Review article

Current management of febrile seizures in Japan: An overview

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Abstract

Febrile seizures (FS) require both acute and chronic management. Acute management includes the treatment and differential diagnosis of FS and depend on the presence of seizures and a patient’s level of consciousness upon arrival at hospital: a patient may be discharged after physical examination if there are no seizures and no alteration of consciousness; close observation and laboratory examinations may be indicated in cases when there are no seizures but the patient exhibits altered consciousness; and intravenous diazepam (DZP) is indicated if seizures persist. Central nervous system infections should be ruled out: if the patient has signs of meningeal irritation or increased intracranial pressure, disturbed consciousness for >1 h, atypical seizures (partial seizures, seizures for >15 min, or recurrent seizures within 24 h), cerebrospinal fluid examinations and/or computed tomography/magnetic resonance imaging are warranted. Chronic management includes the prevention of recurrent FS, counseling parents, and vaccination. Japanese guideline for the prevention of recurrent FS defines two types of warning factors (WF) for selecting patients who should be monitored carefully: factors related to the onset of epilepsy (EP factors) and recurrence of FS (FS factors). The EP factors consist of neurological or developmental abnormalities prior to the onset of FS, atypical seizures, and history of epilepsy in parents or siblings. The FS factors include the onset of FS before 1 year of age and a history of FS in one or both parents. The guideline recommends no medication for children with two or fewer past episodes of FS without WF: prophylactic DZP for children with prolonged FS exceeding 15 min, or two or more episodes of FS with two or more WF; and daily administration of phenobarbital or valproate for children in whom FS occur under 38 °C or who have prolonged FS despite prophylactic DZP. To reduce parents’ anxiety, the natural history of FS should be explained. A child can be given all current vaccinations 2–3 months after the last episode of FS by his/her family doctor with information provided to the parents as to how to cope with fever and convulsions.

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1. Introduction

Febrile seizure (FS) is an age-related seizure disorder in infants and young children that are associated with a fever of 38.0 °C or higher without evidence of any definite causative disease, such as central nervous system (CNS) infection, metabolic abnormality, intoxication etc. FS is almost always convulsive and generalized, but 5% are non-convulsive, presenting with unconsciousness, staring, eye deviation, atonia, or cyanosis [1].

FS is a common neurological disorder in young children, with the reported prevalence in Japan ranging between 3.4% and 9.3%. A community survey of all children under 5 years of age in Tamano City, Okayama Prefecture, reported a prevalence of FS of 3.4% [2], whereas a retrospective survey at the mandatory health screening examination of infants aged 3 years in Tokyo metropolitan districts found the prevalence of FS to be 5.5–8.3% [3]. One survey of all 10,391 children in all nursery schools in Kawasaki City, close to Tokyo,
reported a prevalence of FS of 9.3%, with a gradual increase in cumulative prevalence with increasing age: 1.0% in children under 1 year of age, 6.8% in those under 2 years of age, 8.0% in those under 3 years of age, 10.4% in those under 4 years of age, 11.0% in those under 5 years of age, and as high as 12.1% in children aged 5 and 6 years [4].

In terms of the pediatric emergency setting, FS is the most commonly seen major neurological disorder. FS accounted for 60% of 267 patients with seizures in one emergency room [5], 70% of 167 patients admitted to hospital because of status epilepticus [6], and 57% of 201 patients with prolonged (>15 min) or clustered (>3 seizures/24 h) seizures [7].

FS requires both acute and chronic management. Acute management includes treatment of persistent seizures and the differential diagnosis of seizures, whereas chronic management includes prevention of recurrent FS, counseling parents or guardians, and vaccination. In Japan, guideline has been proposed for the chronic management of FS to prevent their recurrence [8].

