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REVIEW

Actual insights into the clinical management of febrile seizures

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Abstract Febrile seizures (FS) are a benign epileptic manifestation of infancy occurring between 3 months and 5 years of age and affecting an estimated 2–5 % of children. They have usually no important negative effects on motor and cognitive development. Simple FS (generalized seizures, lasting less than 10 min and single episodes during the same febrile event) have a benign prognosis in almost all cases and do not require an extensive diagnostic workup. In complex FS (focal semiology and lasting more than 10 min, more than one episode during the same febrile event), a more detailed clinical, electroencephalographic, laboratory, and neuroimaging evaluation is necessary because of a higher percentage of underlying detectable causes and a mildly higher risk for later development of epilepsy. Febrile status epilepticus is the most severe type of complex FS even if its morbidity and mortality is extremely low. Simple FS plus (more than one convulsive episode in 24 h) have the same benign prognosis of simple FS. Neither intermittent nor continuous prophylaxis is actually recommended both in simple and complex FS because its side effects outweigh its possible benefits. *Conclusion*: This review summarizes recent developments into the clinical management of FS including a suggested algorithm for simple and complex FS, the concept of simple FS plus, the controversies about the relationships between FS and hippocampal sclerosis, the relationships between FS and complex syndrome such as Dravet syndrome, genetic epilepsy with FS plus or febrile infection-related epilepsy syndrome, and the results of recent epidemiologic studies on febrile status epilepticus.

Keywords Febrile seizures · Febrile status epilepticus · Hippocampal sclerosis · Fever · Epilepsy · Children

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Introduction

Febrile seizures (FS) are typically observed during a febrile illness, in children without prior afebrile seizures, in the absence of a central nervous system infection or acute electrolyte imbalance [5]. They can be divided in two groups including simple FS (generalized seizures, lasting less than 10 min and single episodes during the same febrile event) and complex FS (focal semiology, lasting more than 10 min and occurring twice or more within the same febrile episode) [11, 13].

FS represent the most common epileptic pattern in early infancy occurring between 3 months and 5 years of age and affecting an estimated 2–5 % of children [42]. A peak of incidence at 18 months and a prevalence of about 3–7 % in children up to 7 years have been reported [42]. A history of FS in childhood involves 6–15 % of all epileptic patients with a higher risk of developing epilepsy being observed under 14 years of age and in subjects with previous complex FS [11, 33]. The present review is focused on the more important actual diagnostic and therapeutic issues in the practical management of children with FS.

Diagnostic management of the first febrile seizure

Diagnostic workup should follow different pathways in children with simple and complex FS (Fig. 1).

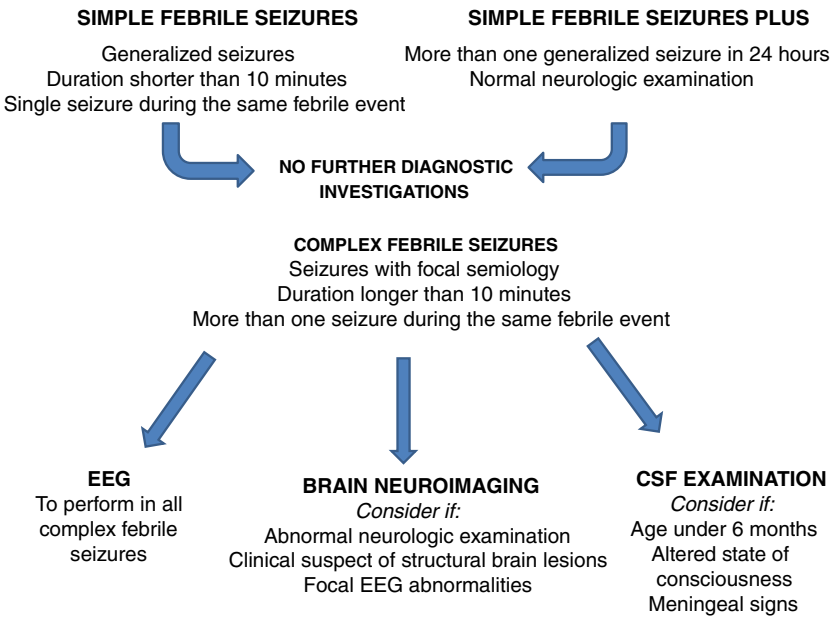

Fig. 1 Diagnostic algorithm for the evaluation of children with febrile seizures

Approach to simple febrile seizures

In children with simple FS, hospital admission should be taken into account only in two selected cases: in children younger than 18 months of age (because of the higher difficulties in the differential diagnosis with central nervous system infections) and in children without a responsible familial context [8]. In all the other cases, a careful parental education should be carried out [8]. The decision to hospitalize is often influenced by some aspects depending on the local situation such as the country, the distance from the hospital, or the availability of medical care [8]. Diagnostic investigations other than a careful history taking and a complete neurologic examination are not currently recommended by the American Academy of Pediatrics in patients with a first simple FS [2].

