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Focal epilepsy without interictal spikes on scalp EEG: A common finding of uncertain significance

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ABSTRACT

Objective: Interictal epileptiform discharges (IEDs) are important to identify the epileptogenic zone and to define epileptic syndromes. However, not all patients show IEDs on scalp EEG. We evaluate the likelihood of not findings spikes on prolonged Video-EEG Monitoring (VEM) in patients with focal epilepsy, and explore clinical correlates.

Methods: We retrospectively reviewed the VEM reports for all the patients admitted to the seizure monitoring unit in the Calgary Epilepsy Program between July'10 and August'17. Adult focal epilepsy patients, using the diagnostic criteria of the International League Against Epilepsy, who had at least three consecutive VEM days and one recorded seizure were included. Patients were categorized as spikers or non-spikers if any or no spikes were seen on VEM. We compared demographic, neuroimaging, epilepsy risk factor and seizure data.

Results: Of 933 patients, 345 fulfilled our eligibility criteria, 17% [55% males] non-spikers and 83% [53% males] spikers. There were no statistically significant differences between non-spikers and spikers in the studied clinical variables at our epilepsy centre. Average age and average duration of epilepsy were 39 and 13 years for non-spikers and 38 and 16 years for spikers. The average duration of VEM was 8–9 days in both groups. The most frequent seizure focus was in the temporal lobe in both groups (53% in non-spikers vs. 64% in spikers, $p = 0.06$). An epileptogenic lesion on MRI was identified in 26 (46%) of non-spikers and 158 (57%) of spikers ($p = 0.16$).

Significance: Approximately one out of six patients with focal epilepsy showed no IEDs despite prolonged VEM. There was no significant difference among the investigated clinical variables between these two groups of patients in our epilepsy centre. We hypothesise that patients without IEDs on scalp EEG may have smaller, deeper generators with lower levels of neuronal synchrony, which precludes the expression of high amplitude spikes detectable on scalp EEG.

1. Introduction

Interictal epileptiform discharges (IED) on scalp EEG represent the extracellular correlate of a synchronous and excessive discharge of cortical neuronal networks. A single IED is associated with a burst discharge characterized by a rapid sequence of fast action potentials at 200–500 Hz, superimposed on a slow depolarizing potential, the paroxysmal depolarizing shift (PDS) (De Curtis et al., 2001). IEDs in human epilepsies are crucial in the diagnosis of epilepsy and the differentiation of epileptic syndromes (De Curtis et al., 2001), but not all patients with epilepsy have IEDs on their scalp EEGs. In one study (Narayanan et al., 2008), 56% of patients with a history of epilepsy had IEDs on one routine EEG. This increased to 92% with three routine EEGs (Marsan and Zivin, 1970). Lee et al (Lee et al., 2000) reported that 22 out of 109 (20%) patients with temporal lobe epilepsy had no spikes on a 2-hour EEG prior to temporal lobectomy. Burkholder et al found that, in outpatient routine EEG, the rate of capturing IEDs increased by 19% when monitoring time was increased from 30 to 60 min (Burkholder et al., 2016). Prolonged video-EEG monitoring (VEM) provides an opportunity not only to capture seizures, but also to evaluate more fully the occurrence of IEDs. This approach has received limited attention. Narayanan et al (Narayanan et al., 2008) showed that 89% of 46 patients with epilepsy had IEDs within 24 h of their seizures, but 8% of patients had no IEDs even after 72 h of EEG monitoring. Studies by Faulkner et al. (Faulkner et al., 2012) and Friedman et al. (Friedman and Hirsch, 2009), with different sample sizes and time durations, have reported on average 8–12% patients with proven epilepsy had no IEDs during standard VEM.

