Febrile Seizures and Febrile Status Epilepticus

30

Nicola Specchio and Giusy Carfi' Pavia

30.1 Introduction

Febrile seizures (FS) are nosological entities that affect 2–5% of children aged 6 months to 5 years [1, 2]. In most cases, these seizures are isolated or sporadic, of short duration, and with no focal semiological features; in such cases they are defined as simple febrile seizures. However, a febrile seizure that lasts more than 15 min, which has focal signs, or that recurs within 24 h is defined as "complex" febrile seizure [2, 3]. Prolonged febrile seizure (PFS) is therefore a particular type of complex febrile seizure. PFS are events that last more than 10–15 min (there is debate about which is the cutoff to be considered): according to some authors, it would be more appropriate to consider 10 min, but for the risk assessment of status epilepticus or response to treatment, 15 min seems a most appropriate benchmark [4, 5]. In case the duration exceeds 30 min, the more appropriate definition is febrile status epilepticus (FSE). FSE occurs in approximately 5% of children with ongoing febrile seizures and in about 25% of all status epilepticus in childhood. There are reports concerning the possible association of PFS/FSE and hippocampal lesions, which might justify the subsequent onset of temporal lobe epilepsy [6].

30.2 EEG in FS and FSE

Electroencephalogram (EEG) is not indicated in the routine evaluation of simple febrile seizures; on the other hand, the role of EEG in children with complex febrile seizures including febrile status epilepticus is not well-known [7]. One of the most remarkable findings in EEGs done within 1 week after febrile status epilepticus is focal slowing. The acute EEG findings after prolonged febrile seizures reveal abnormal activity in at least one third of cases across different series. Usually what is seen in those cases is slowing of background activity with wide amplitude over bilateral posterior regions (Fig. 30.1). Even if it has been estimated that about one third of patients with prolonged febrile seizures might develop epilepsy in the future, this has not been correlated with the presence of slowing at EEG, which therefore do not confer any added risk.

In old series it has been reported that focal slowing at EEG might be of added value in predicting the subsequent development of epilepsy [8] even if this is not completely clarified [9]. Moreover, in both reported series, the follow-up was limited to less than 5 years (Fig. 30.2).

Regarding the possible association with temporal lobe epilepsy, it is likely that the previous mentioned series had no sufficient follow-up in order to ascertain whether an initial abnormal EEG was predictive of subsequent temporal lobe epilepsy [10].

The FEBSTAT study [11] is a multicenter study that is prospectively identifying children with febrile status epilepticus. The children have both an MRI and EEG along with additional studies performed at baseline and at 1 year as well as if they develop epilepsy and are being followed long term. These EEGs are being interpreted by two readers blinded to the clinical histories and outcomes.

Consensus is reached on the findings in all studies. Early findings [12] confirm that focal slowing is a common finding with a frequency similar to that reported in the older series. Correlations between EEG findings and the MRI as well as the long-term outcomes are inconsistent. The study is adequately powered to eventually address the question of the relationship between prolonged febrile seizures and subsequent mesial temporal sclerosis and mesial temporal lobe epilepsy as well as the predictive value of the EEG for short- and long-term outcomes. The physiological mechanisms underlying the slowing are unknown.

A small portion of children at the age of 3 years and below with EEG was recorded soon after a febrile status epilepticus

N. Specchio (✉) · G. C. Pavia
Rare and Complex Epilepsy Unit,
Department of Neuroscience and Neurorehabilitation,
Bambino Gesù Children's Hospital, Rome, Italy
e-mail: nicola.specchio@opbg.net