Complete blood cell count, electrolytes or glucose, and taking cultures should be directed toward the identification of the cause of the fever rather than as a step of routinary evaluation of simple FS themselves [2, 46]. Infants under 6–12 months of age presenting with FS often represent difficult differential diagnostic questions with central nervous system infections and require a more detailed diagnostic evaluation [2, 46]. Lumbar puncture should be performed only in symptomatic children presenting with a seizure, fever, and meningeal signs, while it should be considered as an option in infants younger than 12 months with a possible deficient immunization against *Haemophilus influenzae* type B or *Streptococcus pneumoniae* or in subjects that had previously received antibiotics [2]. In well-appearing and fully immunized infants with a simple FS, systematic lumbar puncture should be avoided because of the extremely low risk of meningitis [2, 9].

Electroencephalogram (EEG) should have no role both in the diagnostic management of the acute phase and as a predictor of recurrent FS or future afebrile seizures [35]. Both brain CT and MRI are not necessary if no other neurological indications are provided because cerebral structural abnormalities are uncommon in this population [2, 22].

Approach to complex febrile seizures

Complex FS implicate a more variable number of possible underlying conditions than simple FS [38]. In the affected patients, an extensive diagnostic workup should be considered to exclude severe neurologic disorders (including central nervous system infections, cerebral malformations, neurocutaneous disorders, neurometabolic diseases, coagulopathies, demyelinating or inflammatory diseases), even if it results negative in most of the patients [8, 21, 46]. For these reasons, children with a first complex FS, including those with a febrile seizure stopped pharmacologically within the first 10 min, should always be admitted to the hospital [8]. Blood investigations should be guided, as for simple FS, by a specific diagnostic suspect to search for fever etiology [40].

Although lumbar puncture should be considered in the same context than in children with simple FS, physicians should be aware that complex FS are more frequently associated with meningitis than simple FS (prevalence of 4.81 vs 0.86 % in a recently published series) [2, 3, 27, 33]. However, the overall rare occurrence of meningitis in children presenting with a complex FS indicates that lumbar puncture should not be performed if no other risk factors, such as post-ictal drowsiness or associated neurological deficits, are present [3, 14].

Brain neuroimaging should be particularly taken into account in focal and prolonged complex FS while the prevalence of structural abnormalities requiring surgical approaches or specific emergency treatments in the other cases is very low [6, 28]. In this context, the performance of an emergency neuroimaging is usually unnecessary [6, 45]. A particularly low risk of intracranial pathology has been reported in children presenting with more than one seizure within 24 h [6, 28]. A higher rate of neuroradiological pathologic abnormalities should be expected if clinically evident neurological deficits or abnormal focal electroencephalographic features are detected [41, 48]. Hippocampal sclerosis is the most important injury that has to be excluded through MRI in children with recurring focal and prolonged FS because of its possible association with the later development of drug-resistant temporal lobe epilepsy [42]. Other common MRI abnormalities in children with complex MRI include subcortical focal hyperintensity, changes in white matter signal, and focal cortical dysplasia, while other intracranial lesions such as hemorrhages or tumors are rare [22, 28, 38].

