Simple Febrile Seizures: New Cut Off for the Duration of the Crises

Raffaele Falsaperla
University Hospital "Policlinico-Vittorio Emanuele, " PO “San Marco”
Giovanna Vitaliti (giovitaliti@gmail.com)
University of Ferrara
Anna Bonadies
Department of Pediatric A.O.R.N. Santobono Pausilipon, Naples, Italy.
Marino Simona Domenica
University Hospital "Policlinico-Vittorio Emanuele, " PO “San Marco”
Pavone Piero
University Hospital A.U.O. “Policlinico-Vittorio Emanuele”
Romano Catia
University Hospital "Policlinico-Vittorio Emanuele, " PO “San Marco”
Savoia Fabio
Department of Epidemiology A.O.R.N. Santobono Pausilipon, Naples, Italy.
Calì Camilla
Department of Epidemiology A.O.R.N. Santobono Pausilipon, Naples, Italy.
Martino Ruggieri
University of Catania, AOU “Policlinico”, PO “G. Rodolico”
Lubrano Riccardo
"La Sapienza" University
Tipo Vincenzo
Department of Pediatric A.O.R.N. Santobono Pausilipon, Naples, Italy.

Research Article

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Abstract

Background: Our study aimed to identify a new cut-off for febrile seizure (FS) with a good prognosis, thereby replacing the 15 min described in the standard definition of simple febrile seizure (SFS).

Methods: Our study was a retrospective observational study (from January 2016 to December 2016) on children admitted to the Pediatric emergency room of the Santobono-Pausilipon Hospital, Naples, Italy, and Policlinico-Vittorio-Emanuele University Hospital, Catania, Italy, for fever, which developed SFS during the hospitalization.

All included patients had their seizures classified as SFS according to the international criteria for epilepsy. We assumed a cut-off of 5 min duration, and we analyzed the EEG results, neurological follow up at 12 months, and the recurrence of the febrile seizures the following year. Then, with another calculation, we identify an optimal cut-off of 6 min. Finally, we divided the population into two groups: children with seizures having a duration greater than or less than 6 min.

Results: We found that the population with FS with a duration greater than 6 min presented EEG alteration at follow up visits, neurological disorders, and a recurrence of FS during the following year.

Conclusions: We suggest to introduce a new cut-off for the duration of FS that better represents the benign nature of a simple febrile event.

Introduction

Febrile seizures (FSs) are the most common neurologic disorders in childhood. FSs affect about 2–5% of all children, they mainly occur between 6 months and 5 years of age, and have a peak incidence at 18 months of age (1–4).

FSs can be classified as simple febrile seizures (SFSs), complex febrile seizures (CFSs), and febrile status epilepticus (FSE) (5–7). SFSs have a duration of less than 15 min, are self-limiting, usually presenting as tonic-clonic generalized seizures, with no positive history for other neurologic disorders, with one-time occurrence in 24 h. CFSs are complex seizures lasting more than 15 min; while FSEs have a duration of more than 30 min.

While most patients with FSs should never progress to epilepsy, literature data report a slightly increased risk of subsequent epilepsy in patients with FSs: 1–2.4% of patients with SFS and 4–6% of patients with CFS might develop epilepsy later in life (4).

Factors known to be associated with a higher risk of epilepsy include: familial and personal past history of epilepsy, recurrence and duration of FSs, frontal epileptiform discharges at EEG, abnormal neuroimaging, and presence of genetic abnormalities (8, 9).

Herein, the authors present a retrospective observational study on children with SFS, diagnosed according to the International League Against Epilepsy criteria (5–7). We analyzed SFS lasting more than 5 mins and their EEG findings. We also studied the neurological exam of children with FSs and the mean recurrence of FSs per month. Our aim was to establish the best cut-off of FS duration in order to identify “benign FSs”, and differentiating FSs with better prognosis from those tending to evolve into epilepsy later in life.

Materials And Methods

A 12-month (from January 2016 to December 2016) retrospective study was performed. We randomly included patients admitted to the emergency room for fever, who developed SFSs during the hospitalization. The two centers participating to the study were: the Pediatric Emergency Unit of Santobono-Pausilipon Hospital, Naples, Italy and The Pediatric Emergency Unit of Policlinico-Vittorio-Emanuele University Hospital, University of Catania, Italy.

All children between 3 months and 5 years of age, who were diagnosed with SFS according to the International League Against Epilepsy criteria (5–7) were included in this study.

Children with CFSs, a personal history of afebrile seizures, on therapy with antiepileptic medications, with a personal history of cerebral disorders and/or neurologic diseases (brain malformations, cerebral palsy, stroke, intracranial tumors, central nervous system infections or concomitant head injuries) were excluded from this study. We excluded also patients who presented febrile seizures before the admission to the emergency unit, in order to be able to correctly detect the timing of seizures. Considering the real-life setting, we included only patients who performed externally an electroencephalography (EEG) regardless our will. The patients’ parents the showed us the result of EEG at follow-up.