2. Acute management of FS

2.1. Acute treatment for FS

Acute management of FS in a hospital or clinic focuses on maintenance of cardiovascular/respiratory function, treatment of convulsions, treatment of high fever, and investigation of the causes of the seizures and fever. The acute management of FS depends on seizure status and the level of consciousness of the patient upon arrival at the hospital or clinic (Fig. 1) [9]. If the child has no seizures and fully recovers consciousness, he/she can go home after a physical examination, with the exception of children who may develop convulsions with gastroenteritis (CwG) associated with fever. For these cases, it is prudent to administer a single dose of carbamazepine (CBZ), 5 mg/kg, because up to 80% of patients with CwG tend to have clusters of seizures, and Ichiyama et al. reported marked efficacy of a single dose of CBZ at 5 mg/kg in preventing clusters of seizures in patients with CwG [10].

In children without seizures but who have altered consciousness, close observation and some laboratory examinations are required. When seizures are ongoing, intravenous (i.v.) administration of diazepam (DZP) is mandatory. If i.v. DZP fails to stop the seizures, the child should be hospitalized and receive treatment for status epilepticus [9].

2.2. Differential diagnosis of FS

Table 1 outlines the procedures for the differential diagnosis of FS upon arrival in a hospital or clinic. Among the differential diagnoses of FS, CNS infections, including meningitis and encephalitis/encephalopathy, are particularly important. Seizure characteristics and physical findings as listed in Table 2 should be evaluated and, if the child has one or more of the findings listed in Table 2, CNS infection rather than FS should be suspected. In these cases, computed tomography (CT), magnetic resonance imaging (MRI) and/or cerebrospinal fluid (CSF) examinations are recommended. A spinal tap should be performed after the possibility of increased intracranial pressure has been excluded on the basis of clinical signs and/or CT or MRI.

3. Nature of FS

It is essential for the good chronic management of FS that the parents or guardians understand the nature of FS, to reduce their anxiety or fear and to enable them to cope with episodes of FS.
3.1. Prevalence

As noted above, the prevalence of FS in Japan has been reported to range between 3.4% and 9.3% [2–4], and parents or guardians should be made aware that FS is the most common, but not grave, neurological disorders in infants and young children.

3.2. Age of onset and age at last FS

FS first occurs most commonly in the second year of life (approximately 50%) and rarely before 6 months and after 3 years of age. The incidence of FS decreases markedly after 4 years of age and FS rarely occurs in children older than 6 years of age. The oldest child in whom FS was reported was 9 years of age [2]. In the US, FS that occur before 6 months of age always raise the suspicion of CNS infection [11].

3.3. Family history and risk of FS

Family history has an impact on the risk of FS. For children with both parents having had FS, the incidence of FS has been reported to be in the range 13–17%; this compares with 20–24% for children with siblings who have FS. If neither parent has a history of FS, the risk of FS in siblings of patients with FS is 18–19%, compared with 23–31% if either parent had FS and 39–67% if both parents had FS [12,13].

3.4. Seizure symptoms

Over 90% of FS are generalized tonic or tonic-clonic, with generalized onset in two-thirds of cases and partial onset with secondary generalization in one-third of cases [14]. Approximately 5% of FS are non-convulsive, presenting with atonia, staring, eye deviation, cyanosis, or unconsciousness [1].

3.5. Electroencephalographic features

Many electroencephalographic (EEG) features have been identified for FS by Japanese investigators. Epileptiform discharges on the EEG of FS patients are not uncommon; however, they are uncommon in children under 3 years of age and on EEG obtained within 1 week after the FS episode. Epileptiform discharges tend to appear at 3–5 years of age and disappear at 4–8 years of age [15,16].

Epileptiform discharges are detected in as many as 40–50% of affected children by the time they enter elementary school [17,18] and in approximately 70% of children with FS by 9 years of age [17]. Epileptiform discharges are more often detected in children aged 3 years or older, in patients with complex or frequent FS, and by recurrent EEG examinations [17]. Epileptiform discharges are seen 6–11% more frequently in patients with complex FS than in patients with simple FS. Rolandic discharges are seen in 4% of FS patients [18]. However, epileptiform discharges are not correlated with the recurrence or disappearance of FS and cannot predict the later development of epilepsy.

3.6. Prognosis

3.6.1. Recurrence of FS and associated risk factors

Japanese studies have reported that the rate of recurrence of FS is approximately 45% [19,20], compared with a rate of 29–55% (mean 34%) following a meta-analysis of the English literature [21].