Management of recurrent febrile seizures

The estimated general recurrence risk of FS after a first episode ranges between 30 and 40 % [8, 17]. The risk is 50 % in the first year after the first FS, while it is higher than 90 % within the second year [50]. The most common risk factors for recurrence of both simple and complex FS include an age of onset lower than 15 months, a positive familial history for FS or epilepsy, a maternal preponderance in the positive familial history for FS, an episode of complex FS at onset, previous multiple episodes within the same febrile illness, and a lower temperature prior to the initial seizures [8]. The more predictors, the greater the risk for FS recurrence [39]. An earlier age at onset of FS and a positive family history represent the main predictors for the first recurrence, while a low temperature before the first seizure is the most powerful predictor for three or more recurrences [39]. Hospitalization is generally not indicated in both simple and recurrent FS especially if they are not prolonged and easily stopped with pharmacological acute treatment [8]. Diagnostic approaches are not different from the ones we have described for the first FS [8]. A prolonged initial FS can increase the risk for prolonged recurrent FS even if episodes of febrile status epilepticus do not necessarily implicate a higher risk of recurrent FS or epilepsy [49]. In a recent series, the lack of EEG and neuroimaging abnormalities in almost all the children with more than one FS in 24 h, no focal features, and no abnormalities in the state of consciousness between each seizure defined a group of seizures with the same favorable prognosis of simple FS [18]. Therefore, the term simple febrile seizures plus (SFS+) was proposed instead of "complex FS" for these seizure types [18].

Febrile status epilepticus

Febrile status epilepticus (FSE) is the most severe type of complex FS even if its morbidity and mortality is extremely low [10]. The FEBSTAT study, still in progress, plans to analyze the relationship between FSE and temporal lobe epilepsy (TLE) and has recently contributed to characterize various clinical, electroencephalographic, laboratory, and neuroradiological features of FSE [12, 15, 23–25, 34, 43]. The most commonly reported risk factors for FSE in the FEBSTAT cohort (199 patients) were younger age of the patients, lower temperature, and longer duration of temperature recognition before the seizure at the onset. The median age at the onset of FSE was 16 months, the male/female ratio was 1.11, and the mean duration of seizures was 70 min [24]. Most of the patients had prior normal developmental milestones even if developmental delay was most commonly associated with more prolonged seizures [23]. Prior FS were reported in one fifth of the cases [24]. Seizure types were prominently continuous, secondarily generalized, and constantly evolving toward a generalized tonic-clonic seizure [24]. EEG abnormalities were recorded in 45.2 % of FEBSTAT patients within 72 h since the onset of seizures [34]. Epileptiform discharges were observed in a minority of patients (6.5 %) [34]. The prominent abnormalities were represented by focal slowing (23.61 % of the patients) or attenuation (12.56 %) with a significant association with acute T2 hippocampal signal abnormalities at MRI [34]. Hippocampal T2 signal abnormal increase was reported in 11.5 % of the 191 children who underwent MRI in the acute phase of FSE and 10.5 % of them had evident abnormalities in hippocampal development [43]. Cerebrospinal fluid anomalies were detected in none of the 136 patients who received a nontraumatic lumbar puncture [15]. Human herpes virus 6B (HHV6B) and 7 (HHV7) viremia was observed, respectively, in 32 and 7.1 % of the 169 patients who underwent specific blood investigations (polymerase chain reaction and antibody titration), but no substantial differences in clinical, EEG, and neuroimaging features were found between children with or without the infection [12]. Unlike previous reports, the FEBSTAT study failed to demonstrate both HHV6B and HHV7 in cerebrospinal fluid in the 23 patients who underwent a nontraumatic lumbar puncture [12, 20].

Febrile seizures and epilepsy

Different prospective cohort studies have demonstrated an overall estimated risk of developing epilepsy in children with previous FS ranging from 2 and 7 % according to the different duration of the follow-up [33]. The risk of developing epilepsy after a FS is higher in the age range of 0–14 years than in the following ages [33]. In children with a history of simple FS, the risk is quite similar to the one occurring in the general

population (1–1.5 vs 0.5–1 %), while in children with complex FS, it is higher (between 4 and 15 %) [8]. Family history for epilepsy, prior neurological and neurodevelopmental abnormalities, the occurrence of complex FS, and the presence of epileptiform discharges at the EEG have been proposed as the most common predictors for the development of epilepsy [50].

Some surgical series included a history of FS in 30–70 % of patients with hippocampal sclerosis with a higher occurrence in subjects with prior complex FS than in the ones with simple FS (14.8 vs 11.4 % in a recently published series) [22]. Various data from several prospective studies have not confirmed a similar strong association [1, 11]. Among these patients, the later occurrence of TLE has been more commonly observed in the ones with a lower age at the onset of FS, a higher prevalence of FS among first-grade family members, a prominence of simple partial or generalized tonic-clonic seizures, and frequent vertiginous and autonomic symptoms [26]. Other current prospective studies, such as the FEBSTAT study itself, are looking for definitive answers about this focus [24].

