized EEG protocols will contribute to clarifying the usefulness of EEG for differential diagnosis. The formulation of guidelines for the management of acute encephalopathy is in process by the working group of the Japanese Society of Child Neurology, and this group will suggest the role of EEG in detail.

5. Prophylactic diazepam

The prophylactic use of diazepam is one of the most important topics in the guidelines. The effectiveness of oral or suppository diazepam during febrile illness for prophylaxis of FS is reported in the literature [36–38]. On the other hand, two thirds of children with first FS do not have recurrence of the FS, and these patients do not need diazepam prophylaxis [32,39]. From that standpoint, it is reasonable to use prophylactic diazepam for children who have a high risk for relapse of FS. Berg et al. studied 428 children with first FS, and suggested predictors of recurrent FS as: (1) young age at onset, (2) history of FS in a first degree relative, (3) low degree of fever while in the emergency department, and (4) brief duration between the onset of fever and the initial seizure [39]. Pavlidou et al. prospectively studied 260 children with first FS and revealed the prognostic factors for FS recurrence as the following: low age at onset, positive family history of FS, abnormal perinatal history, low temperature prior to the initial seizure, recurrence within the same illness, partial onset or focal features of FS, and frequent febrile episodes [40].

Another point of prophylaxis is to prevent the occurrence of SE. As many reports suggest harm of febrile SE to children, the prevention of febrile SE should be considered [25–29]. Although it is not clear if children with a history of febrile SE will have another febrile SE, we consider children with a history of febrile SE as candidates for prophylactic use of diazepam. From studies on the risk factors for recurrence of FS and the concept of preventing febrile SE, we have set criteria for the use of prophylactic diazepam in the 2015 guidelines as follows: (1) children with a history of a prolonged FS lasting 15 min or longer, or (2) children with repeated FS and two of the following risk factors: (1) focal or repeated seizures within 24 h, (2) preexisting neurological abnormality or developmental delay, (3) family history of FS or epilepsy, (4) age younger than 12 months, (5) seizure within 1 h after onset of fever, and (6) seizure occurring with body temperature less than 38 °C. While we have set the criteria for using prophylactic diazepam based on the predictive factors for the relapse of FS, we also should consider the anxiety of families and the medical circumstances in the indications for use of prophylactic diazepam.

6. Antipyretics

Given the nature of fever-induced seizures, one opinion is that antipyretics may prevent FS. Conversely, another opinion is that re-elevation of fever after using antipyretics may increase the risk of FS. Several randomized controlled trials have investigated the efficacy of antipyretics for preventing FS [41–43]. None of these studies showed any difference in the number of patients with recurrence of FS who had or had not received antipyretics. From these observations, it can be concluded that the use of antipyretics does not affect the incidence of FS. The indication for use of antipyretics should be decided as in children without a history of FS for improving children's comfort and overall condition.

7. Drugs needing special attention

The 2015 guidelines discuss two drugs that need special attention for children with a history of FS. Animal studies have indicated that sedative antihistamine agents possibly reduce the seizure threshold [44]. However, there is no clear clinical evidence that sedative antihistamine agents induce FS. Retrospective analyses of children with FS found that seizure duration was longer in children who received antihistamine agents than in children who did not receive antihistamine agents [45–47]. However, the dose and duration of antihistamine agent use were not clearly described in these studies. Although it has not been clarified if regular doses of antihistamine agents directly prolong seizure duration in humans, special attention should be given to the use of sedative antihistamine agents in children with a history of FS.

Theophylline is used as a bronchodilator in the treatment of bronchial asthma. Experimental studies have suggested that xanthines such as theophylline have an effect of inducing or prolonging seizures [48]. However, there is no clinical evidence that xanthines induce FS in children. Retrospective observational studies have indicated that theophylline has a possible effect in prolonging FS. Fujimaki et al. analyzed children with FS and reported that seizure duration was longer in patients who received theophylline than in patients who did not receive theophylline [49]. Haruyama et al. reported

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that the duration of FS was longer in children who received theophylline and antihistamines than in children who did not receive these medications [50]. Other reports have suggested clinical characteristics of children with seizures while taking theophylline. Odajima et al. analyzed 334 patients who were reported to have seizures while receiving theophylline (255 patients with oral medication and 79 with intravenous administration), and reported that 68% of those patients had a previous history of epilepsy, afebrile seizures, EEG abnormality, or FS [51]. Yoshikawa analyzed 54 children who experienced seizures while receiving theophylline and reported that 87% of those patients had a fever at the time of the seizure and that 60% of the patients were 3 years of age or younger [52]. Although it is not clear if theophylline administered in the therapeutic range has a causative relationship with seizures, caution is needed in the use of xanthines in patients with a history of FS. Clinical studies are needed that provide a higher level of clinical evidence concerning whether xanthines or sedative antihistamine agents in therapeutic doses produce aggravation of FS.

8. Vaccines

In Japan, the Preventive Vaccination Act was revised in 1994. Before the revision, vaccination had been contraindicated in persons who had experienced a seizure within 1 year. The revised act suggested that persons with history of seizures require special attention, but vaccination was not contraindicated [53]. In 2002, the Committee of the Japanese Society of Child Neurology proposed criteria for vaccination in children with a history of FS [53]. The proposal suggested that children with FS were able to receive vaccination after 2–3 months of observation from the last seizure. We could not find special criteria in our literature search on vaccination in children with FS from European and North American countries. Differences in the incidence of FS, number of vaccines, and perspective on vaccination may produce different attitudes between Japan and Western countries toward vaccination in children with FS. The new 2015 guidelines propose a recommendation that children with a history of FS can receive all currently available vaccines if the caregiver understands both the benefits and risks of the vaccines. There is no evidence regarding the time period between a seizure and vaccination in cases of first FS. The 2015 guidelines recommend a span of 2–3 months or less between a seizure and vaccination to allow time for differentiating other neurological disorders that would be contraindications for vaccination or would need special attention with respect to vaccination. If FS is prolonged and recurrent in infants aged less than 1 year, the possibility of Dravet syndrome should be considered.

9. Limitations and future direction

While the 2015 guidelines contain updated clinical recommendations, there are still many unsolved or controversial problems. Many limitations are caused by the lack of convincing clinical evidence, especially regarding the use of prophylactic diazepam, antihistamine agents and theophylline, vaccination for children with FS, and febrile SE. Future clinical research is needed to clarify these unsolved questions. We expect that the 2015 guidelines will play a role in raising issues in the treatment of FS and in prompting further investigations.

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Conflict of interest

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