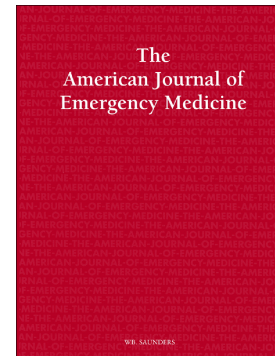


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Title:

Should patients with complex febrile seizure be admitted for further management?

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ABSTRACT:

Background and aims: Children with first complex febrile seizure (CFS) are often admitted for observation. The goals of this study were 1) to assess the risk of seizure recurrence during admission, 2) to determine whether early EEG affects acute management.

Design/Methods: We retrospectively reviewed a cohort of children 6-60 months of age admitted from a Pediatric Emergency Department for first CFS over a 15 year period. We excluded children admitted for supportive care of their febrile illness. Data extraction included age, gender, seizure features, laboratory and imaging studies, EEG, further seizures during admission, and antiepileptic drugs (AEDs) given.

Results: One hundred eighty three children met inclusion criteria. Seven patients had seizures during the admission (7/183 or 3.8%) Since 38 children were loaded with anti-epileptic medication during their visit, the adjusted rate is 7/145 or 4.8

Increased risk of seizure recurrence during admission was observed in children presenting with multiple seizures ($P=0.005$).

EEG was performed in 104/183 children (57%) and led to change in management in one patient (1%, 95% C.I. 0.05- 6%). Six of the 7 children with seizure had an EEG. The study was normal in 3 and findings in the other 2 did not suggest/predict further seizures during the admission.

Conclusions: Children with first CFSs are at low risk for seizure recurrence during admission. Multiple seizures at presentation are associated with risk of early recurrence and may warrant an admission. EEG had limited effect on acute management and should not be an indication for admission.

INTRODUCTION

Complex febrile seizures are a common cause for an Emergency Department (ED) visit. The prevalence of febrile seizures is ~2-5% in the United States, and approximately 25-35% of febrile seizures are classified as complex.¹⁻⁴ Complex febrile seizures (CFSs) are defined as those with focality, prolonged duration (greater than 15 minutes), and/or multiple seizures within 24 hours.² Approximately 20- 30% of children with a first febrile seizure will have subsequent febrile seizures.³⁻⁶

There are currently no clinical practice guidelines regarding management of CFS in the US. There are international guidelines by the Italian league against epilepsy (the Ad Hoc Task Force of LICE Guidelines)[5], the Joint Working Group of the Research Unit of the Royal College of Physicians and the British Paediatric Association Commission[6] and the world health

organization guidelines[7], all calling for routine admission for observation for all patients presenting with CFS. These recommendations echo algorithms published in several review articles in the medical literature .[8, 9]

Recent literature suggest that routine lumbar puncture and urgent neuroimaging are low yield and are not indications for admission after CFS.⁹⁻¹³ Thus indication for admission would typically be for observation or supportive care.

Recommendations on if and in what time frame to perform EEG after CFS vary.^{2,3,14} There is limited data on the utility of EEG in the acute period (<72 hours) after first time CFS.^{11, 15-17} Early EEG could be performed as inpatient or outpatient in most centers, but this study focuses on the inpatient setting

The goals of this study were to assess the risk of recurrent seizures during admission and to determine whether EEG in the in the first 72 hours affects acute inpatient management.

METHODS

Study Design

This is a retrospective cohort review of consecutive patients admitted for observation after their first CFS at a single urban tertiary care center over a fifteen year period. Electronic medical records (EMR) of all patients presenting with first CFS were reviewed. The study protocol was approved by the Children's Hospital Institutional Review Board committee.

Case Identification

Case identification was conducted in two phases. First, for the initial screening, we created a computer-assisted screening tool similar to key word search tools, only using regular expressions²². The technique of regular expression matching provides a more comprehensive and inclusive search than key word searching by including possible misspelled and mistyped variations of the key word(s) of interest. The second step was a manual chart review of those patients identified by the screening tool, using the inclusion and exclusion criteria below.

Inclusion Criteria

All patients with available EMRs during the study period were evaluated for inclusion in this study. We included otherwise healthy patients ages 6 to 60 months with a first time CFS who were admitted to the hospital for observation. Temperature was documented as 38.0 or higher at home or in the emergency room. Seizures were classified as complex if they met the

any one of the following criteria: duration >15 minutes, focal features by history or examination, or multiple seizures in <24 hours¹.

Exclusion Criteria

Patients were excluded if they had previously diagnosed epilepsy. Intubated patients were excluded, because they would require admission regardless of the seizure characteristics. Patients were excluded if they required admission for associated conditions, such as pneumonia, gastroenteritis, or dehydration.