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Rosati et al (Rosati et al., 2003), presented data on 31 patients with drug resistant temporal lobe epilepsy (TLE) with no or few IEDs, so-called oligospikers. That group of patients had a later age of seizure onset, less frequent and less severe seizures, and a lower incidence of hippocampal atrophy, but otherwise there were no differences between the two groups in the frequency of family history of epilepsy, risk factors, febrile convulsions, and type of medication. The similarity of etiologic factors compared with patients with frequent IEDs suggests that the rarity of spikes could reflect a similar disease but less severe. This study was well done but it was limited to a small sample size and TLE cases. In the current study, we intend to overcome these limitations and evaluate a lager group of patients with temporal and extra temporal lobe epilepsies. To our knowledge, there are no comprehensive and large scale published reports on the frequency with which IEDs are found in patients with proven epilepsy during VEM. Our two main objectives were to evaluate the proportion of patients with focal epilepsy who demonstrated IEDs during scalp VEM, and to assess significant difference between those with and without IEDs.

2. Methods

2.1. Patients and study design

We retrospectively reviewed the medical records including detailed VEM reports of all 933 patients who were admitted to the seizure monitoring unit (SMU) in the Calgary Comprehensive Epilepsy Program between July 2010 and August 2017. At our centre, VEM recordings are reviewed in their entirety, as opposed to reviewing only samples and triggered events. We included adults with focal epilepsy based on criteria of the International League Against Epilepsy (ILAE) (Scheffer et al., 2017), who had at least three consecutive days and nights of scalp VEM and at least one recorded electrographic seizure. We excluded 588 patients, of whom 364 were diagnosed with psychogenic non-epileptic seizures, 106 had no electrographic seizures, 25 had primary generalized epilepsy, 10 had less than 3 days of VEM, 7 were younger than 18 years, and the remaining 73 patients did not have a conclusive diagnosis of focal epilepsy as per the final discharge summary and evaluation. We used standardized forms, and abstracted demographic information, epilepsy risk factors, type and number of seizures, and neuroimaging data on 345 patients who fulfilled eligibility criteria. Drug-resistance was diagnosed using ILAE criteria (Kwan and Brodie, 2000). The EEGs were interpreted by qualified epileptologist in charge of patient care during VEM. Majority of cases, but not all, were also presented and discussed in our weekly seizure rounds where six or more epileptologists reviewed the EEG data. Only those discharges with at least two of three epileptic features (morphology of sharp/spike, following slow wave and disturbing the EEG background) described by Gloor were categorized as epileptic (Gloor, 1975). The seizure type and frequency were extracted from our electronic admission and discharge notes. These data are routinely gathered by admitting physician after a detailed interview with patients and their family as well as reviewing their seizure logs on the first day of admission. Based on the presence or absence of IEDs during the entire period of scalp VEM, we categorized patients as spikers and non-spikers, respectively. Institutional ethics approval was obtained for this study.

2.2. Data analysis

Epilepsy duration was determined using the age of seizure onset to the time of VEM. Seizure frequency separated into focal and bilateral tonic clonic (BTC) seizures. The seizure type and frequency were extracted from our electronic admission and discharge notes. These data are routinely gathered by admitting physician after a detailed interview with patients and their family as well as reviewing their seizure logs on the first day of admission.

To determine statistical significance ($P < 0.05$), student's *t*-test was used for the continuous variables and Pearson chi-square test of independence was used for those nominal clinical marker. While our variables exhibited normality, we concluded robustness of our tests to any possible non-normality because our sample sizes were large (> 30) in both groups (Kwak and Kim, 2017).

Table 1
Principal clinical characteristics of the two groups.

	Spikers (n = 287) n (%) or mean ± SD	Non-Spikers (n = 58) n (%) or mean ± SD
Female	136 (47%)	26 (45%)
Age (years)	38 ± 14	39 ± 15
Epilepsy duration (years)	16 ± 15	13 ± 14
VEM (days)	9 ± 9	8 ± 10
Drug resistant	156 (54%)	26 (45%)
Previous epilepsy surgery	31 (11%)	4 (7%)
Average monthly seizure frequency (focal:BTC)	13:2	15:1
Lobe		
Temporal (p 0.060)	184 (64%)	31 (53%)
Frontal	50 (17%)	11 (19%)
Fronto-Temporal	9 (3%)	4 (7%)
Other lobes	13 (5%)	5 (9%)
Non-localized	31 (11%)	7 (12%)
Lateralization		
Right	88 (31%)	17 (29%)
Left (p 0.053)	109 (38%)	30 (52%)
Bilateral (p 0.056)	26 (9%)	1 (2%)
Left and right independent	24 (8%)	2 (3%)
Non-lateralized	40 (14%)	8 (14%)

VEM = video EEG monitoring, BTC = bilateral tonic clonic. None of the differences were statistically significant.