In a minority of patients, FS can be part of a more complex epileptic pattern [19, 31]. Dravet syndrome and genetic epilepsy with febrile seizure plus (GEFS+, previously known as "generalized epilepsy with febrile seizure plus") represent two valuable examples in this context [19, 31]. Dravet syndrome (Online Mendelian Inheritance in Man number 607208) is an early-onset intractable epileptic encephalopathy with recurrent polymorphic seizures and developmental milestones impairment, mental delay, spasticity, and ataxic gait in the advanced stages [31]. Dravet syndrome can be related to mutations in the sodium channel neuronal type 1a subunit (SCN1A) gene or in the protocadherin 19 gene [31]. GEFS + is also often related to SCN1A and it is an autosomal dominant disorder that is characterized by FS occurring beyond the common ages, subsequent afebrile generalized or partial seizures, a normal psychomotor development, and a milder clinical severity than Dravet syndrome [31].

A distinct clinical entity that should be considered in the differential diagnosis of classic FS is represented by febrile infection-related epilepsy syndrome (FIRES) [29]. FIRES is a catastrophic epileptic encephalopathy following a febrile episode with onset during the early infancy (range 4–9 years) [29]. Its clinical presentation includes recurrent life-threatening status epilepticus in the acute phase and drug-resistant seizures and intellectual impairment at the follow-up [29]. The etiopathogenesis of FIRES is still unknown [29].

Treatment of febrile seizures

Therapeutic approach to prolonged febrile seizures

Simple and most of the complex FS usually last less than 2–3 min with a spontaneous resolution in most of the cases [39]. In this context, a different approach should be taken into account for complex FS with known underlying etiologies requiring specific therapies [38]. The duration of 5 min for a seizure has been recently suggested as the limit for an active therapeutic intervention [7]. This observation was made because seizures lasting more than 5 min often do not stop spontaneously and have a higher potentiality to induce permanent neuronal injury and/or drug resistance [7].

Out-of-hospital rescue requires a well-managed pediatric basic life support and the eventual administration of rectal diazepam or oromucosal midazolam (according to differences in commercially available formulations in the different countries) if no intravenous accesses are available [16, 30]. In hospitals, management of prolonged FS does not differ from afebrile seizures and status epilepticus and it includes a three-step-based therapeutic approach [30, 32]. These steps include (a) benzodiazepines for seizures lasting less than 30 min; (b) phenytoin/fosphenytoin, phenobarbital, valproate, levetiracetam, or lacosamide for seizures lasting 30–90 min; and (c) anesthetics for refractory seizures lasting more than 90 min [30, 32].

Prevention of recurrences

Strategies for pharmacological prophylaxis of FS include intermittent (antipyretics, oral/rectal diazepam, oral clobazam) or continuous treatments (valproic acid, phenobarbital, primidone) [37]. Antipyretic agents have been proven to be not effective in the prevention of FS [4]. The administration of oral/rectal diazepam or oral clobazam at the beginning of the febrile episode and the chronic antiepileptic treatments with valproic acid, phenobarbital, or primidone have been demonstrated to be effective, but their use is currently not recommended because of the severity of the possible side effects (transient mild ataxia, hyperactive behavior, sedation or lethargy, and more rarely, respiratory depression, bradycardia, or hypotension) and the relatively low risks associated with both simple and most of the complex FS [35, 36, 44, 47]. In this context, an adequate parental education is required to teach parents the basis for acute rescue, to reduce their anxiety, and to inform them about the benignity of the phenomenon and the advantages of minimal therapeutic interventions in most of the patients [35, 36, 44, 47].

Conclusions

FS is a commonly benign epileptic disorder in childhood. Their pathogenesis is multifactorial and it is probably based on interactions between several factors including individual and familial susceptibility, modulation of immune response, regulation of neuronal excitability, and exogenous agents. An extensive diagnostic workup in the acute phase is required

only in selected patients (mostly with complex FS, febrile status epilepticus, or infants under 12 months of age requiring a differential diagnosis with central nervous system infections). The risk for a later development of epilepsy is similar to the general population in children with simple FS, while it is mildly higher in complex FS. Neither intermittent nor continuous prophylaxis is recommended because its side effects outweigh its possible benefits.

Conflict of interest None of the authors have any conflict of interest to declare.

