Research Paper: Sleep-Related Seizures in Refractory Focal Epilepsy: Electroclinical Findings and Surgical Outcome

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ABSTRACT

Background: Sleep Seizures (SSs) generally occur in refractory focal epilepsy, but their detailed characteristics and circadian patterns are still controversial. The effect of SSs on epilepsy surgery outcome has been addressed in few studies without definitive prognostic value.

Objectives: This study investigated the characteristics of SSs and their prognosis in refractory focal epilepsy.

Materials & Methods: This retrospective cross-sectional study was conducted in the referral epilepsy center in Isfahan, Iran from 2011 to 2015. It investigated SSs in patients with refractory focal epilepsy who underwent pre-operative evaluation. Demographic data, electroclinical findings, pathology, and postsurgical outcomes were analyzed and compared to Wake Seizures (WSs). Before the main analysis, Shapiro-Wilk test of normality was performed. Then the Independent sample t test, Chi-square test, Fisher's exact test, Mann-Whitney U test and 1-way ANOVA were used to analyze the obtained data in SPSS. All probability tests were two-tailed and the level of significance was defined as P≤0.05.

Results: A total of 371 seizures in 113 patients were studied. The sleep/wake seizure ratio in Temporal Lobe Epilepsy (TLE) and Extratemporal Lobe Epilepsy (ETLE) were 0.54 and 0.91, respectively. The peak incidence of SSs in TLE and ETLE were during 4.00 to 8.00 and 0.00 to 4.00, respectively. SSs were considerably associated with EEG changes before clinical signs. Ictal EEG localization was more successful in SSs of extratemporal origin. Based on pathology findings, Focal Cortical Dysplasia (FCD) was highly associated with SSs. Left epileptogenic zone and FCD accompanied a less favorable outcome in SSs.

Conclusion: SSs are significantly more frequent in patients with ETLE and follow specific circadian patterns based on epileptogenic zone. Seizure semiology and EEG findings are in favor of more localized onset of epileptic activity in SSs of extratemporal origin. The side of epileptogenic zone, circadian pattern of seizures, well-defined epileptogenic lesion in MRI and pathology, could affect postsurgical outcomes in SSs.

Keywords: Circadian rhythm, Sleep, Epilepsy
Introduction

The interaction between sleep and epilepsy is abstruse and complicated. Sleep-related seizures accompany certain epileptic syndromes and nonsyndromic focal and generalized epilepsies. Sleep influences onset, frequency, and semiology of seizures. It also has a pronounced effect on Electroencephalographic (EEG) findings of epileptic patients [1]. Interictal epileptiform discharges have an increased frequency in non-rapid eye movement sleep in focal and generalized epilepsies and most Sleep Seizures (SS) occur in this stage [2].

Studies suggest that mechanisms like loss of inhibitions and thalamocortical facilitation are responsible for propagation of epileptiform activity leading to clinical seizures with or without secondary generalization [3]. Studies that compared SS in various types of focal epilepsy have reported differences in the stage of seizure onset, the distribution of seizures in sleep/wake state, rate of secondary generalization and etiology [4-6]. Furthermore, it has been postulated that circadian rhythm strongly affects the incidence of various seizure types. There are certain differences in circadian patterns between generalized epilepsy syndromes like Juvenile Myoclonic Epilepsy and focal epilepsies [7, 8].

The results are also different and controversial in various subtypes of focal epilepsy [7, 9]. Sleep-onset seizures may also affect the prognosis of epilepsy surgery. But limited studies specifically investigated the prognostic value of SS in postsurgical outcome. Considering the insufficient data, this comprehensive study was conducted to analyze SS recorded in a long-term video-EEG monitoring of patients with drug-resistant Temporal Lobe Epilepsy (TLE) and Extratemporal Lobe Epilepsy (ETLE). We investigated the time of onset, circadian pattern, clinical characteristics, EEG findings, pathology and surgical outcome of SSs and compared them with Wake Seizures (WSs).

