## PATHOLOGICAL EEG PATTERN, PREDICTIVE FACTOR FOR RECURRENCE OR EPILEPSY IN FEBRILE SEIZURES?

## RALUCA MARIA COSTEA<sup>1</sup>, BOGDAN NEAMȚU<sup>2</sup>, GEORGE CONSTANTIN MANIU<sup>3</sup>

<sup>1,2</sup>Research and Telemedicine Center of Neurological Diseases in Children, <sup>1,2</sup>Clinical Pediatric Hospital Sibiu, <sup>2</sup>Faculty of Medicine, "Lucian Blaga" University of Sibiu, <sup>3</sup>Faculty of Sibiu, <sup>2</sup>Faculty of Engineering "Lucian Blaga" University of Sibiu, <sup>3</sup>Faculty of Science, "Lucian Blaga" University of Sibiu

**Keywords:** Febrile seizure, electroencephalography, recurrence Abstract: The value of the pathological electroencephalographic (EEG) pattern in febrile seizures (FS) as predictive factor for recurrence or for epilepsy is controversial. A limited number of studies associate epileptiform discharges, mainly focal (frontal), with later epilepsy. The aim of the study was to identify possible predictors for recurrence or unprovoked seizures by studying the pathological EEG pattern depending on the time of recording, patient's age, location, type of abnormalities in patients with simple (SFS) and complex febrile seizures (CFS). A retrospective study, with an 1 year follow up, was conducted on 108 children with FS: 96 with SFS and 12 with CFS. For each subject 2 EEG recordings were performed: 48-72 hours and 21-28 days after the FS. 3 EEG patterns: normal, unspecific and epileptiform were recorded. The pathological EEG pattern was less present in the SFS group. For both FS groups the unspecific pattern was more prevalent in the early EEG and the epileptiform discharges in the late EEG. Early frontal epileptic discharges and temporal and parietal distribution of the unspecific pattern in the late EEG were associated with a higher recurrence risk. No recommendations could be made regarding epilepsy risk due to the small number of patients with later unprovoked seizures. The EEG recording could be considered a predictive factor for recurrence especially in association with other risk factors.

### INTRODUCTION

Febrile seizures (FS) are epileptic events facilitated by fever and age related (1 month -5 years) with a peak incidence at 1-2 years. FS are clinically classification in simple and complex FS. The simple febrile seizures (SFS) appear as a single episode in a 24 hours period in children without neurological or psychiatric abnormalities on examination, they last under 15 minutes, having a generalized aspect and do not associate postictal deficits. The complex febrile seizures (CFS) are characterized by one of the following features: 1. an over 15 minutes duration, 2. focal aspect or postictal deficit, 3. recurrence within 24 hours.(1,2,3) The interictal pathological EEG pattern is defined by two trace types 1. Unspecific characterized by amplitude or frequency asymmetry of the background trace, slow background, isolated and grouped slow waves, and 2. Epileptiform - with spikes, sharp waves, sharpwave complexes, polyspike-wave complexes.

The recurrence risk of FS depends on anamnesis and clinical factors (family history, age, temperature, focal character of the seizures) and it seems that also on the changes in the EEG pattern.(4.5,6.7)

Using the intercritical EEG recording to determine if any changes in the EEG patterns may be considered to be predictors for recurrence FS or for epilepsy is controversial.

There is little data in the literature that correlates epileptiform EEG discharges irrespective of the recording moment with later afebrile seizures.(8) Moreover some cases are described in the literature referring to relatives of patients with FS or epilepsy or even healthy individuals who may present an epileptiform EEG pattern.(9)

*The objective* of the study was to identify possible predictors for recurrence or for future seizures without fever by

studying the pathological pattern of the EEG depending on the time of registration, patient age, location, type of abnormalities, in patients with SFS, CFS and epilepsy.

## MATERIALS AND METHODS

We performed a retrospective study between October 2013-March 2016 in the Center for Research and Telemedicine of Pediatric Neurological Diseases in the Pediatric Hospital Sibiu, Romania resulting in a group of 108 children with FS (simple and complex) with ages in the range of 6 weeks and 4 years and 11 months. We applied the criterion of age as defined by the revised ILAE (International League of Epilepsy) definition, namely age range 1 month-5 years.(10) We excluded patients with central nervous system infections and preceding afebrile seizures. The retrospective study was approved by the Ethics Committee of the Hospital.