For each patient, the following data were collected: age at admission, gender, personal history of FSs, familial history of epilepsy, neurological disorders; physical examination upon arrival (including body temperature, SpO2, heart, and respiratory rate); neurological examination; age at seizures onset; number of episodes before admission; associated neurological disorders; seizure semiology (according to the classification of Trinka et al. (11)); duration (the interval time between the reported onset and the cessation of clinical seizure activity); electroencephalography (EEG) results at 6-month and 12- month follow-up; anticonvulsant therapy administered as rescue medication; number of FSs during the follow-up period; and recurrence of FS during the following year.

When EEG results had a normal background activity and absence of any electrical abnormalities, it was considered “normal”. On the contrary, any pathological activity was described in detail. All the EEG studies were read by two independent neuropediatricians, and their interpretations were performed by the same two specialists, according to the International Guides on Epilepsy (5–7, 12). All patients’ data were recorded in an Excel database and then reported into a central database to perform statistical analysis.

The ethics committee of our institution approved the study (Policlinico-OVE Ct 12578). All research was performed in accordance with international relevant guidelines/regulations. Informed consent was obtained from all the parents' of the studied patients. The research was performed in accordance with the Declaration of Helsinki guidelines (10).

An written informed consent was asked to the patients' parents to participate to the present study.

Statistical analysis

For statistical analysis we used the software STATA, StataCorp LLC, version 14.2.

Univariate and multivariate analyses were performed considering as clinical outcomes the following variables: EEG alterations at 6 and 12 months, neurological signs at 12 months, and the recurrence of FSs one year after the inclusion in our study. Some features of the cohort were selected as covariates of the statistic model: gender, age of onset, psychomotor development, temperature, family history, and duration of seizures. These data were analyzed according to logistic regression.

Subsequently, by ROC analysis, the same outcome variables were assessed with respect to the duration of the crisis to establish an optimal cut-off value which could better determine the benignity of the disease. There are numerous methods to evaluate the optimal cut-off, but herein we have chosen to use the Youden index, which identifies the value of the test that maximizes the difference between true positive and false positive results. Once the optimal cut-off had been chosen, the study population was divided into two groups and the different clinical outcomes were analyzed by an exact Fisher test, obtaining a p-value.

Results

In our study, we evaluated 263 patients with FSs of simple nature, and 48 have been excluded according to exclusions criteria. 215 children with SFSs were included in the study, 190 of the center of Naples and 25 of the University of Catania, 115 male (53%) and 100 female (47%), with an average age of 2.2 ± 1.4 years (mean ± SD).

Univariate and multivariate analyses considering the following variables: EEG results at 6 and 12 months, the neurological objectivity at 12 months, and the recurrence of seizure as clinical outcome, we found that the statistically most significant prognostic factor to determine whether a SFS was benign or could evolve into epilepsy was the duration of seizures.

A ROC analysis was carried out relating all the clinical outcome variables to the duration of seizures, and the Youden index was used to define the optimal cut-off of duration to determine the benignity of the studied seizures.

Table 1 shows the cut-off values for each clinical outcome with the respective value of the area under the ROC curve (AUC) and confidence interval at 95%. The AUC is greater in the analysis involving as clinical

outcomes EEG alterations at 6 months (0,89; CI95%:0,84 – 0,94) and EEG alterations at 12 months (0,82; CI95%:0,68 – 0,95). In these cases, the cut-off value corresponds to 6 min, so this value was used for subsequent analysis.

Table 1
The cut-off values for each clinical outcome with the relative value of the area under the ROC curve (AUC) and confidence interval at 95%.

Clinical outcomes	Cut-off	AUC	CI 95%	
EEG 6 months	6 min	0.89	0.84	0.94
EEG 12 months	6 min	0.82	0.68	0.95
Recurrence of seizures at 12 months	5 min	0.81	0.68	0.95

	Seizures <6 min		Seizure ≥ 6 min		p-value
	n.	%	n.	%	
	178	83%	37	17%	
Normal EE study at 6 months	129	100%	27	77%	<0,001
Normal EEG study at 12months	166	99%	29	85%	0,002
Normal follow up at 12 months	158	97%	19	70%	<0,001

Different diagnostic criteria were analyzed for children with a seizure lasting less than 6 mins (178, 83%), and for children with seizures lasting more than or equal to 6 mins (37.17%).

Table 2 shows differences between the two groups obtaining a p-value through the exact Fisher test. Patients with FSs greater than 6 mins have a higher probability of presenting EEG alterations at 6 and 12 months and of seizures occurrence the following year. The neurological objectivity is abnormal when the duration of seizure is greater than 6 min.

Table 2

P-value and distribution of clinical outcome variables among children with a seizure under 6 min and children with seizure greater than or equal to 6 min.

Normal neurological objectivity at 12 months	169	95%	25	69%	< 0,001

Discussion

Currently, the diagnostic criteria for SFSs state a cut-off of 15 min to define the benignity, the seizure should be self-limiting, tonic-clonic generalized, with normal EEG, neuroimaging, and lab results. In our

study, we found that most FSs end within minutes, typically less than 5 mins. Therefore, we decided to study those seizures lasting more than 5 minutes, evaluating what happens from the 6th minutes of seizure, by the study of EEG alterations at 6 and 12 months, and the neurological clinical signs during follow-up.