Data Collection

Data regarding the ED or hospital course and management was then retrieved from EMRs. Specific data extracted included: age, gender, history of prior febrile seizures, seizure features, imaging studies during admission, EEG results during admission, further seizures during admission, and antiepileptic medications given. If a trainee was involved in the patient care, both the trainee and the attending physician's notes were reviewed. Findings were considered present if they were documented either by the resident or attending physician.

Definitions

Age was recorded in months. Seizure features were defined as focal, prolonged, recurrent, or a combination of these observations. Focal seizures were defined as having unilateral features, such as eye and/or head deviation or unilateral movements. A prolonged seizure was defined as lasting >15 minutes. A recurrent seizure was defined as >1 febrile seizure within 24 hours. Imaging was recorded if it took place after the patient was admitted to the hospital, and was classified as normal or abnormal. EEG reports were reviewed in detail as outlined below. Seizures after admission were documented as present or absent after review of discharge summaries and neurology follow up notes. Antiepileptic loading medications were documented as any antiepileptic drug given with the exception of benzodiazepines (i.e. fosphenytoin or phenobarbital).

EEG data

EEG results were reviewed and scored by two neurologists according to the following categories in Table 1

Descriptive statistics were used to assess rates of EEG abnormalities among separate subgroups. Category 1 is of particular interest, as this is the group for which urgent inpatient MRI may be warranted.

Outcome Measures

The primary outcome was seizure during admission. Secondary outcome was effect of EEG on acute management following CFS, or percentage of patients in category 1 as defined above.

Statistical Analysis: Data were analyzed using SPSS for Windows (Chicago, 2005). We performed univariate analysis using χ^2 analysis for categorical data and Mann-Whitney U test for continuous data..

RESULTS

Patients

Of 581 children with first CFS, 332 were admitted to the hospital during the study period, and 183 patients met inclusion criteria. Patient identification and exclusion is shown in Figure 1. Patient characteristics are shown in Table 2.

CFS features were as follows: 108 (59%) had >1 seizure in 24 hours, 72 (39%) had focal features and 68 (37%) had a prolonged seizure. There were 75 patients (41%) with more than one feature. Twenty four patients had seizures lasting > 30 minutes (febrile status epilepticus).

Seizure Recurrence

Thirty eight (21%) patients received a bolus dose of an antiepileptic drug (fosphenytoin, phenobarbital, levetiracetam) in the ED setting, and none of these patients had breakthrough seizures. One additional patient received a bolus of levetiracetam during admission for multiple generalized seizures, and did not have further breakthrough seizures after the bolus. Seven patients had seizures during the admission (7/183 or 3.8% of all patients, and 7/145 or 4.8% of those who did not get an antiepileptic load). Multiple seizures (more than 3 in 24 hours) were associated with risk of recurrence (P=0.005).

Six of the seven patients with seizures during admission had multiple seizures (more than one seizure in 24 hours) as their presenting feature, while only one patient with focal features and none of the patients presenting with prolonged seizure had recurrence during admission.

Of those who were not loaded with antiepileptic drugs, the risk of seizure recurrence for those who had ≤ 3 seizures in 24 hours was 4/137 (3% 95% CI 1, 7.9%) while those with >3 seizures in 24 hours was 3/8 (37.5% 95% CI 10.2, 74.1%).

EEG Results

Of the 183 patients who met inclusion criteria 104 (57%) had EEGs during admission. The EEG result lead to change in management in the acute setting in one patient (1/104 1% - 95% C.I. 0.05- 6%), as it diagnosed a generalized epilepsy.

This patient had eight tonic and one myoclonic seizure during the period of recording, all generalized on EEG. In 23/104 patients (22% 95% C.I. 15-32%) EEG was likely to have an effect on management but not in the acute setting. For example, the EEG result may guide medication anti-epileptic drug (AED) choice (focal versus generalized versus broad spectrum) in the situation in which the child progresses to have afebrile seizures. In 6 patients (6% 95% C.I. 2.4-12.6%) EEG was unlikely to have an effect on management. In 74 patients (71% - 95% C.I. 61-79%), EEG was normal.

Results related to patient characteristics are presented in Table 3. Notably, except in one patient who also had clinical seizures, the EEG findings did not correlate well with further seizures during admission or use of an anti-epileptic drug. Six of the seven patients with recurrent seizures had an EEG, which was abnormal in 3 (50%). One captured generalized seizures as above (category 1), one showed paroxysmal central midline slowing and continuous background slowing (category 2), and one showed generalized slowing (category 3). Thirty-six percent of patients who received an AED bolus during admission had an abnormal EEG, and 55 % of those discharged home on an AED had an abnormal EEG. The patient for whom the EEG diagnosed generalized epilepsy (category 1) was bolused with levetiracetam during admission and discharged home on a maintenance dose of levetiracetam.

