JICNA® | Journal of the International Child Neurology Association
A peer reviewed open access e-journal in Child Neurology

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ORIGINAL RESEARCH

Electrical Status Epilepticus in Sleep: Is this a Focal or Generalized Electroencephalographic Pattern?

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https://doi.org/10.17724/jicna.2020.152

Received: August 01, 2018
Accepted: December 10, 2020

Abstract

Objectives: To evaluate the spatial distribution of the epileptiform activity in electrical status epilepticus in sleep (ESES) and to correlate data from electroencephalograms (EEGs) with clinical and neuroimaging variables. **Methods:** From 2008 to 2015, ESES was detected in 162 reports (1%) from nearly 16,000 EEGs, from 23 patients. We selected one representative EEG per patient. Clinical data was collected retrospectively. Neuroimaging examinations were reviewed. The EEGs were classified as generalized ESES (ESESg) and focal ESES (ESESf) according to the predominant distribution of epileptiform discharges. **Results:** From the 23 patients, 5 were classified as ESESg and 18 as ESESf. In ESESf, focal epileptic discharges occurred most commonly in the centrotemporal regions. Abnormal neuroimaging occurred in 100% of the patients with ESESg and in 39% of the patients with ESESf (p=0.037). Other clinical data did not show significant differences between the groups. All patients with ESESg had structural abnormalities, with only 39% of patients with ESESf had structural etiology and the remaining 61% potentially genetic epilepsies of the rolandic spectrum. Conclusion: ESESg occurred predominantly in patients with structural lesions, while most patients with ESESf had normal neuroimaging scans and electrical dysfunction mainly in the rolandic region. **Significance:** ESESg seems to occur mostly in structural epilepsies. Distinctly, ESESf occurs in epileptic syndromes within the functional spectrum of rolandic epilepsy.

Keywords: electrical status epilepticus in sleep (ESES), continuous spike and wave during slow sleep (CSWS), Landau-Kleffner syndrome (LKS), rolandic epilepsy, EEG, epileptiform activity.

Highlights

- The focal pattern of ESES seems to be more frequent than the generalized pattern.
- Patients with generalised ESES usually have structural abnormalities, while most patients with focal ESES do not.
- Most patients who present with ESES have structural lesions or atypical rolandic epilepsy, including Landau-Kleffner syndrome.

Introduction

Since 1971, when Patry, Lyagoubi, and Tassinari first described six children with almost continuous epileptiform discharges during sleep, this electroencephalographic pattern has gained the interest of those studying childhood epilepsy [1]. The nomenclature is not uniform in the literature, but, in the present study, we use the term electrical status epilepticus in sleep (ESES) to describe this type of abnormality in the electroencephalogram (EEG) [2, 3]. The other entity, sometimes considered synonymous, is continuous spike and wave during slow sleep (CSWS) [4], which represents a clinical-electroencephalographic syndrome and constitutes an epileptic encephalopathy.

The ESES is usually described as a generalized [1, 2] or secondary bilateral synchronized pattern [3, 5] and little is reported about eventual focal characteristics of the continuous discharges in sleep [6, 7].

The ESES may occur in several conditions: structural epilepsies related to different etiologies, Landau-Kleffner syndrome, opercular syndrome caused by polymicrogyria, atypical evolution of benign childhood epilepsies, and CSWS [3].

Brain MRI is normal in several patients with ESES [8]. However, the presence of structural brain abnormalities may be found in up to 70% of ESES patients [9, 10].

The main aim of this study was to evaluate the spatial distribution of epileptiform activity in the EEG records of patients with ESES and the possible distinctive clinical and neuroimaging variable associated with different distributions of the epileptiform activity.

Methods

We analyzed the reports of 15,983 EEGs performed between 2008 and 2015 in the electroencephalography unit of Clinic Hospital of UNICAMP. All examinations were performed on 32-

channel Nihon Kohden digital devices. The electrodes were placed according to the 10-20 International System [11]. Among these, 162 exams (1.01%) had been performed in 23 patients who, at some point in their follow-up at the pediatric neurology outpatient clinic, presented ESES. An average of seven EEGs had been performed per patient, varying from two to 15 exams for each patient. Twenty-three assessments (one representative EEG per patient) were selected, according to the following inclusion criteria: i) the presence of continuous or almost continuous epileptiform discharges occupying more than 85% of the record during slow-wave sleep; ii) the presence of periods of sleep and wakefulness and a significant increase of the occurrence of spikes during the sleep period. There is no consensus on the methodology for calculating epileptic activity in sleep. In our study, the proportion greater than 85% of the epileptiform activity in the EEG during sleep was obtained by counting every page throughout the sleep pattern, arithmetically, and considering the number of seconds with at least one epileptiform discharge. Therefore, a spike percentage was calculated as the average of seconds with spikes per page (10 seconds). Two independent neurophysiologists reviewed each EEG.