In the analysis of the database we found out that for each patient two EEG investigations in dynamics were conducted: first in the first 48-72 hours postictally (EEG1), the second 21-28 days after the seizure (EEG2). For all patients awake EEG was performed and on 40% of them natural sleep EEG recording was performed. The characterization of the study group was made on clinical criteria in: SFS and CFS, and in three groups according to the appearance of the EEG recording: a) a group with normal trace, b) a group with epileptiform abnormalities (spikes, sharp waves, spike-wave, polyspike-wave complexes) and c) a group with unspecific abnormalities (asymmetry in amplitude and frequency of the background trace, slow background trace, presence of isolated or grouped slow waves).

Recordings were performed using the equipment of the Department of Neurophysiology and of the Neurology

<sup>&</sup>lt;sup>1</sup>Corresponding author: Raluca Maria Costea, Str. Pompeiu Onofreiu, Nr. 2-4, Sibiu, România, E-mail: ralucacostea2004@yahoo.com, Phone: +4072 8981091 Article received on 07.11.2016 and accepted for publication on 05.12.2016 ACTA MEDICA TRANSILVANICA December 2016;21(4):22-26

Outpatient clinics.

From the database we selected only those patients whose follow up was conducted for a minimum of one year and with data about: the number, appearance of FS, type and location of EEG abnormalities and recurrence and association of afebrile seizures were recorded.

The data were generated from the digital library of the Pediatric Hospital Sibiu in Excel format. The resulting Excel file was processed using the data-mining software Rapid Miner. Data analysis was performed using SPSS software. We used decision trees and Chi-square test (categorical variables) to correlate the type of EEG abnormalities with the time of the recording (first or second EEG performed). To study the distribution of EEG abnormalities in relation to age, we used the Mann-Whitney test or T-type for the continuous variable. Dendrograms were used for the synoptic analysis of all involved parameters.(11,12)

#### RESULTS AND DISCUSSIONS

We will present, using the above mentioned statistical parameters, an initial characterization of the patient's groups with pathological EEG pattern (epileptiform or unspecific) for each CFS, SFS or both groups, depending on a number of variables: time of the EEG recording, patients' age and EEG abnormalities location. Later we will detail the applicability of the same variables and pathological EEG pattern as predictors for recurrence or epilepsy.

108 cases were identified, 96 children with SFS and 12 children with CFS (including 1 patient with febrile status epilepticus). By comparing the EEG appearance in the study group, 66 patients present with a normal EEG and 42 patients with an abnormal EEG trace. Regarding the abnormal pattern we distinguished 26 patients with unspecific pattern and 16 with epileptiform pattern.

- 1. Characterization of the study group:
- 1.1. Distribution by groups of cases studied:

After analyzing the distribution of the abnormal and normal EEG in the 2 groups of patients with SFS and CFS we have found out that all 12 patients with CFS had abnormalities on the EEG trace compared with only 30 children in the group of 96 patients with SFS (31%). Our results confirm some of the literature data, according to which EEG abnormalities are less frequent in the SFS patients when compared with CFC.(3) In antithesis are the data obtained by Maytal et al. which describe a similar rate of anomalies in the CFS compared to that of SFS subjects, but under the mention that in the study groups only children with normal neurological exam were included and that the interpreting results were based on a single EEG examination (in the first week postictally).(13,14,15,16) Currently available data in the literature are based on the postictal EEG recording made in the first month. Our results on a group of patients regardless of their neurological status converge with the recommendations of the other authors to value the EEG recording especially for CFS associated with other risk factors: atypical seizures, neurological abnormalities, extreme ages, suggestive family history.

Analyzing the two groups with pathological EEG pattern (epileptiform and unspecific) in relation to the clinical appearance of FS (SFS or CFS) we noticed in the patients with unspecific abnormalities that of the total 26 cases, 20 patients (76.9%) had SFS, as opposed to only 10 patients (62.5%) of the total of 16 with epileptiform abnormalities. Thereby there is a higher frequency of SFS in the group with unspecific EEG abnormalities (76.9%) compared with epileptiform EEG abnormalities (62.5%).