Materials and Methods

Study patients

This retrospective cohort study was conducted at the Epilepsy Surgery Center in University Hospital of Isfahan Medical School, Iran, from 2011 to 2015. We searched the relevant database and enrolled the adult patients with medically refractory, including TLE and ETLE who were admitted for pre-operative evaluation and consequently underwent epilepsy surgery. We included adult patients (>18 y) who their Seizure Onset Zone (SOZ) was specified during noninvasive long-term video-EEG monitoring and had MRI lesion relevant to SOZ. They were followed for at least 1 year after epilepsy surgery. Patients with more than one lesion in MRI, prior epilepsy surgery and inadequate data were excluded from the study.
Data collection

We collected patients’ data including age, gender, hand- edness, marital state, age of seizure onset, seizure semi- ology and frequency, Antiepileptic Drugs (AEDs), risk factors for epilepsy, family history, irritative zone, preop- erative MRI findings, type and side of surgery, and patho- logical findings of the patients in their medical records.

Video-EEG analysis

We retrospectively reviewed recorded data of 113 pa- tients with 371 reported seizures. Patients had prolonged scalp EEG monitoring using Nihon Kohden system. Electrodes were arranged according to the international 10–20 system with additional temporal electrodes (F9, F10, T9, T10, T1, T2). The sampling rate was set at 200 Hz, 0.1 s time constant and 60 Hz notch filter. We analyzed all recorded cases of less than 10 seizures in every patient. Otherwise, we considered the first 10 appropriate ones. The incidence of seizures was evaluated during sleep/wake state, every 4 hours at 24-hour intervals. Patients with seizures occurring exclusively during sleep were determined and investigated separately. We used a classification based on seizure semiology [10].

Ictal rhythms were studied in longitudinal bipolar and referential montages with common filtration (LLF 1 Hz, HLF 70 Hz). During the evaluation, digital filtering and gain were adjusted to improve the EEG display. The interval between clinical manifestations and ictal EEG onset, morphology, and the side and location of ictal discharges during seizures were studied in detail. We also noted the duration of seizure, incidence and the time of ipsilateral and contralateral propagation of epileptic discharges.

Surgical outcomes

Post-operative outcomes were classified as good and poor. The good outcome was defined as per class I of Engel outcome scale [11] and poor outcome was de- termined as per classes II-IV. We collected the results of 1-year follow-up from the records of post-operative outpatient visits.

Statistical analysis

Statistical analysis was performed using SPSS. Con- tinuous variables were presented as Mean±SD. Quali- tative variables were reported as number (percentage). Shapiro-Wilk test of normality was performed, before conducting the main analysis. The Independent sample t test, Chi-square test, Fisher’s exact test, Mann-Whit- ney U test, and 1-way ANOVA were used. All probabili- ty tests were two-tailed and the level of significance was defined as P≤0.05.

Results

Patients’ characteristics are presented in Table 1.

General findings

There was no differences between the patients with SSs and others, in terms of sex, handedness, marital status, age of disease onset, duration of the disease, seizure frequency, AED number, and risk factors for the disease. Positive family history of epilepsy was significantly higher in TLE patients with exclusive WSs (P=0.008).

Clinical seizure data

A total of 139 seizures (106 TLE, 33 ETLE) occurred during sleep and 232 seizures (196 TLE, 36 ETLE) were recorded in wakefulness. The sleep/wake seizure ratio in TLE and ETLE were 0.54 and 0.91, respectively and SSs were significantly more frequent in ETLE in comparison with TLE (P=0.04).