Further documentation involving follow up visits was available for 109/183 patients (59.5%). Given that this is a retrospective study over a span of 15 years, follow up duration ranged from 1-15 years. Seven patients carry the diagnosis of seizure disorder or epilepsy at time of the data review, 11 had recurrence of febrile seizure involving consecutive visits, and of those patients where imaging reports were available (89 patients) 16 had static brain abnormality described. These numbers should not be interpreted as prevalence, as patients with a follow up are likely to be a skewed population within our cohort

DISCUSSION

We have presented data showing that patients with CFS admitted for observation have a low rate of seizure recurrence unless they had multiple seizures (greater than 2) leading to the

admission. We have also shown that early EEG findings did not correlate with the use of AED and/or further seizures during the admission.

Patients are frequently admitted for observation after first time CFS. Two studies have shown crude admission rates of 47% and 52%. (Seltz et al and Kimia et al) These crude rates include patients who were intubated, those requiring supportive care like IV fluids, oxygen or antibiotics and probably patients with high parental anxiety. No data is provided on patients admitted solely for observation. This manuscript addresses aspects related to routine admission for CFS as suggested by some of the international guidelines and review articles. Diagnostic evaluation of children with CFSs may include EEG, brain imaging, and in select patients lumbar puncture.^{9,10} EEG and brain imaging can often be deferred to the outpatient setting, and are not typically the main goals of admission. One of the main reasons for observation is the concern for further seizures in the acute setting. The question then is should we admit all children with CFS, including those who do not require supportive care, are back to baseline, and their parents are comfortable with outpatient management?

The Italian league against epilepsy (the Ad Hoc Task Force of LICE Guidelines)[5], the Joint Working Group of the Research Unit of the Royal College of Physicians and the British Paediatric Association Commission[6] and the world health organization guidelines[7], all calling for routine admission for observation for all patients presenting with CFS. These recommendations echo algorithms published in several review articles in the medical literature. Armon et al[8] published an evidence and consensus based guideline for the management of a child after a seizure, calling for admission of all children under 18 months old, those who have had a complex seizure, or after pretreatment with antibiotics. In a 2008 review called 'Assessment of febrile seizures in children' Fetveit[9] suggest an algorithm calling for admission for all patients with CFS.

Though our sample is too small to stratify by CFS feature, it is evident that those patients with 3 or more seizures in 24h have an increased risk for further seizures. The authors believe that some subsets of patients, such as those with febrile status epilepticus, represent a unique population who merit a conservative approach and observation even in the absence of strong evidence.

We have shown that EEG has limited impact on the acute inpatient management after CFS. EEG findings did not correlate well with further seizures during admission or use of anti-epileptic drugs. Situations in which an urgent EEG may be indicated include evaluation for

subclinical seizures or non-convulsive status epilepticus if the patient is not returning to baseline, or monitoring to evaluate response to treatment of non-convulsive febrile status epilepticus. If there are frequent febrile seizures during admission, EEG may help identify a focus or an etiology, such as PLEDs in herpes simplex virus associated encephalitis.¹⁸ It may also provide clues toward a generalized epilepsy or a specific epilepsy syndrome (i.e. Dravet syndrome).

Rates of paroxysmal epileptiform abnormalities on routine EEGs in normal children and adults has ranged from 0.3 – 9% in various series.¹⁹ The predictive value of paroxysmal activity on EEG varies according to the clinical situation and type of abnormality. For example in children with central-mid-temporal spikes there is a 50-70% association with overt seizures and with occipital spikes in the 3-5 year age range the association with epilepsy is even lower.¹⁹ There has not been strong evidence that paroxysmal activity on EEG after CFSs is predictive of later epilepsy in most series^{3, 15} One series suggested that focal slowing in patients with febrile status epilepticus may predict a later epileptic focus, and a recent manuscript suggesting a higher risk for epilepsy in patients with febrile seizures who have frontal paroxysmal EEG abnormalities compared to patients with paroxysmal activity in other areas on EEG.^{16,20} Our study addresses the question of utility of EEG for management in the acute inpatient setting only, and does not address the question of the predictive value of early EEG with regards to later development of epilepsy.