Under clinical aspect the most common type of

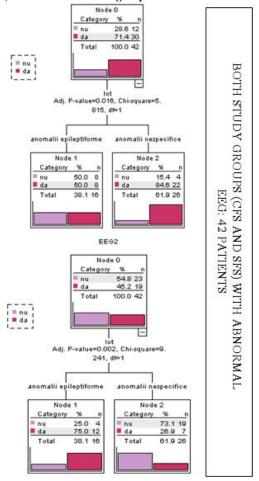
seizure in both groups with abnormal EEG pattern is the generalized tonic-clonic seizure (55%), which is mentioned in the literature as the most common type of FS.(17)

# **1.2.** Type of EEG abnormalities and time of recording (the first or the second EEG):

To determine whether the type of FS causes variability in the EEG appearance in dynamics we have modulated the pathological EEG pattern depending on the time of recording for the two distinct groups: SFS and CFs. Thus we noticed in patients with SFS associated with EEG abnormalities (both epileptic and unspecific) that 73.3% of the children had changes in the first EEG and only 43.3% in the second EEG, while in the case of CFS 66.7% of EEG abnormalities were recorded early compared to only 50% in late EEG. Although this pathological EEG pattern is recorded predominantly early for each FS group a characterization of the type of EEG abnormalities (epileptic or unspecific) is required to identify the best moment for the recording and to limit false results.

To highlight the type of EEG abnormalities (epileptic and unspecific) depending on the time of recording for both FS groups, we used decision trees. We found out that the unspecific abnormalities are more common in the early EEG (84.6%) than in the late one (26.9%), in antithesis to the epileptiform abnormalities that are found predominantly in the late EEG (75% versus 50%) (figure no. 1).

Figure no. 1. Prevalence of epileptiform or unspecific EEG pattern according to timing of EEG recording (early or late EEG) in both SFS and CFS groups



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We continued with a subanalysis of data to determine whether the distribution of EEG abnormalities (unspecific at early EEG and epileptiform at late EEG) is maintained for each separate group of FS or if there is variability in the appearance of EEG in dynamics in the context of a new parameter (FS type).

Thus in order to relieve the type of EEG abnormalities (epileptiform and unspecific) depending on the time of registration for the SFS group we used decision trees. The group of patients with SFS respects the association of unspecific abnormalities with the early EEG and of epileptiform abnormalities and late EEG: abnormal unspecific EEG early versus late (80% versus 25%) and epileptiform abnormalities in the late (80%) versus early EEG (50%).

For the CFS, we established predominant unspecific EEG abnormalities in the early versus late EEG (83.3% versus 33.3%) and predominant epileptiform abnormalities in the late (66.7%) versus early EEG (50%).

The results advocate for conducting EEG recordings after the first week postictally. Our data are consistent with studies of other authors. In a study that includes only patients with CFS Yucel describes a high incidence of pathological EEG pattern postictally in the first week.(15) Lennox-Buchthal, Kajitani et al. observed the rarity of the pathological EEG pattern in the first week after the FS.(18, 19) However, there are antithetical data that recommend the EEG in the first week after the seizure. Some authors describe in patients with CFS a higher frequency of all changes or for only the paroxysmal discharges in the first week postictally. In a study on 175 patients with CFS, Joshi et al. ascertain as a predictor for pathological pattern the EEG in the first week postictally.(13) In a group composed of 23 patients with CFS (63.9%) and 13 SFS (36.1%) Karimzadeh suggests that the timing of the EEG does not influence the EEG sleep pattern.(20) The results should be considered by regarding the type of the EEG recording used (pharmacologically induced sleep EEG), as the influence of Chloralhydrate and its metabolites on the EEG is not yet determined.(21, 22) The variability of the results derives from the studied seizure group (SFS, CFS or both) and from the type of EEG recording. The benefit of our results is that it is not mandatory to carry out the EEG recording early, so the access to this investigation is facilitated without limiting the value of the investigation.(13,14,15,16)

#### 1.3. Distribution of the EEG abnormalities related to age:

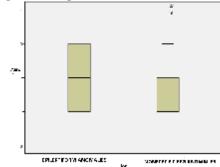
To examine the type of pathological EEG patterns (unspecific or epileptiform) depending on the age for the entire group of patients with FS (CFS and CFC) we resorted to the graphic below.