The overall peak incidence of seizures in patient with TLE was at 8.00-12.00. However, in ETLE the peak incidence was 0.00 to 4.00 for FLE, 8.00 to 20.00 for PLE and 12.00-16.00 for OLE. The most frequent time of SSs in TLE was 4.00 to 8.00 interval followed by 8.00-12.00, 0.00 to 4.00, 12.00 to 16.00, 16.00 to 20.00 and 20.00 to 24.00. In ETLE, SSs more frequently occurred at 0.00 to 4.00, followed by 4.00 to 8.00, 12.00 to 16.00, 20.00 to 24.00, 8.00 to 12.00 and 16.00 to 20.00. WSs in TLE more frequently occurred at 12.00 to 20.00 interval (12.00 to 16.00 and 16.00 to 20.00 with similar frequency). In ETLE, the most frequent time for WSs was 8.00 to 12.00 followed by 16.00 to 20.00.

Although not statistically significant, in TLE, automo- tor and simple motor seizures were more frequent in WSs and dialeptic semiology and hypermotor semiology had a higher frequency during sleep. Nevertheless, the most frequent semiology was automotor in both daytime (8.00 to 20.00) and nighttime (20.00 to 8.00) seizures. SSs were more frequently associated with simple motor and hypermotor features and the most frequent semiology in daytime and nighttime seizures were detected as automotor and simple motor, respectively in ETLE. The most prevalent semiology in Frontal Lobe Epilepsy (FLE) was simple motor (40.9%), but automotor semiol-
Table 1. Study patients’ characteristics

<table>
<thead>
<tr>
<th>Variables</th>
<th>Quantity</th>
</tr>
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<tbody>
<tr>
<td>Gender: Male/Female (%)</td>
<td>54/46</td>
</tr>
<tr>
<td>Handedness: R/L (%)</td>
<td>90.3/9.7</td>
</tr>
<tr>
<td>Marital status: Single/Married (%)</td>
<td>62.8/37.2</td>
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<tr>
<td>Age of surgery, y</td>
<td>28.3±8.4</td>
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<tr>
<td>Age of disease onset, y</td>
<td>10.5±8.1</td>
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<tr>
<td>Seizure frequency</td>
<td></td>
</tr>
<tr>
<td>Daily</td>
<td>24(21.2)</td>
</tr>
<tr>
<td>Weekly</td>
<td>66(58.4)</td>
</tr>
<tr>
<td>Monthly</td>
<td>15(13.3)</td>
</tr>
<tr>
<td>Seasonal</td>
<td>8(7.1)</td>
</tr>
<tr>
<td>Epilepsy duration, y</td>
<td>17.9±10.4</td>
</tr>
<tr>
<td>No. of AEDs</td>
<td>2.7±1.1</td>
</tr>
<tr>
<td>Perinatal complication</td>
<td>11(9.7)</td>
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<tr>
<td>Febrile convulsion</td>
<td>31(27.4)</td>
</tr>
<tr>
<td>CNS infection</td>
<td>4(3.5)</td>
</tr>
<tr>
<td>Developmental delay</td>
<td>7(6.2)</td>
</tr>
<tr>
<td>Head trauma</td>
<td>30(26.5)</td>
</tr>
<tr>
<td>Family history: +/- (%)</td>
<td>9.7/90.3</td>
</tr>
<tr>
<td>TLE (%): Right/Left (No.)</td>
<td>78.8; 44/49</td>
</tr>
<tr>
<td>ETLE (%): Right/Left (No.)</td>
<td>16.9; 9/11</td>
</tr>
<tr>
<td>Seizure type</td>
<td></td>
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<tr>
<td>Frontal</td>
<td>14 (70%)</td>
</tr>
<tr>
<td>Parietal</td>
<td>5 (25%)</td>
</tr>
<tr>
<td>Occipital</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Sleep/Wake seizures (TLE/ETLE)</td>
<td></td>
</tr>
<tr>
<td>100% sleep</td>
<td>17(18.3)/4(20)</td>
</tr>
<tr>
<td>100% wake</td>
<td>40(43)/6(30)</td>
</tr>
<tr>
<td>Both sleep and wake</td>
<td>36(38.7)/10(50)</td>
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<tr>
<td>Pathological findings</td>
<td></td>
</tr>
<tr>
<td>MTS</td>
<td>65(57.5)</td>
</tr>
<tr>
<td>Tumor</td>
<td>22(19.5)</td>
</tr>
<tr>
<td>Gliosis</td>
<td>19(16.8)</td>
</tr>
<tr>
<td>FCD</td>
<td>4(3.5)</td>
</tr>
<tr>
<td>CA</td>
<td>3(2.7)</td>
</tr>
<tr>
<td>Engel’s surgical outcome</td>
<td></td>
</tr>
<tr>
<td>Engel I (good)</td>
<td>98 (87.5)</td>
</tr>
<tr>
<td>Engel II, III, IV (poor)</td>
<td>14 (12.5), 1 death</td>
</tr>
</tbody>
</table>