3. Results

3.1. Patient data

Among 345 patients included, 58 (17%) did not have any IEDs (non-spikers) and, 287 (83%) had IEDs (spikers). The proportion of females was similar in spikers (47%) and non-spikers (45%), as was mean age (38 ± 14 years and 39 ± 15 years, respectively) and duration of epilepsy (16 ± 15 years and 13 ± 14 years, respectively) (Table 1 and Fig. 1). The monthly frequency of focal (with or without impaired awareness) and BTC seizures were similar in both groups (Table 1). Overall, 54% of spikers and 45% of non-spiker had drug resistant epilepsy. The average duration of VEM was not different between spikers (9 ± 9 days) and non-spikers (8 ± 10 days) (Table 1).

Seven percent of non-spikers (four patients) and 11% of spikers (31 patients) had previous epilepsy surgery. Among non-spikers, five patients underwent intracranial EEG and all had spikes recorded from the cerebral cortex.

3.2. Seizure data

All patients had more than three days of VEM, during which at least one electrographic seizure was recorded for each patient. Reduction of anti-seizure medications and sleep deprivation were used as activation methods in 74% and 57% of non-spikers and 82% and 68% of spikers respectively. The most frequently seen seizure onset zone was in the temporal lobe in both groups (53% in non-spikers vs. 64% in spikers). The second most common seizure onset zone in both groups was the frontal lobe, 19% and 17% in non-spikers and spikers respectively (see Table 2). Disregarding non-lateralized, for both groups, seizures were predominantly originating from the left hemisphere. This included 52% for non-spikers and 38% for spikers. In 16% of non-spikers and 23% of spikers, the seizure onsets were indeterminate or bilateral with no clear lateralization/localization. In addition, 3% of non-spikers and 8% of