While we have shown that in most cases it does not impact acute management, some studies have suggested that focal slowing, that lasts up to 10-15 days, may be predictive of a later epileptogenic focus.¹⁶ Results from the FEBSTAT (Consequences of Prolonged Febrile Seizures) study suggest that focal slowing on EEG within 72 hours of febrile status epilepticus is associated with MRI evidence of acute hippocampal injury.¹⁷ With regards to timing of EEG after CFS, some may consider this a justification for early though not emergent EEG. Others may suggest that EEG after CFS is not indicated because it will not likely affect treatment decisions unless the child has an unprovoked seizure. We recommend to consider obtaining an EEG within the first few days after CFS in order to have the best chance of finding focal slowing or epileptiform abnormalities, though this does not need to be in the inpatient setting. If there is a distinct focus on EEG, this would also provide indication for early neuroimaging.

Limitations

Data was extracted retrospectively, therefore admission for observation was either specified or implied, yet we have reviewed all available documentation, including consultation notes, admission notes, discharge summaries, and any available follow up notes.

Not all patients were admitted. Rates of seizure recurrence in children discharged is unknown. The admitted children are unlikely to be 'healthier' than those discharged. Even in this selected population of admitted children, the rate of seizures recurrence is low and the yield of early EEG is low.

This was a single center study. Criteria and threshold for admission after CFS may vary from institution to institution.

Observation times varied. Some children were admitted shortly after the seizure and others almost 24h after the seizure (especially if transferred). In addition, length of admission varied. There are no clear criteria for length of observation.

CONCLUSIONS

Patients admitted for observation after CFS have a low rate of seizure recurrence, though patients with multiple seizures as the presenting feature are at higher risk for seizure recurrence. EEG findings had limited effect on acute management and should not be a sole reason for admission of these children.

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Category		Example of findings on EEG
1	Likely to change management in the acute setting (72 hours)	Electrographic or electro-clinical seizures on EEG
2	Likely to have an effect on management but not necessarily in the acute setting	Focal or generalized epileptiform activity or focal slowing
3	Abnormal but unlikely to affect management	Generalized slowing
4	Normal	Normal

Table 1. Scoring of of EEG findings

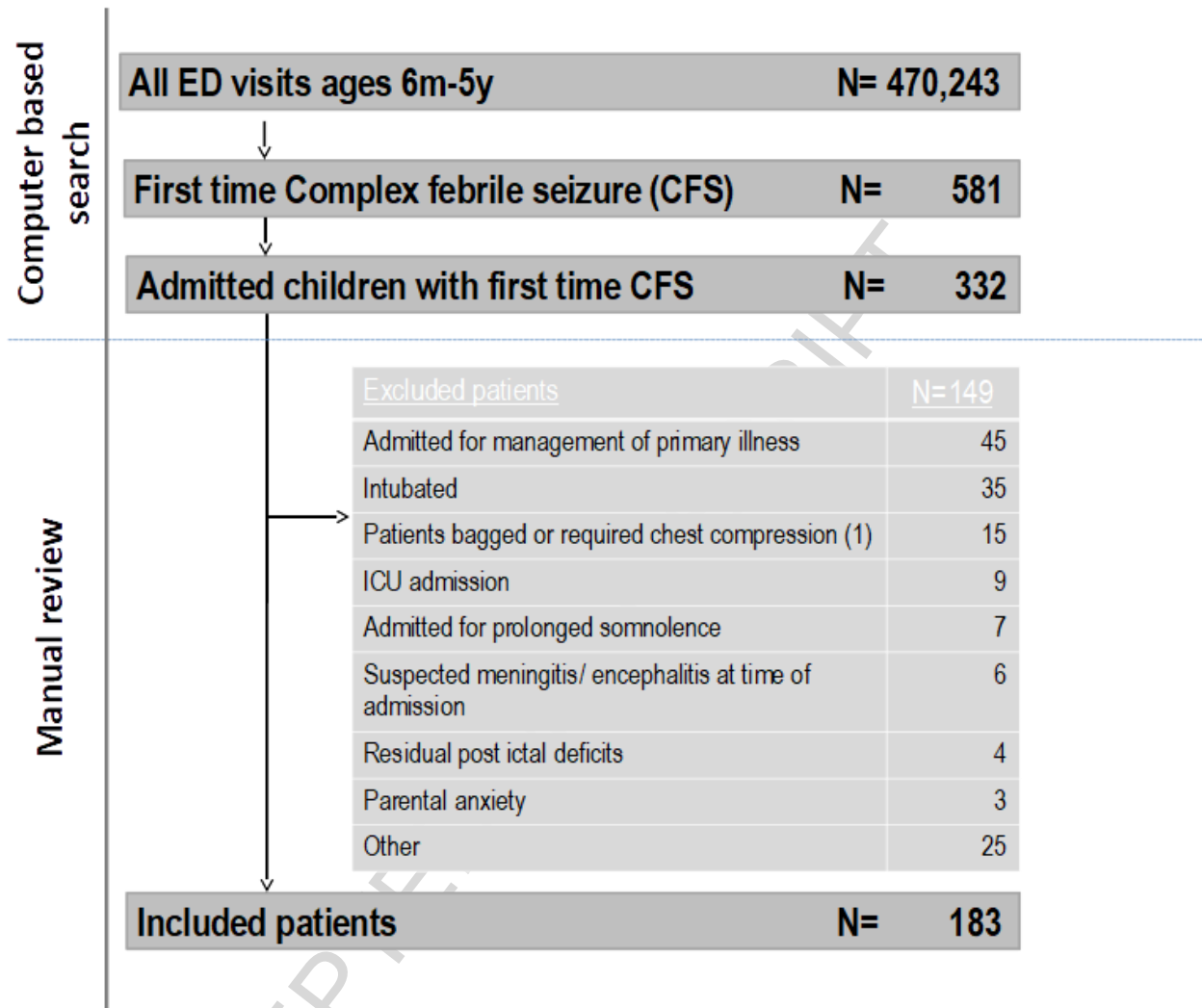
Number of Patients	183
Median age, months (IQR)	16 (13, 23)
Female (%)	50 %
Prior history of simple febrile seizure	38 (21%)
Received loading dose of antiepileptic drug	38 (21%)
Admitted to neurology service	108 (59%)
Admitted to medicine service	75 (41%)
EEG during admission	104 (57%)
Further seizure during admission	7 (3.8%)
Later diagnosed with epilepsy	7 (3.8%)