Data are presented as percentage, number (%), or Mean±SD. Abbreviations: AEDs: Antiepileptic Drugs; TLE: Temporal Lobe Epilepsy; ETLE: Extratemporal Lobe Epilepsy; MTS: Mesial Temporal Sclerosis; FCD: Focal Cortical Dysplasia; CA: Cavernous Angioma.
ogy was observed in most recorded seizures of Parietal Lobe Epilepsy (PLE) (70.6%) and all seizures of Occipital Lobe Epilepsy (OLE) patients. Aura was present in 14.9% of seizures and was significantly accompanied by WSs (P<0.0001). Secondary generalized seizures (13.7%) occurred more often during SSs in all patients (P=0.12). More data are presented in Tables 2 and 3.

Ictal EEG findings

Ictal EEG findings in TLE patients showed that in comparison to WSs, in a significantly higher number of SSs, EEG changes could be detected earlier than clinical signs but the mean duration of interval was not significantly different in sleep and wakefulness. Similar but less considerable results were found in ETLE (P=0.16). Median duration of SSs in ETLE (49, range:10-556) was shorter than TLE (69, range:7-306) but no considerable differences existed between sleep and wake seizures.

Regardless of sleep/wake state, RT was the most frequent initial ictal pattern in TLE. However, other rhythms including fast activity seizures, rhythmic alpha and background attenuation had more significant pres-
Ipsilateral propagation of ictal EEG patterns was detected in all SSs in comparison with 95.4% and 71.4% of WSs in TLE and ETLE, respectively. Contralateral propagation was also more frequent in SSs (97.5% vs. 93.6% in TLE and 93.8% vs. 75% in ETLE). Detailed results are presented in Tables 2 and 3.

Pathology and postoperative outcome

Seizures induced by underlying tumors, Mesial Temporal Sclerosis (MTS) and cavernous angioma had a
higher prevalence in WSs. SSs were more frequently accompanied with gliosis and Focal Cortical Dysplasia (FCD). All FCD-induced seizures in ETLE and 86.6% of total seizures in patients with FCD occurred at sleep (P=0.01 and P=0.001, respectively). Automotor was the most frequent semiology accompanied with MTS and cavernous angioma in both sleep and wakefulness. Automotor seizures were more frequent in wakefulness in tumors and gliosis, and dialeptic semiology was frequently seen during sleep. However, the most frequent semiology was simple motor seizures in FCDs.

No correlation was found between the surgery outcome and age of onset, age of surgery, sex, the duration of disease or seizure frequency, neither in patients with exclusive SS, nor in those with both sleep/wake seizures. Patients who took 3 or less AEDs experienced a more favorable outcome (P=0.02 in patients with WSs and P=0.09 in others).

Prognostic factors of postsurgical outcome are demonstrated in Table 4. The worst outcome according to pathology was associated with FCD (46.2% favorable outcome in comparison to at least 85% in other pathologies), but the finding was not statistically significant due to small number. Independent of epileptogenic zone, patients with SSs had a more favorable postsurgical outcome (90.9% vs.82.6% in those with WSs), but the difference was not statistically significant.