This hypothesis refers to the specific pathogenesis described in the model suggested by Riazi et al. (13). The Authors performed an *in vivo* study on animal models demonstrating how peripheral inflammation can alter hippocampal neuronal excitability. These authors induced colitis in mouse models by injecting 2,4,6-trinitrobenzene sulfonic acid (TNBS) and they showed that TNBS could induce a Th1cell-mediated inflammation of the mice bowel (13–17). After 2,4,6-TNBS colitis-induction, the authors found an increase in serum Tumor Necrosis Factor-alpha (TNF-*a*), which was responsible for mice' blood-brain barrier disruption and acted as a trigger for seizures (13). They, therefore, identified a model of microglial-dependent, TNF-mediated neuronal excitability that might represent a potential link between peripheral and central inflammation. This pathogenic model explains how peripheral inflammation, phenotypically expressed by the onset of fever, can trigger seizures, and typically fever-induced seizures. These last are brief, strictly linked to the ongoing inflammatory process, with a rare occurrence, without post-ictal consequences or further evolution to epilepsy.

Other Author suggests the correlation between plasma interleukin-6 (IL-6) levels and the onset of febrile seizures (FS). Previous studies showed significantly higher serum IL-6 levels in FS patients than in controls. However, the mechanism underlying this association remains unclear (18). Chen et al provided knowledge regarding the association of IL-6 polymorphisms with susceptibility to FS (18).

The current classification of SFS considers a duration as long as 15 min for a fever associated seizure, that corresponds to prolonged inflammatory status altering neuronal susceptibility and hyperactivity. Studies have found that prolonged FSs are associated with an increased risk of subsequent epilepsy compared to a complex FS that was less prolonged (19–22). In regards, studies on animal models showed that prolonged seizures lead to brain injury in paralyzed and mechanically ventilated baboons (20).

In our study, we decided to identify the optimal cut-off to determine the benignity of simple febrile seizures, and based on our statistical analysis (Youden index) we found this cut-off at 6 mins. After 6 mins of duration, we found a higher probability of presenting EEG alterations and abnormal neurological objectivity, such as psychomotor retardation. After 6 mins, the risk of recurrence of FSs during the following year is higher. Moreover, literature data showed that the occurrence of multiple FSs is also associated with a slight but statistically significant increase in the risk of subsequent epilepsy (17–22).

In our study, only 2% of the studied children developed epilepsy, in particular, children who had a seizure with a duration greater than 6 mins. These were the only children who developed epilepsy.

Limits of the study

The EEG study was performed outside the two Hospital centres. It was not prescribed by our neuropediatricians, but it was requested by the General Medical Doctor after specific request of parents. In fact, the most of parents coming to our observation with their children for FSs faced this disease as a dramatic event, feeling the need to further diagnose eventual neurologic problems by EEG study.

Unfortunately, in the south of Italy, there is a lack of concern on the benignity of febrile seizures, and parents often face the disease with fear and preoccupation.

For this reason, EEG was prescribed by their Medical Doctor to exclude potential brain damage.

Conclusions

In conclusion, we suggest to assign a new cut-off of 6 mins to determine the benignity of a FS, reducing the standardized cut-off of 15 mins. This cut-off is important because when a child arrives at the emergency room with a FS of fewer minutes (less than 6 min), physicians can reassure parents about the benign prognosis. A FS lasting more than 6 min should be evaluated for neurological follow-up, making the parents aware that the seizure could recur and that their child is likely to undergo an antiepileptic therapy.

Everything defined as SFS can take place according to our study in less than 6 min. Therefore, we propose introducing a new entity: typical FS, characterized by self-limiting, generalized tonic-clonic seizure, lasting < 6 min, with normal EEG and imaging, occasional recurrence (once/twice in 1 year, once in a lifetime, does not recur within the same illness) in a child of typical age, with no neurological disorder. Other studies are mandatory to thoroughly test this proposal.

Statement And Declaration

Research Methods:

All research was performed in accordance with international relevant guidelines/regulations. Informed consent was obtained from all the parents' of the studied patients. The research was performed in accordance with the Declaration of Helsinki guidelines (10).

Ethical Approval:

This clinical research was approved by the ethic committee of the University of Catania.

Consent for publication statement:

not applicable.

Availability of data and materials:

All data generated or analysed during this study are included in this published article [and its supplementary information files]

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authors declare not to have any competing interest in publishing the present paper. We moreover declare not to have received any funding.

Conflict of interests:

all authors declare not to have any conflict of interest to declare.

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Authors' contribution:

RF, GV, BA, and MSD. designed the study; RF, MSD, PP, CR performed experiments; GV, MSD, SF, CC. collected and analyzed data; RF, GV, MSD, MR, TV wrote the manuscript; MR, and RL gave technical support and conceptual advice. All authors read and approved the final manuscript.

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