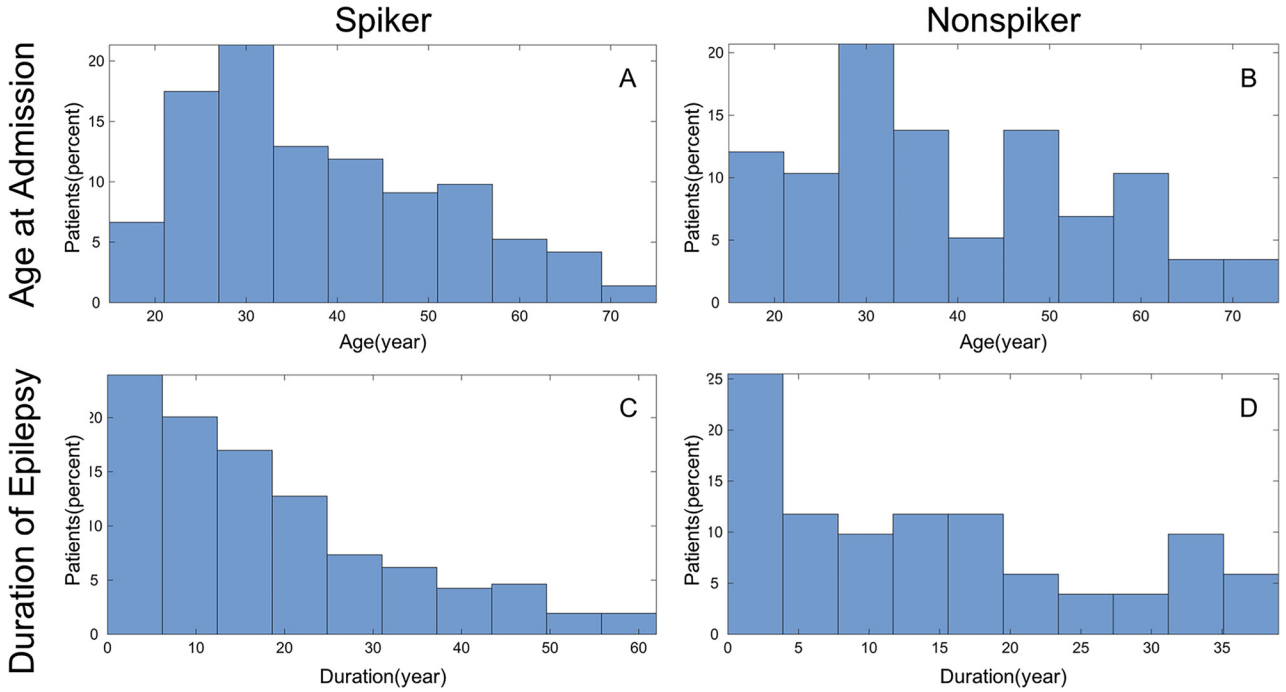

Fig. 1. Age and duration of epilepsy. A and B show age distribution at the time of admission for spikers and non-spikers. Both groups have a similar distribution for age (average 40 years in both). C and D show the duration of epilepsy, with a similar distribution in both groups.

spikers had independent bilateral epileptic foci (see Fig. 2). While there were no statistically significant differences, near significance was found for seizure onset zone in the temporal lobe (p 0.060), left hemisphere (p 0.053) and bilateral onset (p 0.056).

3.3. Seizure risk factors

We evaluated the five major epilepsy risk factors (RF) in our patients including; head trauma, febrile convulsion (FC), CNS infections, strokes, and family history (FH) of epilepsy (Fig. 3).

Overall, 37 (64%) of non-spiker and 186 (65%) of spikers had at least one epilepsy RF, of which head trauma (either minor or major) was the most common (33% of non-spikers and 39% of spikers). Post traumatic changes on MRI, an indicator of moderate to severe head injury, were seen in 3% and 4% of non-spikers and spikers, respectively. Family history of epilepsy was the second most common RF in both groups, reported in 13 (22%) of non-spikers versus 93 (32%) of spikers.

A CNS infection (meningitis or encephalitis) and stroke were reported in eight (14%) and three (5%) of non-spikers versus 21 (7%) and six (2%) of spikers, respectively. Among non-spikers, 44% had only one RF, 17% had two and 2% had three RFs. Similar numbers were found for spikers, 44% had only one RF, 19% had two, and 3% had three RFs. No patient more than three RFs.

3.4. Brain MRI

The majority (97%) of the patients had 1.5 or 3 T brain MRI using an epilepsy protocol. Clinically relevant lesions were found in 26 (45%) of non-spikers and 158 (55%) of spikers (p = 0.16). Hippocampal sclerosis, the most common lesion, was seen in 10 (17%) of non-spikers (left: 12%, right: 5%, bilateral: 0%) and 64 (22%) of spikers (left: 11%, right: 9%, bilateral: 2%). Malformation of cortical development such as cortical dysplasia and neuronal migrational disorders were seen in, six (10%) non-spikers and 36 (13%) spikers. Brain tumors were found in 5% and 3% of non-spikers and spikers, respectively. Other lesions, including aneurysms, encephalomalacia, and post-surgical changes accounted for 16% and 20% of non-spikers and spikers, respectively (see Fig. 4).

In this study, 41% of non-spiker patients had only one type of lesion, 3% had two types and no one with three types of lesions. Likewise, 50% of spiker patients were reported with one type of lesion, 5% with two types and 1% with three types of lesions.

3.5. Intracranial EEG data of non-spikers

Findings from five patients with no interictal epileptiform discharge (IED) on scalp EEG who also underwent intracranial video-EEG monitoring using depth or subdural electrodes are shown in Table 2. Three did not have a clear MRI lesion and two had mesial temporal sclerosis and focal cortical dysplasia. The area of electrode placements was

Table 2
Summary of intracranial EEG findings in five patients with no interictal epileptiform discharge on scalp EEG.