The study confirms a detection rate of epileptiform abnormalities which increases with age and a higher frequency of unspecific anomalies at younger ages.(23) The frequency of epileptiform discharges is 54.6% in children older than 2 years, and those of the unspecific abnormalities of 69.3% in children younger than 2 years.

As shown in figure no. 2, the median age for epileptiform abnormalities (M = 2, SD = 1.36) is greater than the average age in the case of unspecific anomalies (M = 1.31, SD = 1.1), tending statistical significance (p = 0.094).

The results are consistent with the data available in the literature according to which there is a limitation of the sensitivity of the EEG in unprovoked seizures under the age of 3 years, and a rare pattern detection rate of epileptiform at young ages.(19,20,24) Thus EEG recordings could prove useful especially at older ages (over age 3), when the frequency of FS should be falling. Further studies are required for larger groups of patients.

Figure no. 2. Median age in the groups with epileptiform and unspecific EEG pattern



**1.4. Distribution of EEG changes according to the age and location:** Regarding the **distribution of anomalies (not differentiated by the type of changes) to the age and location** we observed predominantly frontal localization in higher ages: 3-4 years (80%), 4-5 years (60%) but also in the old infant (62.5%) and parietal-occipital localization in the age group 1-3 years (70%) probably in correlation with the maturation and the defining brain activity (from posterior to anterior) processes.

**1.5. Distribution of EEG abnormalities compared to the timing of recording and location:** We initially evaluate the **pathological EEG (without distribution by type of pathological anomalies) depending on the location and the timing of the EEG** recording by using the decision tree. Thus in the early EEG prevail the frontal (53%), parietal (60%) and occipital (60%) changes, and in the late EEG the frontal (73%) and central (59%) anomalies. According to the literature the distribution of the anomalies is variable: generalized or focal spikes (75% frontal, rolandic 28.5%); central (55.6%) and temporal (16.7%), occipital asymmetric slowing or even missing elements like absence or generalized or occipital spikes are described.(14,19,25,26)

Starting from the previous parameters, but structuring the analysis on groups of patients with epileptiform or unspecific abnormalities we did not identify a statistically significant difference between the distribution of abnormalities in the early or late EEG: the predominantly parietal-occipital (77.3% vs. 76.9%, 77.3% vs. 80.8%) distribution of unspecific and front-central anomalies (87.5% vs. 93.8%, 37.5% vs. 50%) of epileptic discharges is maintained in dynamics (early and late EEG). The studies identified in the literature have not established a repeating pattern of distribution regarding the EEG changes: Lennox-Buchthal et al., Maytal et al. note in the early EEG route substantive slow asymmetric background predominantly occipital and parietal-occipital, Wo et al. note epileptiform discharges predominantly central spikes (55.6%), and Kanemura associates both early and late EEG with generalized epileptiform discharges of predominantly frontal (75%) focal discharges.(14,16,18) In the FEBSTAT study on inaugural febrile status epilepticus Nordli et al. locate both anomalies temporal - unspecific (background slowing) and epileptiform in the EEG performed within 72 hours postictally.(27)

#### 2. The risk or recurrence reported to EEG anomalies:

The role of the EEG pattern as predictor for recurrence in FS is under debate. Most studies could not correlate the pathological EEG pattern with the recurrent FS (28, 29, 30). Generally in a patient with a normal neurological exam, who presents with a first, short, generalized, unique epileptic event within 24 hours the presence of a pathological EEG determines a risk of recurrence of 41% in the first year and 56% over the next 3 years compared with 15% in the first year and 26% in the next 3 years if case of normal EEG.(31,32) We also discussed the predictive value for recurrence taking into account all parameters described in the section above: timing of the EEG recording and identified EEG abnormalities, finally achieving a synoptic analysis by: localization, type of EEG abnormalities and EEG recording time.