**Discussion**

The present retrospective cohort study investigated seizures occurring during sleep and wakefulness in patients with refractory TLE and ETLE. We reviewed their electroclinical findings and pathology and recorded the outcomes of their 1-year follow-up.

**General findings**

No significant differences were observed between the characteristics of patients with and without SSs. The only exception was the higher positive family history of epilepsy in TLE patients with WSs which is in concordance with the study by Bernasconi and associates [12]. Obviously, this correlation did not exist in ETLE, because our patients were all MRI positive with non-inherited pathologies.
Circadian rhythm

Recent studies on the time of seizure onset in focal epilepsies indicated that seizures occur in a non-random fashion and circadian rhythm may play a role in this regard [7, 9, 13, 14] but their results are somewhat controversial.

Pavlova et al. in their study on day and night pattern of seizures reported that seizures of temporal lobe origin more frequently occurred during daytime with a peak from 15.00 to 19.00 [7]. Durazzo et al. also found bimodal occurrence in temporal lobe seizures with the primary peak in the late afternoon between 16:00 and 19:00 and secondary peak in the morning between 7:00 and 10:00 [9]. In contrast, Hofstra et al. reported its peak incidence in 11.00 to 17.00 [14]. Most of seizures in our TLE patients occurred at 8.00 to 12.00, closely followed by 12.00 to 16.00, which is somehow in concordance with the second peak mentioned by Durazzo et al. and the study by Hofstra et al. [9, 14].

Results of investigations on extratemporal lobe seizures have shown a total peak incidence of 19.00 to 23.00 [7]. In a more detailed study, the highest seizure onset was reported in 4.00 to 7.00 for FLE and PLE and 16.00 to 19.00 for OLE [9]. In another study by Hofstra et al. frontal seizures were seen mostly between 23:00 and 5:00 [14]. In line with the study by Hofstra et al., our results showed more frequent onset of seizures in 0.00 to 4.00 for FLE patients. However, PLE patients of the current study had a uniform distribution of seizures during daytime (8.00 to 20.00) and the peak incidence for OLE was at 12.00 to 16.00.

In accordance with previous studies, the incidence of SSs in FLE was significantly higher than TLE patients in our survey [5-7, 15]. Our findings indicated that SSs had different distributions during night in TLE and FLE, as most of SSs with frontal lobe origin occurred in 0.00 to 4.00, while the peak incidence of SSs in TLE was detected at 4.00 to 8.00. Although most studies on the circadian rhythm of TLE have reported peak frequencies at late morning and afternoon, the detailed data for SSs were disregarded [7, 9, 14]. In a recent study on circadian rhythm of patients with TLE after epilepsy surgery [16], seizures are reported to be more frequent at 6.00 to 8.00 and 15.00 to 17.00.

Although the authors did not indicate the peak for SSs separately, the possible role of human arousal mechanisms in seizure occurrence of mesial TLE were suggested to explain the early morning peak, from which it can be inferred that the morning peak is related to SSs. Our results regarding peak frequency of SSs in FLE were in agreement with previous studies [14, 17]; however, reports of more delayed peak also exist [9].

Electroclinical findings

Previous findings have suggested that the hypersynchrony during sleep facilitates both initiation and propagation of partial seizures and promotes secondary generalization in temporal and occipitoparietal but not frontal seizures [4, 5, 18, 19].

Although not statistically significant, we found such relation between SSs and secondary generalization in our patients but no difference between FLE and other types in this regard. In agreement with this finding, the contralateral propagation of ictal discharges was also more frequent in all reviewed SSs. Despite the nonsignificant higher incidence of secondary generalized seizures in SSs of study FLE patients, 2 of our findings were compatible with more focal onset of SSs in FLE. First, simple motor and hypermotor seizures which are often semiologically attributed to frontal lobe origin were more frequent during SSs. In contrast, clinical signs indicative of propagation of ictal discharges (e.g. automotor semiology with temporal type automatisms) were more frequent during WSs. In addition, localization by initial ictal EEG pattern was significantly more possible in frontal lobe seizures that occurred during sleep.