The EEG data were analyzed and divided into two groups: one comprising EEGs with a predominance of generalized epileptiform discharges that occurred in more than 85% of the sleep record, named generalized ESES (ESESg) (Figure 1).

A second group comprised EEGs with a predominance of focal epileptiform discharges that occurred in more than 85% of the recording in sleep, named focal ESES (ESESf) (Figure 2). Focal epileptiform discharges usually present with phase reversals mostly on the centrotemporal areas as shown on Figure 2.

The EEGs were categorized as generalized or focal following the predominance of the distribution of the epileptiform discharges. We classified the spikes as focal or generalized on the basis of the sleep tracing without considering the wakefulness period.

All patients had their records analyzed and clinical and neuroimaging data was collected retrospectively. Clinical information included: seizure semiology (type and frequency of seizures); behavioral changes; drop in school performance; neurocognitive changes; motor neurological deterioration and epilepsy syndrome. Neuroimaging data were collected from the charts; whenever possible, examinations were reviewed.

The two EEG groups were compared using Mann-Whitney or Fisher exact tests. Logistic regression and stepwise multiple analysis were used as appropriate. All tests were performed with a significance level of $p<0.05$.

The Institutional Review Board of UNICAMP approved the present study.

Results

From the 23 patients included, 57% were male and 43% were female, with mean age of 6.3 years (ranging from 3.5 to 11 years) at the time of the EEG exam. Mean age of epilepsy onset was 32.8 months (ranging from 1 to 96 months).

Two groups were identified: 5 patients with predominance of generalized epileptiform discharges in the EEG (ESESg); and 18 patients with a predominance of focal epileptiform discharges (ESESf). There was no difference of sex distribution (p= 1.00), age at the time of the EEG exam (p=1.00) and age of epilepsy onset (p=0.65) between ESESg and ESESf. Focal epileptiform activity occurred predominantly in the central region in seven patients with focal discharges. Discharges were also observed in the frontal, parietal, temporal and occipital regions.

Table 1. Clinical characteristics of patients with ESES.

	ESESg	ESESf	Total	p-Value
Number of patients	5	18	23	
Focal epileptic seizures	4 (80.0%)	12 (66.8%)	16 (69.6%)	1.00
Daily frequency	3 (60.0%)	5 (27.8%)	8 (34.8%)	0.30

ESESg: generalized electrical status epilepticus in sleep
ESESf: focal electrical status epilepticus in sleep

Table 2. Distribution of neurological abnormalities before and after ESES.

	ESESg	ESESf	Total	p-Value
Behavioral change	3/5 (60%)	12/18 (67%)	15/23 (65%)	1.00
Drop in school performance	1/2 (50%)	5/13 (39%)	6'15 (40)%	1.00
Neurological exam change: neurocognitive	5 (100%)	16 (89%)	21 (91%)	1.00
Neurological exam change: motor	3 (60%)	9 (50%)	12 (52%)	1.00

ESESg: generalized electrical status epilepticus in sleep
ESESf: focal electrical status epilepticus in sleep

The details of the epileptic seizures can be seen in Table 1. There was no statistical difference between the two groups. The results of behavioral change and drop in school performance did not show any statistical difference between the two groups (Table 2). Neurocognitive and motor changes are also shown in Table 2. There was no statistical difference between the two groups either. Deterioration of neurocognitive and/or motor neurological status associated with ESES was observed in 91% of the patients.

Neuroimaging abnormalities were present in 100% of the patients with ESESg and in 39% of the patients with ESESf. The difference between the two groups was statistically significant (Table 3).

Out of our 12 patients who had abnormalities in neuroimaging examation, nine had malformations of cortical development and three presented with changes compatible with pre- and perinatal vascular insults. Only three patients had focal structural abnormalities (one patient had gliosis on the left temporal region; one had polymicrogyria on the right cerebral hemisphere; and, one had right frontal focal cortical dysplasia). All other nine patients had bilateral abnormalities.

Figure 1. The figure shows a sample of an EEG with the generalized pattern of electrical status epilepticus in sleep (ESES).