© Springer Nature Switzerland AG 2019

O. Mecarelli (ed.), *Clinical Electroencephalography*, https://doi.org/10.1007/978-3-030-04573-9_30

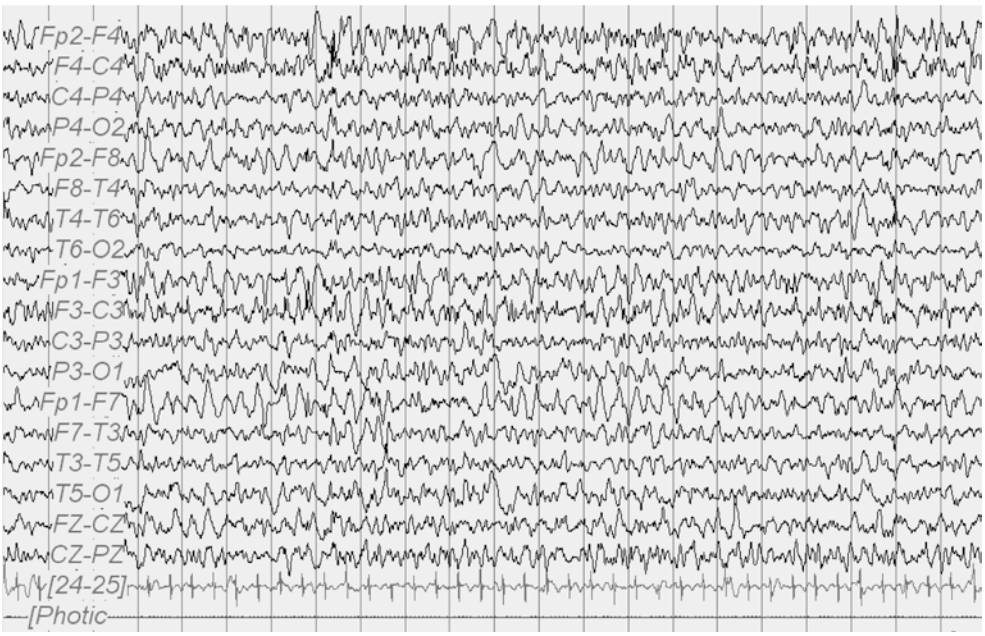

Fig. 30.1 Post-ictal EEG in a patient with complex febrile seizures (buccal midazolam was administered 30 min before the EEG). Background activity is slightly slow. Over frontal and fronto-temporal left regions some theta-delta waves are evident

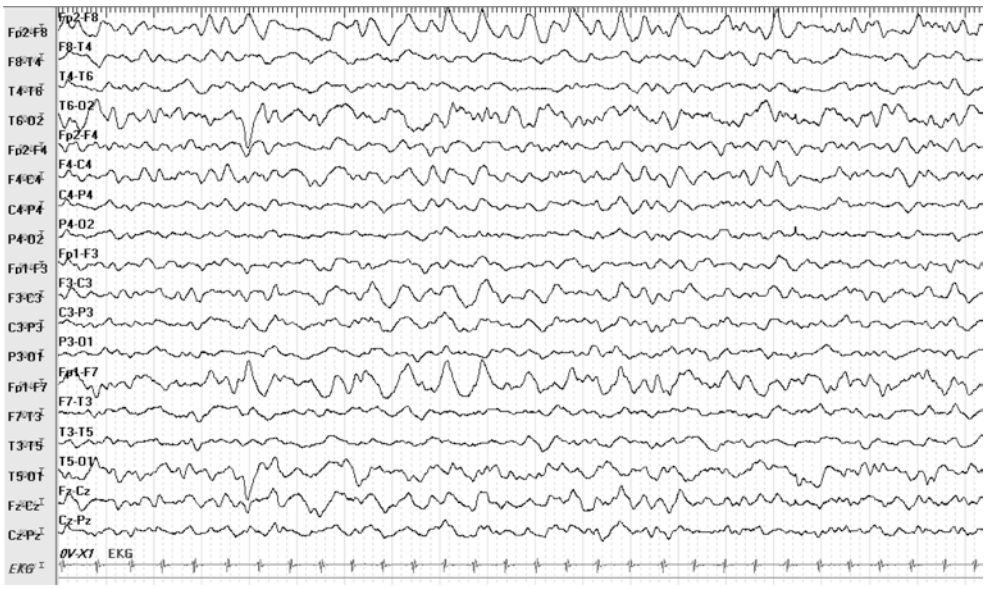

Fig. 30.2 Post-ictal EEG of a patient with simple febrile seizure. Rare slow waves are evident over frontal bilateral regions