Of patients who have had an episode of FS, more than 50% will not experience recurrence, 9% will experi-
ence three or further episodes, 6–8% will experience four or more further episodes, and 1–3% will experience nine or more further episodes. Recurrence occurs within 1 year after the first seizure in 70% of patients and within 2 years in 90% of patients [22]. The risk factors for FS recurrence include onset of FS at age <1 year and a positive family history of FS in the parents. These two factors are associated with a 48% and 46% risk of recurrence, respectively [23].

3.6.2. Incidence of later epilepsy and associated risk factors

The incidence of epilepsy in the general FS population ranges between 2% and 8.8% [18, 24, 25]. However, excluding FS patients with prior brain dysfunction, the incidence of later epilepsy has been found to be 4.7% [26]. Epilepsy develops in 2–3% of FS patients by 5–7 years of age, in 4.5% of patients by 10 years of age, in 5.5% of patients by 15 years of age, and in 7% of patients by 25 years of age [26].

The risk factors for the development of later epilepsy include neurological abnormalities or developmental delay before the onset of FS, atypical seizures (partial seizures, prolonged seizures for >15 min, or recurrent seizures within a 24-h period), and a positive history of epilepsy in parents or siblings [23, 26]. The probability of developing epilepsy by 7 years of age is 1% in FS patients without any risk factors, 2% in patients with one risk factor, and 10% in patients with two or more risk factors [23].

3.6.3. Epileptic syndromes and FS

Some epileptic syndromes often manifest as FS initially. These include severe myoclonic epilepsy in infancy (SMEI), generalized epilepsy with febrile seizure plus (GEFS+), mesial temporal lobe epilepsy (MTLE), and some frontal lobe epilepsy (FLE) presenting with tonic seizures. Patients with SMEI and MTLE have recurrent FS status since early infancy, patients with GEFS+ have many recurrent episodes of FS and a positive family history of FS, and patients with FLE tend to have clustered tonic seizures with febrile episodes.

Other idiopathic epileptic syndromes also have a relatively frequent past history of FS, including benign childhood epilepsy with centrotemporal spike, epilepsy with grand mal seizures, and childhood absence epilepsy.

On the occasion of differential diagnoses of FS and of explaining the prognosis to parents or guardians, this relationship between specific epileptic syndromes and FS should be kept in mind.

4. Prevention of recurrent FS

The Task Committee of The Conference on Febrile Convulsions (Chair: Y. Fukuyama) published a consensus statement and proposed practical guideline for physicians in the management of FS [8].

4.1. Warning factors

In the guideline, the term “warning factors” has been used instead of “risk factors” to designate useful parameters for selecting patients who should be monitored carefully, because the Committee deemed that the term “risk” may bring about unnecessary anxiety or fear in families and is unsuitable for use in counseling families.

From numerous studies on factors related to the recurrence of FS or the subsequent onset of epilepsy, the Committee introduced two types of warning factors, namely those related to the onset of epilepsy (EP factors) and FS factors. The EP factors consist of: (i) neurological abnormalities or developmental retardation before the onset of FS; (ii) atypical seizures (i.e. partial seizures, seizures lasting longer than 15 min, or recurrent seizures within a 24-h period); and (iii) a family history of epilepsy in parents or siblings. The probability of developing epilepsy under 7 years of age is 1% in FS patients without any EP factors (=60% of the FS population), 2% in patients with one EP factor (=34% of the FS population), and 10% in patients with two or more EP factors (=6% of the FS population) [23].

The FS factors are defined as warning factors related to the recurrence of FS and include: (i) FS onset under 1 year of age; and (ii) a family history of FS in one or both parents. Of patients positive for either of these two factors, approximately 50% will have recurrent FS [21].

4.2. Proposed guideline for the prevention of recurrent FS in Japan

Depending on the presence of warning factors, the guideline divides patients with FS into three categories for treatment with either no medication, intermittent DZP, or daily medication with phenobarbital (PB) or valproate (VPA; Table 3).

4.2.1. Category 1: no medication and observation only

If the patient has had only one or two episodes of FS and no warning factors, he/she should be followed up but not treated with antiepileptic medication.