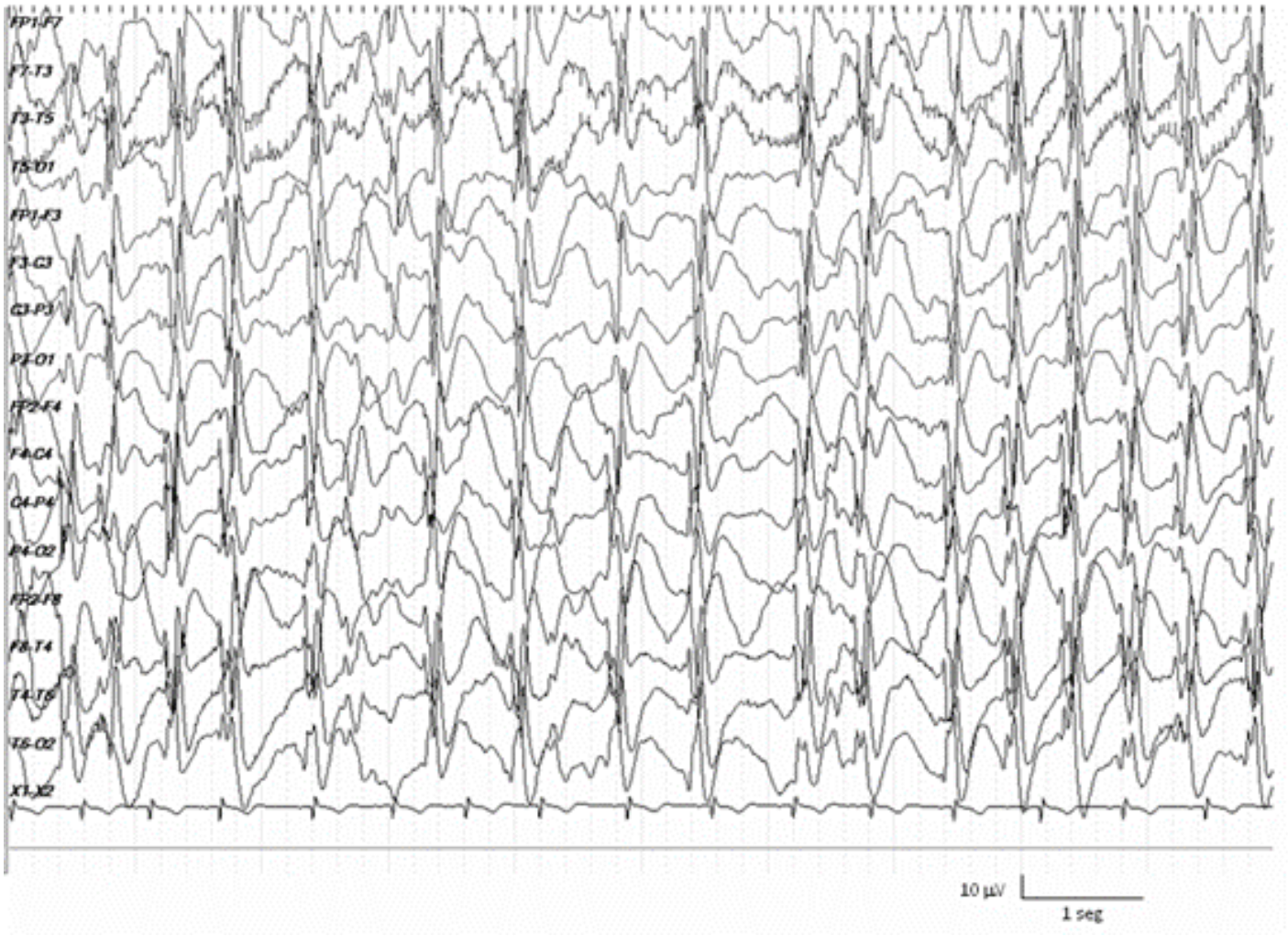


Table 3. Occurrence of abnormalities in the neuroimaging examination.