revealed epileptiform discharges [13]. The clinical significance of these interictal epileptiform discharges is not clear. According to Yucel et al., detection of epileptiform activity is less common in the first week following the prolonged febrile convulsion [14]. The most common type of epileptiform activity to observe in the older children are bursts of generalized spike-wave discharges, although an association with centrotemporal spikes has also been noted [15]. Frantzen et al. reported that generalized spike-wave discharges did not usually appear in the acute EEG, but were found on follow-up, on average 16 months after the febrile convulsion [9]. It is possible that the occurrence of spikes indicates a genetic susceptibility. The long-term value of the early EEG findings after prolonged febrile seizures is not yet known, but the data so far suggest that the focal slowing is not associated with pre-existing focal structural lesions since it is only present for a short period of time. These data suggest that it might be important to correlate the findings with experimentally induced febrile status [16]. The precise relation between the focal slowing and epilepsy is uncertain. Studies to date were underpowered and lacked sufficient follow-up to rigorously assess the risk of focal slowing for the development of epilepsy. In addition the best studies were performed decades ago, long before the advent of MR, so the relationship with

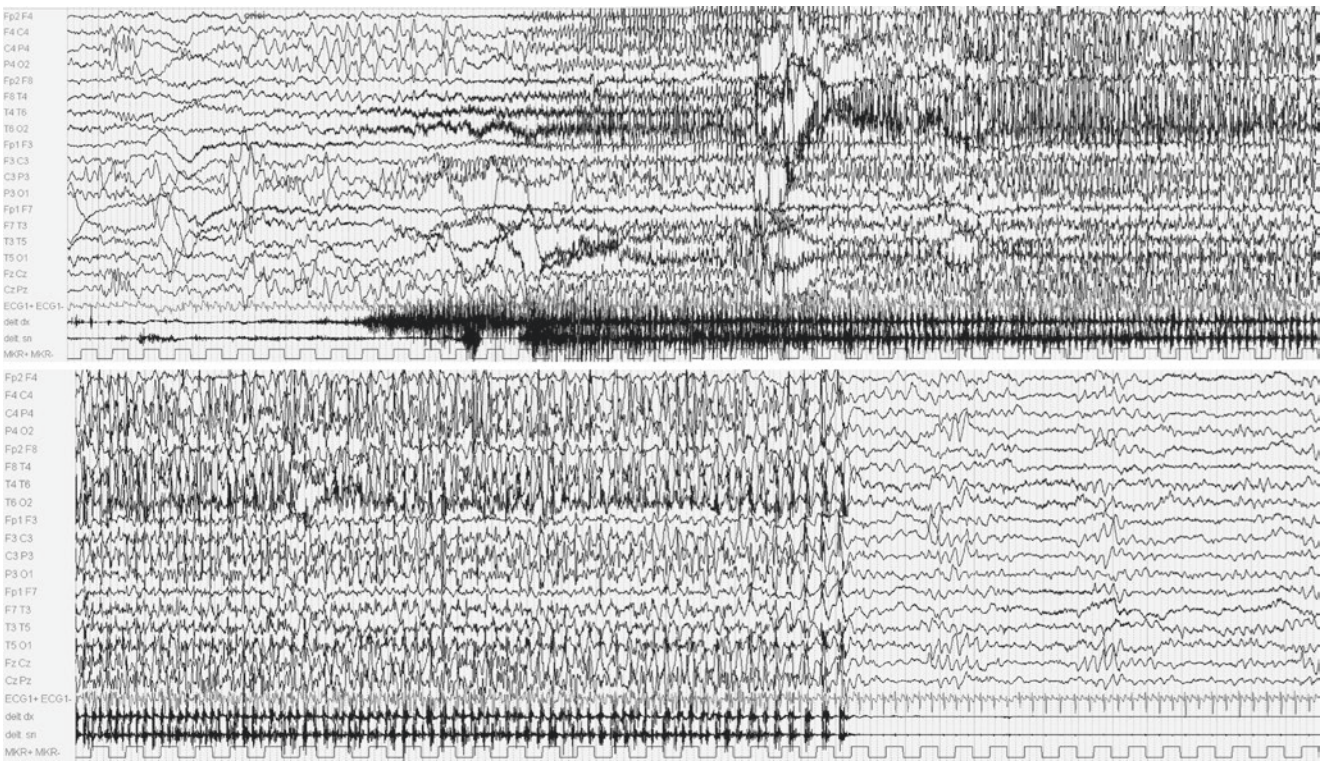

Fig. 30.3 EEG counterpart of a simple febrile seizure in a 2 years old patient. The EEG shows a diffuse attenuation of cerebral activity followed by repetitive spikes more prominent over left frontal region. The EMG trace show a bilateral hypertonus at beginning followed by clonic jerks

mesial temporal sclerosis, if any, is undetermined. Completion of existing prospective clinical studies, refinement of the existing animal models for febrile seizures to better match the clinical characteristics observed in children, and correlation between the two may help to accelerate our understanding of this very interesting phenomenon. Figure 30.3 shows an ictal recording of a simple febrile seizure.

