The role of EEG in febrile status epilepticus (FSE)

D.R. Nordli *, S.L. Moshe, S. Shinnar

Children's Memorial Hospital, 2300 Children's Plaza, No. 29, Chicago, IL 60614, USA

Received 14 February 2009; received in revised form 17 May 2009; accepted 9 September 2009

Abstract

Febrile status epilepticus is an important neurological emergency and a risk factor for later development of epilepsy. There are guidelines recommending against the use of EEG in the evaluation of simple febrile seizures but the role in febrile status epilepticus is not well established. This article reviews the literature on the role of EEG in the evaluation of the patient with prolonged febrile seizures, summarizes the findings, and concludes with some simple recommendations based upon the existing knowledge. At least 30–40% of EEGs obtained within one week of febrile status epilepticus will contain abnormalities including focal slowing. In some series focal slowing appears to be associated with development of a spike focus in the same location. Prospective series with large numbers of patients and follow-up are required to ascertain whether such abnormalities are associated with later development of epilepsy.

1. Introduction

Febrile status epilepticus is an important neurological emergency and the most severe type of complex febrile seizure. Acute morbidity and mortality are low [1], but the long-term consequences of febrile status epilepticus and predictive risk factors of later epilepsy are not well established. Electroencephalograms are not indicated in the evaluation of routine or simple febrile seizures, but the role of EEGs in the evaluation of children with complex febrile seizures including febrile status epilepticus is not well-known [2]. This article will review the existing knowledge regarding EEGs and prolonged febrile seizures in general and febrile status epilepticus in particular.

2. Focal slowing

One of the most remarkable features found in EEGs obtained within one week after febrile status epilepticus is focal slowing. Lennox examined the EEG results of 240 children with febrile seizures [3]. She correlated the findings with various features of the illness and the known details of the seizure. This work was performed as a retrospective chart review with cases obtained from more than one source, but Lennox attempted to contact all of the patients for follow-up. The publication year was 1949 and EEGs were obtained using Grass ink-writing electroencephalographs with 3–8 channels. Electrodes were placed in the frontal, central, parieto-occipital and temporal areas. References were either other scalp electrodes or linked (interconnected) ears. The study compared these findings with normal control EEGs that were obtained in 373 unscreened presumably normal children, some of whom had been studied by both Gibbs. The children with febrile seizures were admitted to hospital and their EEGs were obtained within a variable amount of time following the seizure, but nearly half (48.4%) had EEGs performed within one week.

Forty percent had severe convulsions defined using the criteria of Patrick and Levy as a convulsion or the

* Corresponding author.
E-mail address: dnordli@gmail.com (D.R. Nordli).
The incidence of slowing was greater when the convulsion lasted 30 min or more, had a focal onset or was unilateral or followed by transient hemiparesis that nearly half of the acute EEGs showed marked slowing (47%), corresponding to the most involved hemisphere, as indicated by the clinical localization in all cases but one. They also noted that the incidence of slowing was greater when the temperature was high, and the children had been sick for 36 h of more. Gastroenteritis seemed to be the most likely cause associated with slowing. The number of subjects with febrile status epilepticus was quite small, and follow-up was under five years. During this relatively brief time of follow-up slowing did not predict development of later afebrile convulsions. However, children who subsequently developed a spike focus more often had EEG slowing (11/19 or 58%) than children who never developed a spike focus (26/77 or 34%) and the side of the spike focus corresponded to the site of maximum EEG slowing. Spikes appeared an average of 1.5 years after the febrile seizure. Most often the location of the spike focus was occipital or temporal and it did not shift from one side to the other between examinations. The p value for this correlation was <0.1, and the authors state that the numbers were too small to draw any definitive conclusions. Frantzen et al. observed that these findings were nearly identical to those of Lennox and Lerique-Koeclin, but there was no universal agreement as to the significance of the focal slowing. Some thought leaders of the time attributed it to fever, others to the combination of fever and seizure, noting that kittens showed ganglion cell shrinkage in the same location following febrile convulsions [6]. The authors thought that these findings might exist along a spectrum in the H.H.E. syndrome of Gastaut [7].

In 1960 Millichap and his colleagues studied the EEG records and clinical features of unselected patients with febrile seizures in the Bronx [8]. This study, performed at Albert Einstein College of Medicine, was reported 12 years after Lennox’ work. Millichap reported EEG abnormalities in 36% of patients whose seizures lasted more than 20 min, in comparison to just 10% abnormalities in those children whose seizures were less than 20 min. (p < 0.05) All EEGs were done at least seven days after the seizure. In the short time of follow-up (an average of one year) spontaneous seizures developed in 38% of children with prolonged febrile seizures. Interestingly, 4/18 (22%) patients with later afebrile seizures had focal slowing on their initial EEGs, whereas only 3/58 (5%) had focal slowing without later development of afebrile seizures.