Neuroimaging abnormalities	ESESg	ESESf	Total	p-Value
No	0 (0%)	11 (61%)	11 (48%)	
Yes	5 (100%)	7 (39%)	12 (52%)	**0.037**
Total	5	18	23	

ESESg: generalized electrical status epilepticus in sleep
ESESf: focal electrical status epilepticus in sleep

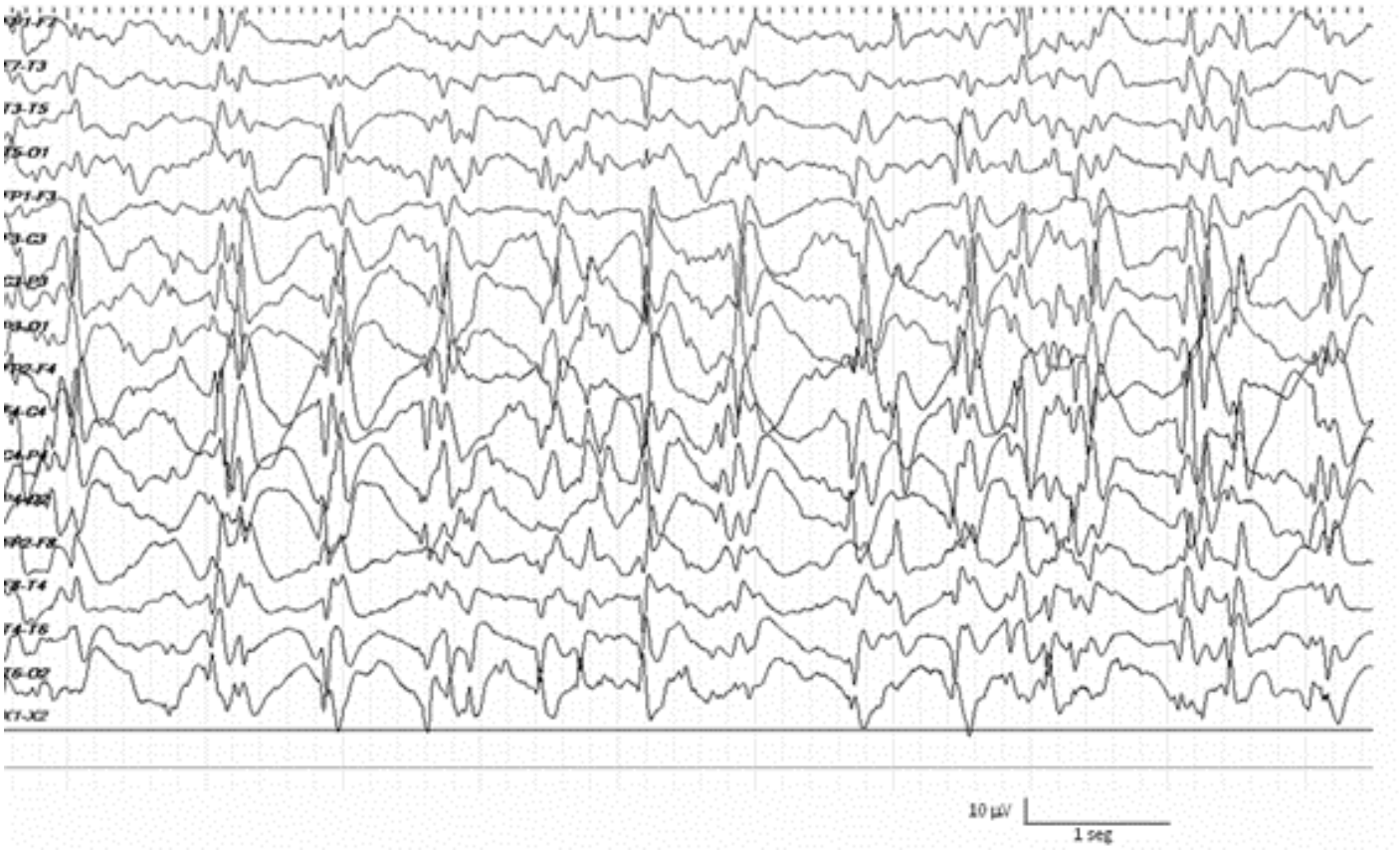
Regarding epileptic syndromes, 12 patients were classified as having structural epilepsies (8 had malformations of cortical development and 4 had abnormalities compatible with perinatal vascular insults), 8 patients were classified as having rolandic epilepsy with atypical evolution, 2 with Landau-Kleffner syndrome and 1 with CSWS syndrome. All patients with ESESg had structural etiology, while only 39% of patients with ESESf had structural etiology and the remaining 61% potentially genetic epilepsies of the rolandic spectrum.

Discussion

In this study, we observed a frequency of ESES in 1% of the routine EEGs performed between 2008 and 2015 in a tertiary epilepsy center. The figures are similar to other studies, which show ESES in 0.5 to 1% of all EEGs performed in tertiary centers [2, 10, 12, 13].