Table 2. Patient demographics and clinical management.

Patient factors	# (% of 104)	Abnormal EEG (%)	EEG affects acute management	EEG affects management but not acutely	EEG has no effect on management
Further seizures during admission	6 (6%)	3 (50%)	<u>1 (17%)</u>	1 (17%)	4 (67%)
AED loaded during admission	32 (31%)	11 (34%)	<u>0 (0%)</u>	8 (25%)	24 (75%)
Discharged home on AED	29 (28%)	16 (55%)	<u>1 (3%)</u>	11 (38%)	17 (59%)

Table 3. EEG findings according to patient characteristics.

Fig. 1



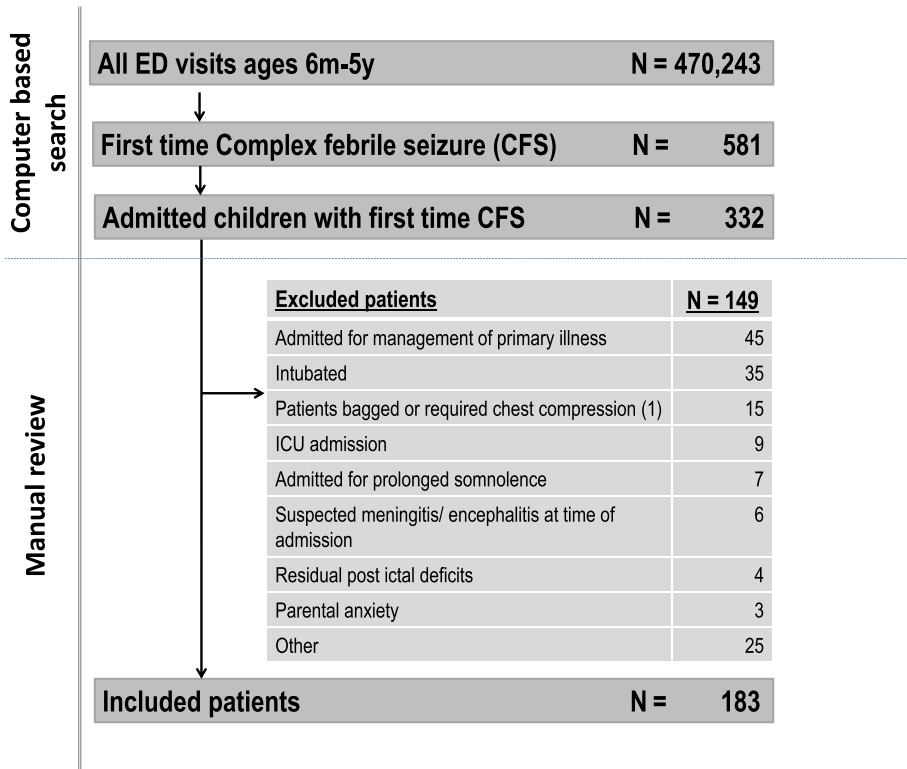


Figure 1