Another influential study was performed by Frantzen et al. They studied the longitudinal EEG and clinical features of children with febrile convulsions in Denmark [9]. They examined 200 consecutive children with febrile seizure who were admitted to hospital. Although it may have been more customary to admit patients at that time, these patients also appeared to be in the more severe end of the febrile seizure spectrum. As in the previous series most had an EEG within one week of the seizure. In one third, the initial EEG showed marked slowing, most prominent or confined to the occipital leads and usually asymmetrical. When seven days or more had passed only one of thirteen show marked slowing. They noted that when the convulsion lasted 30 min or more, had a focal onset or was unilateral or followed by transient hemiparesis that nearly half of the acute EEGs showed marked slowing (47%), corresponding to the most involved hemisphere, as indicated by the clinical localization in all cases but one. They also noted that the incidence of slowing was greater when the temperature was high, and the children had been sick for 36 h of more. Gastroenteritis seemed to be the most likely cause associated with slowing. The number of subjects with febrile status epilepticus was quite small, and follow-up was under five years. During this relatively brief time of follow-up slowing did not predict development of later afebrile convulsions. However, children who subsequently developed a spike focus more often had EEG slowing (11/19 or 58%) than children who never developed a spike focus (26/77 or 34%) and the side of the spike focus corresponded to the site of maximum EEG slowing. Spikes appeared an average of 1.5 years after the febrile seizure. Most often the location of the spike focus was occipital or temporal and it did not shift from one side to the other between examinations. The p value for this correlation was <0.1, and the authors state that the numbers were too small to draw any definitive conclusions. Frantzen et al. observed that these findings were nearly identical to those of Lennox and Lerique-Koeclin, but there was no universal agreement as to the significance of the findings. Their study lacked a sufficient number of patients with prolonged febrile seizures or status epilepticus and did not have sufficient duration to demonstrate a significant association with later development of epilepsy. They did however, reference other authors who found the identical development of spike foci supplanting areas of prior slowing including Doose et al. and Prichard and Mcgreal [10,11].
In summary, the acute EEG features after prolonged febrile seizures are abnormal in at least one third of cases across a number of series. These findings are most marked in the posterior derivations and appear to increase the chance of development of a spike focus in the same region. About one third of subjects with prolonged seizures developed epilepsy but it is uncertain if focal slowing confers any added risk (Table 1).

Regarding sample size, the series by Frantzen et al. had 38 children with severe convulsions, whereas the series by Lennox had 70. Follow-up was limited to less than five years in the Frantzen study and three years in Lennox’ study. In Lennox’ study the development of epilepsy was determined to be between 5% and 12% depending upon the sub-sample examined in the study. Most interesting, based upon a smaller subset, she calculated that 1/3 of the patients with an extremely slow or focal tracing developed epilepsy within this short period of time. Lennox concluded that the EEG was of value in predicting later development of epilepsy, particularly when considering non-epileptiform features like extreme slowing. In contrast, Frantzen et al. only had five children who developed epilepsy during the length of time of follow-up of their study. As a result they could not reach any statistically significant conclusions about the role of EEG in predicting development of epilepsy in those with status epilepticus. If the latency between prolonged febrile seizures and temporal lobe epilepsy is greater than five years then it is likely that these series had insufficient follow-up to ascertain whether there was an association and whether an initial abnormal EEG was predictive of subsequent mesial temporal lobe epilepsy. It is likely that both the Frantzen et al. and the Lennox studies had insufficient numbers and length of follow-up to fully address the association between the EEG findings in children with febrile status epilepticus and later development of temporal lobe epilepsy.

The FEBSTAT study [13] is an on-going multi-center 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 one 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 [14] 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 in progress. 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.

### 3. Possible significance of focal slowing

The EEG findings have several implications. One interpretation of focal slowing is consistent with a focal structural lesion and may be seen with lesions affecting the thalamo-cortical projection systems, often involving the sub-cortical white matter. Focal attenuation is consistent with focal dysfunction of cortical grey or the presence of an extra-axial fluid collection. However, the above literature suggests that the slowing is transient and therefore it is less likely to be caused exclusively by a fixed focal structural lesion. It is conceivable that a subtle pre-existing lesion could be present and that the persistent focal slowing is related to a post-ictal manifestation, but the persistence of the focal slowing for many days argues against this possibility.