The classification of ESES into generalized and focal is not commonly reported. This dichotomy between focal or generalized pattern might, however, improve our understanding of spike generation and sleep potentiation in these patients. Some studies superficially point to the possibility of some focalization in ESES [2, 3, 12, 14]. Only Fernández et al. [6] used a similar classification to ours, but in their study the definition for ESES was broader, including individuals with epileptic discharges in more than 50% of the slow wave sleep. Differently, we only included patients with the classic definition of epileptic discharges in more than 85% of the slow wave sleep. Despite of that, our findings were similar, showing that the majority of patients with ESES present a focal pattern.

Figure 2. The figure shows a sample of an EEG with the focal pattern of electrical status epilepticus in sleep (ESES); observe the phase reversals seen in the centrotemporal regions.



Also similar to the previous report, we did not observe differences of the clinical profile of patients with focal or generalized ESES, including type and frequency of the seizures, drop in school performance, behavioral changes and motor or neurocognitive deterioration [6].

Distinctively, in our study, the presence of neuroimaging abnormalities was more common in the group with generalized ESES pattern. Interestingly, neuroimaging abnormalities were observed in all patients with generalized ESES pattern and in only 39% of those with focal ESES pattern. Out of our patients who had abnormalities in neuroimaging exams, most had malformations of cortical development and only four presented with alterations compatible with pre- and perinatal vascular insults. These findings diverge from the data from other studies in which up to 70-80% of neuroimaging abnormalities were correlated with pre- or perinatal vascular insults [8, 15, 16, 17, 18]. This difference between our findings and data from other studies can be explained by the fact that our sample was taken from a tertiary hospital, which is a referral hospital for epilepsy surgery, therefore having a bias in patient referral.

Extensive pre- and perinatal vascular insults can compromise the thalamus and the thalamic lesion in an early age may justify, at least in part, the association of structural lesions with ESESg [18]. The International League Against Epilepsy (ILAE) reports that generalized seizures can start at one point in any neural network but quickly involve bilaterally distributed neuronal networks [4]. It is known that the generalization of epileptiform discharges results from impairment of neural circuits involving the thalamus [17]. Other studies also support the idea that thalamic involvement is important in the generalization of epileptiform discharges [5, 8, 9, 15, 17, 18].

On the other hand, most patients with a focal pattern of ESES presented with normal neuroimaging examinations. Also, in the focal ESES group, most patients had epileptiform discharges in the central region. These findings suggest that the origin of ESES in these patients depends on electrical dysfunction of the rolandic areas. Indeed, all patients with focal ESES pattern and normal neuroimaging exams had the diagnosis of an epileptic syndrome in the spectrum of rolandic epilepsies, including atypical evolution of benign childhood epilepsy with centrotemporal spikes, Landau-Kleffner syndrome and CSWS [19]. This report of epileptic syndromes associated with ESES was reported by Veggiotti et al. [20]. The authors studied 32 patients and 47% had a symptomatic/structural etiology, without specifying what type of insult, 31% had classical CSWS, 13% had Landau-Kleffner syndrome and 9% had opercular syndrome (perisylvian polymicrogyria).

Our study differs from the one by Fortini et al. [21] where authors reported 21 patients with hemi-status epilepticus and unilateral lesions. Only three of our patients had unilateral lesions.

Still, one of them had ESESg. The numbers are too small to draw any conclusion. The same group published another study conducted with 17 patients [22] and coined the term "unusual EEG patterns" or "variants of ESES syndrome" when focal EEG abnormalities were seen. Focal ESES may be seen both in structural and non-structural cases; however, our findings showed that this unusual focal ESES, particularly when the focality is found on the central regions, is mostly correlated with epilepsies of the rolandic spectrum. To the best of our knowledge, this has not been described before.

This study has some limitations. We found no statistical difference between the two groups, probably due to the limited size of our sample, despite having reviewed almost 16,000 reports. In conclusion, the focal pattern of ESES appears to be more frequent than the generalized pattern. Most patients with ESESf had normal neuroimaging while patients with ESESg presented with structural abnormalities on neuroimaging examinations. Finally, our data showed that ESES occurred more frequently in patients with structural lesions and in those with atypical rolandic epilepsy. Landau-Kleffner syndrome and CSWS were less frequent.

Competing interests

None.

Cite this article as:
Almeida, R.R. *et al*. (2020). Electrical Status Epilepticus in Sleep: Is this a Focal or Generalized Electroencephalographic Pattern? Journal of the International Child Neurology Association, 20(1). https://doi.org/10.17724/jicna.2020.152

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