Regarding recurrence and time to identify EEG anomalies in both groups with pattern pathology, comparing the recurrence state in early EEG respectively the late one, we found that in 66.7% of cases abnormalities were identified in early recording, and in 60% of these cases they occurred in late EEG, without obtaining statistically significant difference. In relation to the types of EEG abnormalities: in 57.1% cases of recurrence epileptic discharges were identified at the early EEG and 85.7% in EEG late, and regarding unspecific changes 75% in the first EEG and 37.5 % in the late EEG.

In relation to the persistence of the EEG abnormalities in dynamics (early and late EEG) the paroxistic discharges are associated with an increased risk of recurrence (42.9% versus 11.1%). The results are consistent with the findings of other studies that recommend EEG reevaluation in patients with EEG abnormalities and other risk factors due to the future possible association with subsequent unprovoked seizures.(33,34) No statistically significant correlations have been established between persistent unspecific changes and FS recurrence.

In the group of patients with epileptiform pattern the dendrogram points towards an association: recurrence-central location (also frontal but less) of the EEG anomalies, late EEG. If in the group of patients with epileptiform pattern we do not find any similarity between variables: recurrence- temporal location, for the group with unspecific EEG abnormality there appears to be an association late EEG, central distribution of the abnormal pattern and recurrence.

In a synoptic analysis of all categories: location, EEG abnormalities type, timing of EEG recording and recurrence, by analyzing the dendrogram new prognostic factors are emerging but they will require a reevaluation on a more substantial patient group.

In the late EEG pattern changes (both epileptiform and unspecific ones) with central location are associated with a statistically significant increased risk of recurrence, similar to those with unspecific parietal or temporal location. In the early EEG the frontal epileptiform changes are associated with a higher recurrence risk (Figure 3 and Figure 4)

Figure no. 3. Synoptic analysis on the dendrogram: EEG, localization of EEG anomalies, recurrence links, epileptiform case

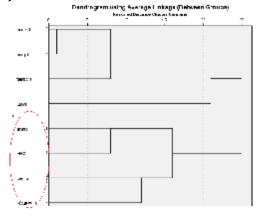
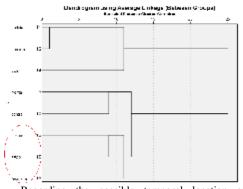


Figure no. 4. Synoptic analysis on the dendrogram: EEG, localization of EEG anomalies, recurrence links, unspecific case



Regarding the possible temporal location of the unspecific EEG changes as a risk factor for recurrence, the association of hippocampal sclerosis and secondary temporal epilepsy and FS history is known. Currently under discussion there are two assumptions: that hippocampal sclerosis could be implicated in the etiology of fever triggered seizures or a complication of the FS. The FEBSTAT study, a prospective, cohort study, which included patients with febrile status epilepticus without preexisting severe neurological abnormalities, reveals within 72 hours postictally unspecific abnormalities in the temporal derivations in 42.7% of the enrolled patients. These are confirmed by functional MRI imaging as markers of acute injury.(27,35,36,37) Therefore, correlating the findings of this study with the data previously obtained we could regard the persistent unspecific temporal EEG abnormalities as negative prognostic factors. A limited number of studies support in FS the predictive ability of epileptiform EEG pattern of epilepsy. In our study no recommendations could be made related to the EEG as a risk factor for epilepsy: only 3 patients associated an afebrile seizure during the 1 year follow up.

#### CONCLUSIONS

In conclusion, although the predictive value for recurrence and epilepsy EEG examination is not yet defined, this study makes a characterization of the EEG in FS with recommendations for possible risk factors for recurrence.

EEG abnormalities were identified more frequently in the CFS group compared to the SFS.

The study confirms that the detection rate of epileptiform abnormalities increases with age, and a higher frequency of unspecific anomalies at younger ages.

In cases of recurrence epileptic discharges were identified more common in late EEG, which would recommend performing the EEG recording in the  $4^{th}$  postictal week 4.

Starting from the correlations obtained in our study between the timing of the EEG, location and recurrence a reevaluation of these parameters on an expanded group of patients is required.

The EEG in patients with CFS can prove its usefulness in the presence of other risk factors, but integration into clinical context is required.

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