4.2.2. Category 2: intermittent prophylactic administration of DZP

If the patient has any of the three conditions listed under Category 2 in Table 3, DZP should be given intermittently. For children in whom DZP is contraindicated, a chloral hydrate suppository can be used as an alternative medication, though it is less effective than DZP suppository [27].

Transient side effects of DZP administration, such as mild ataxia, agitation, and lethargy, occur often, but serious side effects, such as respiratory depression, bradycardia, and hypotension, are very rare.
The emergency preventive use of DZP during an acute febrile episode reduces the relative risk of FS recurrence by 44%. During a mean follow-up of 1.9 years, the frequency of recurrent FS per person-years was 0.10 with DZP, compared with 0.19 for placebo [28]. Failure to prevent FS recurrence in the intermittent therapy group occurred mostly in patients in whom DZP had not been administered appropriately for various reasons. When DZP was administered appropriately, the rate of failure to prevent FS occurrence was 7.5% [29].

4.2.3. Category 3: daily anticonvulsant therapy

When a child has any of the three conditions used to define Category 3 (Table 3), daily anticonvulsant therapy is preferable with PB or VPA. The anticonvulsants should be started initially with half the recommended dose and maintained for 2 weeks; then, the dosage should be increased to the recommended dose from the third week. Anticonvulsant levels should be monitored every 3–6 months and kept within the therapeutic range (15–30 μg/mL for PB and 50–100 μg/mL for VPA). The duration of treatment for the prevention of recurrent FS should be limited to 1–2 years.

Daily anticonvulsant therapy is effective for the prevention of recurrent FS; however, it may not be effective in preventing the development of later epilepsy. Long-term PB therapy appears to influence cognition and behavior and VPA may cause liver dysfunction. Thus, physicians should be cautious when making the decision to initiate daily anticonvulsant therapy and use an appropriate anticonvulsant at optimal dosage.

4.3. Use of antipyretic drugs

The efficacy of administering antipyretic drugs during febrile episodes for the prevention of recurrent FS has not been demonstrated. When a DZP suppository is to be given concurrently with an antipyretic drug, the antipyretic suppository should be given at least 30 min after the DZP suppository because concomitant rectal admin-
istration of an antipyretic suppository will interfere with the early and full absorption of DZP [30]. Oral antipyretics can be given concomitantly with a DZP suppository.

5. Vaccinations

5.1. Principles of vaccination for children with FS

None of the current standard vaccinations is contraindicated in children with FS. All vaccinations should be given individually under the supervision of the patient’s family doctor, who is responsible for providing information regarding the usefulness and potential side effects of any vaccination. The doctor should obtain consent from a child’s parents or guardian before administering the vaccination and provide advice on practical measures to cope with fever and convulsions.

5.2. Criteria for vaccination

Children can be given a vaccination 2–3 months after the last episode of FS. This period may be shortened by the family doctor depending on the child’s condition and the type of vaccine to be administered. A child with a history of prolonged FS lasting >15 min should be given vaccinations under the supervision of a pediatrician or child neurologist.

5.3. Prevention of vaccination-related FS

When a temperature of 37.5 °C or higher develops during the risk period for fever after vaccination, a DZP suppository or oral DZP should be administered prophylactically. For example, the risk period for the development of fever after a measles vaccination is 1–12 days after the vaccination, with a particularly high risk on Days 7–10, compared with 1–6 days after diphtheria tetanus (DPT) vaccination, with a particularly high risk on Days 1–2. The dose and dosing regimen for prophylactic DZP after vaccination are as the same with that for FS [31].

6. Information for parents/guardians

To reduce anxiety and/or fear and to enable parents/guardians to cope with FS, the following explanations are essential: (i) the natural history of FS, including incidence, age dependency, natural course, recurrence rate, incidence in siblings, differences between epilepsy and FS, the probability of onset of later epilepsy, and prognosis for mental/behavioral development; (ii) measures for coping with fever and seizure episodes; and (iii) avoidance of an over-reliance on drug therapy, as well as a full explanation of appropriate choice of antiepileptic drugs and potential side effects [8].

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References