30.3 Other Conditions with Seizures Induced by Fever

Febrile infection-related epilepsy syndrome (FIRES) is a catastrophic epileptic encephalopathy with refractory status epilepticus (SE) in developmentally normal children [17] without a diagnostic biologic marker. FIRES is characterized by the development of seizures in healthy children few days after a short febrile illness that rapidly exacerbated into a SE or a cluster of seizures, followed by a chronic drug-resistant epilepsy and cognitive function deficit [18].

Since most of the patients presented with seizures immediately following a febrile episode, an autoimmune mechanism has been considered. Different antibodies have been investigated in patients with FIRES with negative results; therefore up to now there are no evidence to support that autoantibodies are the etiology of FIRES. Furthermore, poor response to immunotherapy has been reported. FIRES is likely to represent an immune-inflammatory-mediated epileptic encephalopathy rather than an autoimmune process [19]. The syndrome invariably begins with a febrile illness, most commonly a minor upper respiratory tract infection or a gastroenteritis; fever during the infectious illness is sometimes low grade or absent (with a median duration of 4 days); in about half of the patients, it disappears at the time of first seizure occurrence [20] in contrast to febrile seizures and febrile status epilepticus. The clinical course of this disorder is typically biphasic with an initial acute catastrophic phase followed by a chronic refractory epilepsy phase.

After the onset, seizures rapidly became frequent or exacerbated into SE showing resistant to treatment with a variety of antiepileptic drugs (AEDs). It is not uncommon for children with FIRES to have hundreds of seizures a day during the acute phase. Seizures are focal (simple motor with facial twitching or complex partial seizures with lateral deviation of the head, chewing movements, and some autonomous features, suggesting a mesial temporal lobe involvement) with a strong tendency to become bilateral tonic-clonic. Also,