References

1. Abou-Khalil B (2010) The relationship between febrile seizures and epilepsy. Epilepsia 51(S1):40–42
2. American Academy of Pediatrics (2011) Clinical practice guideline—febrile seizures: guideline for the neurodiagnostic evaluation of the child with a simple febrile seizure. Pediatrics 127:389–394
3. Batra P, Gupta S, Gomber S, Saha A (2011) Predictors of meningitis in children presenting with first febrile seizures. Pediatr Neurol 44: 35–39
4. Baumann RJ, Duffner PK (2000) Treatment of children with simple febrile seizures: the AAP practice parameter. American Academy of Pediatrics. Pediatr Neurol 23:11–17
5. Berg AT, Berkovic SF, Brodie MJ et al (2010) Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005–2009. Epilepsia 51:676–685
6. Boyle DA, Sturm JJ (2013) Clinical factors associated with invasive testing and imaging in patients with complex febrile seizures. Pediatr Emerg Care 29:430–434
7. Brophy GM, Bell R, Claassen J et al (2012) Guidelines for the evaluation and management of status epilepticus. Neurocrit Care 17:3–23
8. Capovilla G, Mastrangelo M, Romeo A, Vigevano F (2009) Recommendations for the management of "febrile seizures". Ad hoc Task Force of LICE Guidelines Commission. Epilepsia 50(S1):2–6
9. Casasoprana A, Hachon Le Camus C, Claudet I et al (2013) Value of lumbar puncture after a first febrile seizure in children aged less than 18 months. A retrospective study of 157 cases. Arch Pediatr 20:594–600
10. Chungath M, Shorvon S (2008) The mortality and morbidity of febrile seizures. Nat Clin Pract Neurol 4:610–621
11. Cross JH (2012) Fever and fever-related epilepsies. Epilepsia 53:3–8
12. Epstein LG, Shinnar S, Hesdorffer DC et al (2012) Human herpesvirus 6 and 7 in febrile status epilepticus: the FEBSTAT study. Epilepsia 53:1481–1488
13. Fetveit A (2008) Assessment of febrile seizures in children. Eur J Pediatr 167:17–27
14. Fletcher EM, Sharieff G (2013) Necessity of lumbar puncture in patients presenting with new onset complex febrile seizures. West J Emerg Med 14:206–211
15. Frank LM, Shinnar S, Hesdorffer DC et al (2012) Cerebrospinal fluid findings in children with fever-associated status epilepticus: results of the consequences of prolonged febrile seizures (FEBSTAT) study. J Pediatr 161:1169–1171
16. Garnock-Jones KP (2012) Oromucosal midazolam: a review of its use in pediatric patients with prolonged acute convulsive seizures. Paediatr Drugs 14:251–261
17. Graves RC, Oehler K, Tingle LE (2012) Febrile seizures: risks, evaluation, and prognosis. Am Fam Physician 85:149–153
18. Grill MF, Ng YT (2013) "Simple febrile seizures plus (SFS+)": more than one febrile seizure within 24 hours is usually okay. Epilepsy Behav 27:472–476
19. Guerrini R (2012) Dravet syndrome: the main issues. Eur J Paediatr Neurol 16(S 1):S1–S4
20. Hall CB, Long CE, Schnabel KC et al (1994) Human herpesvirus-6 infection in children. A prospective study of complications and reactivation. N Engl J Med 331:432–438
21. Hardasmalani MD, Saber M (2012) Yield of diagnostic studies in children presenting with complex febrile seizures. Pediatr Emerg Care 28:789–791
22. Hesdorffer DC, Chan S, Tian H et al (2008) Are MRI-detected brain abnormalities associated with febrile seizure type? Epilepsia 49:765–771
23. Hesdorffer DC, Benn EK, Bagiella E et al (2011) Distribution of febrile seizure duration and associations with development. Ann Neurol 70:93–100
24. Hesdorffer DC, Shinnar S, Lewis DV et al (2012) Design and phenomenology of the FEBSTAT study. Epilepsia 53:1471–1480
25. Hesdorffer DC, Shinnar S, Lewis DV et al (2013) Risk factors for febrile status epilepticus: a case-control study. J Pediatr 163:1147–1151
26. Heuser K, Cvancarova M, Gjerstad L, Taubøll E (2011) Is temporal lobe epilepsy with childhood febrile seizures a distinctive entity? A comparative study. Seizure 20:163–166
27. Kimia A, Ben-Joseph EP, Rudloe T et al (2010) Yield of lumbar puncture among children who present with their first complex febrile seizure. Pediatrics 126:62–69
28. Kimia AA, Ben-Joseph E, Prabhu S et al (2012) Yield of emergent neuroimaging among children presenting with a first complex febrile seizure. Pediatr Emerg Care 28:316–321
29. Kramer U, Chi CS, Lin KL et al (2011) A febrile infection-related epilepsy syndrome (FIRES): pathogenesis, treatment, and outcome: a multicenter study on 77 children. Epilepsia 52:1956–1965
30. Lagae L (2011) Clinical practice: the treatment of acute convulsive seizures in children. Eur J Pediatr 170:413–418
31. Mastrangelo M, Leuzzi V (2012) Genes of early-onset epileptic encephalopathies: from genotype to phenotype. Pediatr Neurol 46: 24–31
32. Mastrangelo M, Celato A (2012) Diagnostic work-up and therapeutic options in management of pediatric status epilepticus. World J Pediatr 8:109–115
33. Neligan A, Bell GS, Giavasi C et al (2012) Long-term risk of developing epilepsy after febrile seizures: a prospective cohort study. Neurology 78:1166–1170
34. Nordli DR Jr, Moshé SL, Shinnar S et al (2012) Acute EEG findings in children with febrile status epilepticus: results of the FEBSTAT study. Neurology 79:2180–2186
35. Oluwabusi T, Sood SK (2012) Update on the management of simple febrile seizures: emphasis on minimal intervention. Curr Opin Pediatr 24:259–265
36. Offringa M, Newton R (2012) Prophylactic drug management for febrile seizures in children. Cochrane Database Syst Rev 4, CD003031
37. Offringa M, Newton R (2013) Prophylactic drug management for febrile seizures in children (review). Evid Based Child Health 8: 1376–1485
38. Patel AD, Vidaurre J (2013) Complex febrile seizures: a practical guide to evaluation and treatment. J Child Neurol 28:759–764
39. Pavlidou E, Tzitiridou M, Kontopoulos E, Panteliadis CP (2008) Which factors determine febrile seizure recurrence? A prospective study. Brain Dev 30:7–13
40. Pavlidou E, Hagel C, Panteliadis C (2013) Febrile seizures: recent developments and unanswered questions. Childs Nerv Syst 29:2011–2017