The physiological mechanisms underlying the slowing are unknown. Slowing has been seen in patients with cryptogenic focal epilepsy. Koutroumanidis et al. [15] studied regional slow activity in patients with temporal lobe epilepsy and correlated them with FDG PET findings. Sixteen of 28 patients studied interictal regional slow wave activity (IRSA). This slowing correlated very well with posterior, lateral temporal lobe hypometabolism as measured by PET ($p = 0.0009$) but did not correlate well with the degree of hippocampal cell loss found at surgery, or were there other structural correlates on pathology to explain these findings. These facts lead them to the conclusion that the PET and IRSA indicate a field of reduced neuronal inhibition and they furthermore inferred that the PET findings indicate a reduction in inhibitory synaptic activity [15].

Conventional fixed tissue analysis has shown chronic loss of dendritic spines after seizures in animal models and human tissue. In vivo time-lapse imaging has been used to study the acute effects of seizures. Higher-stage

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Year</th>
<th>% With severe convulsions</th>
<th>% Of those with focal slowing</th>
<th>% Of those with focal slowing who develop focal spikes</th>
<th>% Of develop epilepsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lennox [3]</td>
<td>240</td>
<td>1949</td>
<td>40</td>
<td>34</td>
<td>N/A</td>
<td>33 (of those with focal slowing)</td>
</tr>
<tr>
<td>Lerique-Koechlin, et al. [5]</td>
<td>228</td>
<td>1958</td>
<td>46</td>
<td>34</td>
<td>N/A</td>
<td>32 (of those with severe convulsions)</td>
</tr>
<tr>
<td>Millichap, et al. [8]</td>
<td>110</td>
<td>1960</td>
<td>16</td>
<td>36</td>
<td>N/A</td>
<td>38 (of those with prolonged seizures)</td>
</tr>
<tr>
<td>Frantzen, et al. [9]</td>
<td>200</td>
<td>1968</td>
<td>19</td>
<td>47</td>
<td>29</td>
<td>N/A</td>
</tr>
</tbody>
</table>
kainite-induced seizures cause dramatic dendritic beading and loss of spines within minutes in the absence of neuronal death or de-oxygenation. Dendritic beading improves rapidly, but spine loss recovers only partially over a 24 h period. Zeng et al. demonstrate that these changes were associated with an activation of coflin and a decrease in actin [16]. The EEG signal is generated by summation of post-synaptic potentials in the apical dendrite. It is conceivable that these dendritic alterations could contribute to the focal slowing seen on the acute EEG tracings. Other possibilities would include altered expression of ion channels in the apical dendrites and focal inflammation [17–20].

4. Presence of interictal epileptiform discharges

Only a very small fraction of acute EEGs children less than three years of age with febrile status epilepticus show epileptiform discharges [21]. The clinical significance of these interictal epileptiform discharges are not clear. According to Yucel et al. detection of epileptiform activity is less common in the first week following the prolonged febrile convolution [22]. The most common type of epileptiform activity to observe in the older children are bursts of generalized spike-wave discharges, although an association with centro-temporal spikes has also been noted [23]. 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 convolution [9]. Ultimately, they were found in half of the EEGs obtained in children above age 4 years. It is likely that these spikes indicate a genetic susceptibility. These did not appear to accurately predict recurrence of afebrile or febrile seizures.

In summary, epileptiform activity is less commonly found in the acute EEGs after febrile status epilepticus. Diffuse spike-wave discharges appear later in follow-up EEGs, particularly above age 4 years and do not appear as predictive as the presence of focal slowing for later epilepsy.

5. Clinical significance of focal slowing

The long-term significance 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 approximately one week. Its persistence of several days to one week is longer than one might expect for a typical post-ictal phenomenon, which we commonly see lasting less than one day. The literature suggests that this slowing is significant since (Table 1):

1. It appears to raise the risk of later seizures in one series (Lennox).
2. It is associated with later development of spike foci, on the same side as the focal slowing. (All series that looked at this issue).
3. Focal slowing has been found to be a risk factor for development of intractable epilepsy in other series of children with afebrile seizures [24,25].

The mechanisms involved are unknown. If this data is replicated in the large on-going prospective multi-center study of prolonged febrile seizures than it will be important to correlate these findings with experimentally-induced febrile status [26].

6. Conclusions

A review of the literature shows that focal slowing is the predominant electroencephalographic abnormality seen acutely in children with febrile status epilepticus in about 1/3 of cases. The findings are quite consistent across decades and in different patient populations. It is uncertain if the focal slowing predicts development of epilepsy since 1/3 of patients with focal slowing developed epilepsy in one series, and one third of patients with prolonged febrile seizures developed epilepsy in two other series. Moreover, 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 development of epilepsy. In addition the best studies were performed decades ago, long before the advent of MR, so the relationship with 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.

Acknowledgment

NIH grant information: Supported by Grant NS 43209 NINDS; PI: S Shinnar.

References