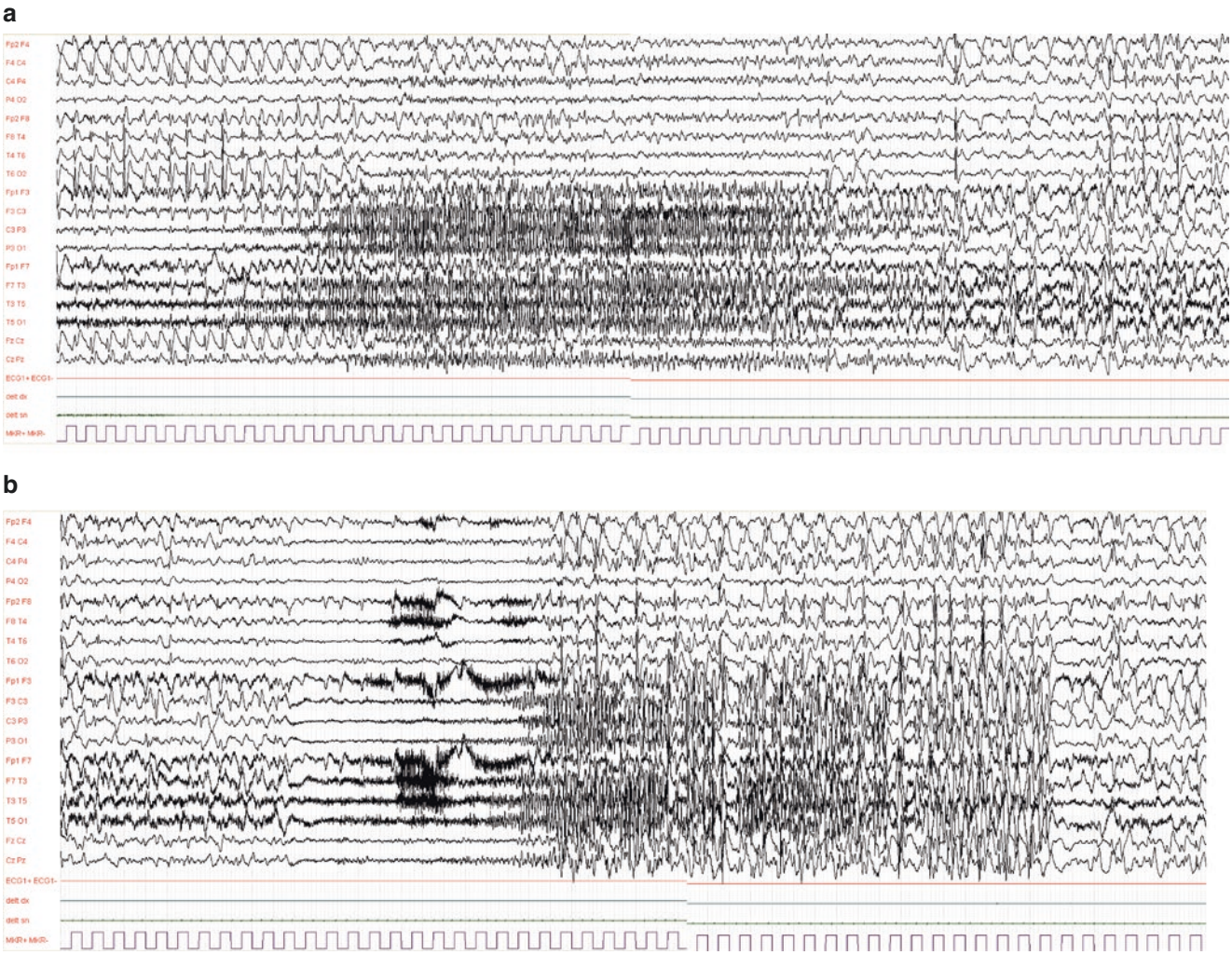

Fig. 30.4 Ictal EEG during a status epilepticus in a 4 years old patient with FIRES. Seizures are brief but subsequent. (**a**) On the right hemisphere there are spikes and spikes and waves discharges as last part of a previous seizure. At the same time a new seizure is staring on the left hemisphere characterized by repetitive spikes over left fronto-temporal region. (**b**) Seizure ends abruptly and after few seconds one more ictal clinical discharge is evident on the same side

myoclonic seizures of facial and oro-buccal muscles have been reported. Consciousness is decreased, including the interictal period. The duration of this acute phase is variable. It can last from a few days to several months. Usually no patient had neurological features other than seizures during the acute phase of illness. Ictal and interictal electroencephalography (EEG) studies revealed focal, generalized, or more frequently bilateral, multifocal pattern, and the location of the epileptic foci was predominantly frontotemporal (Fig. 30.4). Background focal or generalized slowing is common. The EEG between seizures shows slow waves resembling an "encephalitis" pattern.