41. Rasool A, Choh SA, Wani NA, Ahmad SM, Iqbal Q (2012) Role of electroencephalogram and neuroimaging in first onset afebrile and complex febrile seizures in children from Kashmir. J Pediatr Neurosci 7:9–15
42. Sfaihi L, Maaloul I, Kmiha S et al (2012) Febrile seizures: an epidemiological and outcome study of 482 cases. Childs Nerv Syst 28:1779–1784
43. Shinnar S, Bello JA, Chan S et al (2012) MRI abnormalities following febrile status epilepticus in children: the FEBSTAT study. Neurology 79:871–877
44. Steering Committee on Quality Improvement and Management, Subcommittee on Febrile Seizures American Academy of Pediatrics (2008) Febrile seizures: clinical practice guideline for the long-term management of the child with simple febrile seizures. Pediatrics 121:1281–1286
45. Teng D, Dayan P, Tyler S et al (2006) Risk of intracranial pathologic conditions requiring emergency intervention after a first complex febrile seizure episode among children. Pediatrics 117:304–308
46. Teran CG, Medows M, Wong SH, Rodriguez L, Varghese R (2012) Febrile seizures: current role of the laboratory investigation and source of the fever in the diagnostic approach. Pediatr Emerg Care 28:493–497
47. Verrotti A, Latini G, di Corcia G et al (2004) Intermittent oral diazepam prophylaxis in febrile convulsions: its effectiveness for febrile seizure recurrence. Eur J Paediatr Neurol 8:131–134
48. Yücel O, Aka S, Yazicioglu L, Ceran O (2004) Role of early EEG and neuroimaging in determination of prognosis in children with complex febrile seizure. Pediatr Int 46:463–467
49. Waruiru C, Appleton R (2004) Febrile seizures: an update. Arch Dis Child 89:751–756
50. Wo SB, Lee JH, Lee YJ et al (2013) Risk for developing epilepsy and epileptiform discharges on EEG in patients with febrile seizures. Brain Dev 35:307–311