Pathology and postoperative outcome

In a study by Losurdo et al. on patients with refractory focal sleep-related epilepsy and a follow-up of at least 2 years, favorable outcomes were achieved in 76.8% of patients [20]. Another study by Nobili et al. on nocturnal FLE showed similar outcomes (76% Engel class I). The favorable outcome of our study is somehow higher due to the presence of MRI visible epileptogenic lesion as an inclusion criterion [21].

Only few studies have specifically investigated post-operative outcome in SS in spite of the lobe of origin. Suggested prognostic factors associated with a favorable outcome are disregarded in stereo-EEG investigations, positive MRI, complete removal of the epileptogenic zone, and the presence of FCD type II and FCD type IIb [20-22]. Despite the precise investigation of patients’ characteristics, ictal EEG and clinical findings in SSs and comparing findings altogether and separately in patients with exclusive SS, as well as those with both SSs and WSs and merely WSs, only 2 prognostic factors for post-operative outcomes were detected in the present
The first favorable outcome was the occurrence of SSs during 4.00-8.00 in TLE. In contrast, those TLE patients who experienced SSs during 12.00 to 16.00 interval had the worst prognosis (only 33.3% had favorable outcomes). No relationship was found between the time of onset and outcomes in the study ETLE patients.

The second prognostic factor was the side of epileptogenic zone. Left epileptogenic zone was considerably frequent in the right-handed patients of the study and vice versa (not statistically proved due to the small number of left-handed patients). Our data indicated that seizures with left side origin were associated with less favorable outcomes, independent of epileptogenic lobe or pathology which both had a normal distribution between patients. Goel et al. [6] compared sleep and wake seizures and indicated left-side epileptogenic lesion as a predisposing factor for sleep seizures. Studies lacked investigating the relationship between the side of epileptogenic zone and surgical outcomes in SSs.

FCDs were the most frequent histopathological findings in sleep-related seizures [20, 22, 23]. In line with previous studies, we found FCD to be highly associated with SSs. Contrary to FCD type I [24], Taylor-type FCDs often carry a favorable prognosis [22]; however, the worst outcome was seen in FCD in our study. This finding can be explained by 2 main reasons. First, with targeting the precise boundaries of dysplasia that makes its complete resection more probable, invasive monitoring is generally recommended in FCD cases, which was not performed in any studied patient. Second, detailed pathological evaluation was not prepared for the study cases in order to determine FCD types. Therefore, poor outcome in our FCD cases could be due to the lack of invasive monitoring and possible presence of FCD type I pathology.

Since polysomnography was not performed in this study, we could not investigate the correlation between seizures and sleep stages. Furthermore, small number of our ETLE patients limited the statistical interpretation of data in a few cases. The results of this study could be applied to patients with drug-resistant focal epilepsy with visible epileptogenic lesion in MRI and not to all types of sleep seizures.

Conclusion

Focal epilepsies have specific circadian patterns which according to the controversial results of related studies, should be investigated in a larger number of patients in sleep and wakefulness, taking interventional factors into account.

We believe that in comparison to WSs, semiology of SSs in TLE shows more clinical signs in favor of epileptic discharge propagation. While in FLE, semiology of SSs is indicative of a more focal phenomenon. According to this study, different types of pathology cause various clinical signs in sleep and wake seizures, especially FCD is markedly associated with SSs. Non-dominant side of epileptogenic zone and well-defined epileptogenic lesion in MRI with complete removal are associated with favorable postsurgical outcome in SSs. Early morning SS is also considered as a good prognostic factor in TLE patients. However, failure to use intracranial monitoring in FCD cases negatively affects the prognosis.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee of Isfahan University of Medical Sciences.

Funding

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Conflict of interest

The authors certify that they have no affiliation with or involvement in any organization or entity with any financial interest, or non-financial interest in the subject matter or materials dismissed in this manuscript.

References