30.4 Conclusions

Focal slowing is the main electroencephalographic abnormality seen acutely in children with febrile status epilepticus. The findings are quite consistent over time and in different patient populations. If focal slowing is associated with a development of epilepsy later in life is uncertain. Studies to date are not sufficient in order to assess the risk of focal slowing for the development of epilepsy. Future clinical studies, better understanding of animal models, and results from genetic studies might help in this field of knowledge.

References

1. Hauser WA, Kurland LT. The epidemiology of epilepsy in Rochester, Minnesota, 1935 through 1967. Epilepsia. 1975;16:1–66.
2. Nelson KB, Ellenberg JH. Predictors of epilepsy in children who have experienced febrile seizures. N Engl J Med. 1976;295:1029–33.
3. Berg AT, Shinnar S. Complex febrile seizures. Epilepsia. 1996;37:126–33.
4. Hesdorffer DC, Benn EK, Bagiella E, et al. Distribution of febrile seizure duration and associations with development. Ann Neurol. 2011;70:93–100.
5. Shinnar S, Hesdorffer DC, Nordli DR Jr, et al. Phenomenology of prolonged febrile seizures: results of the FEBSTAT study. Neurology. 2008;71:170–6.
6. Shinnar S, Bello JA, Chan S, et al. MRI abnormalities following febrile status epilepticus in children: the FEBSTAT study. Neurology. 2012;79:871–7.
7. Parameter P. The neurodiagnostic evaluation of the child with a first simple febrile seizure. Pediatrics. 1996;97:769–75.
8. Lennox MA. Febrile convulsions in childhood, a clinical and electroencephalographic study. Am J Dis Child. 1949;78:868–82.
9. Frantzen E, Lennox-Buchthal M, Nygaard A. Longitudinal EEG and clinical study of children with febrile convulsions. Electroencephalogr Clin Neurophysiol. 1968;24:197–212.
10. French JA, Williamson PD, Thadani VM, Darcey TM, Mattson RH, Spencer SS, et al. Characteristics of medial temporal lobe epilepsy: I. Results of history and physical examination. Ann Neurol. 1993;34:774–80.
11. Shinnar S, Hesdorffer DC, Nordli DR Jr, Pellock JM, O'Dell C, Lewis DV, et al. Phenomenology of prolonged febrile seizures: results of the FEBSTAT study. Neurology. 2008;71:170–6.
12. Nordli DR, Moshe S, Frank M, Pellock JM, Lewis DV, Marmarou A, et al. Acute EEG findings in children with febrile status epilepticus. Epilepsia. 2005;46(Suppl. 8):266.
13. Aicardi J, Chevrie JJ. The significance of electroencephalographic paroxysms in children less than 3 years of age. Epilepsia. 1973;14:47–55.
14. Yucel O, Aka S, Yazicioglu L, Ceran O. Role of early EEG and neuroimaging in determination of prognosis in children with complex febrile seizure. Pediatr Int. 2004;46:463–7.
15. Kajitani T, Kimura T, Sumita M, Kaneko M. Relationship between benign epilepsy of children with centro-temporal EEG foci and febrile convulsions. Brain and Development. 1992;14:230–4.
16. Baram TZ, Gerth A, Schultz L. Febrile seizures: an appropriate-aged model suitable for long-term studies. Brain Res. 1997;98:265–70.
17. van Baalen A, Häusler M, Boor R, et al. Febrile infection-related epilepsy syndrome (FIRES): a nonencephalitic encephalopathy in childhood. Epilepsia. 2010;51(7):1323–8.
18. van Baalen A, Stephani U, Kluger G, Häusler M, Dulac O. FIRES: febrile infection responsive epileptic (FIRE) encephalopathies of school age. Brain and Development. 2009;31(1):91.
19. van Baalen A, Vezzani A, Häusler M, Kluger G. Febrile infection-related epilepsy syndrome: clinical review and hypotheses of epileptogenesis. Neuropediatrics. 2017;48(1):5–18.
20. Kramer U, Chi CS, Lin KL, et al. Febrile infection-related epilepsy syndrome (FIRES): pathogenesis, treatment, and outcome: a multicenter study on 77 children. Epilepsia. 2011;52(11):1956–65.