Patient	MRI	Area of coverage	Electrodes	SOZ	IED in SOZ	IED outside of SOZ
1	NL	L T, P, I	D	L Hc	Yes	L P &I
2	NL	Bil F &T	D	L F & RT	Yes	R mesial OF
3	NL	Bil F, R T, & RI	D & SS	ROF	Yes	R Hc, A and sub T, LF
4	LMTS	Bil F, T, & P	SS	L Hc	Yes	R Hc & R lateral T
5	LF CD	L F, P	SG, SS, & D	L F	Yes	LF

SOZ: Seizure onset zone, L: left, R: Right, Bil: Bilateral, T: Temporal, P: Parietal, I: Insula, Hc: Hippocampus, F: Frontal, OF: Orbitofrontal, A: Amygdala, D: Depth, SS: Subdural strips, SG: Subdural grid, MTS: Mesial temporal sclerosis, CD: Cortical dysplasia.

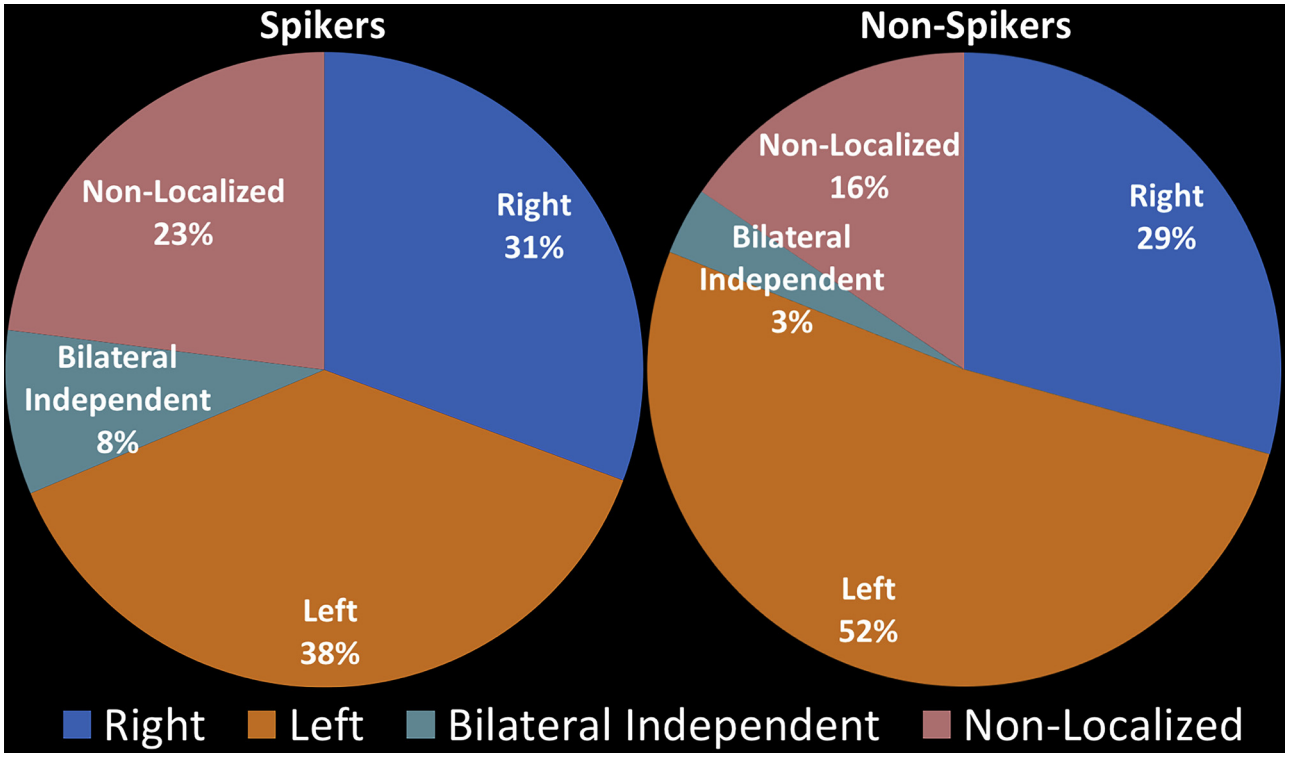

Fig. 2. Localization of seizure onset zone. Both spikers and non-spikers, had predominantly left hemisphere seizure onset zones.

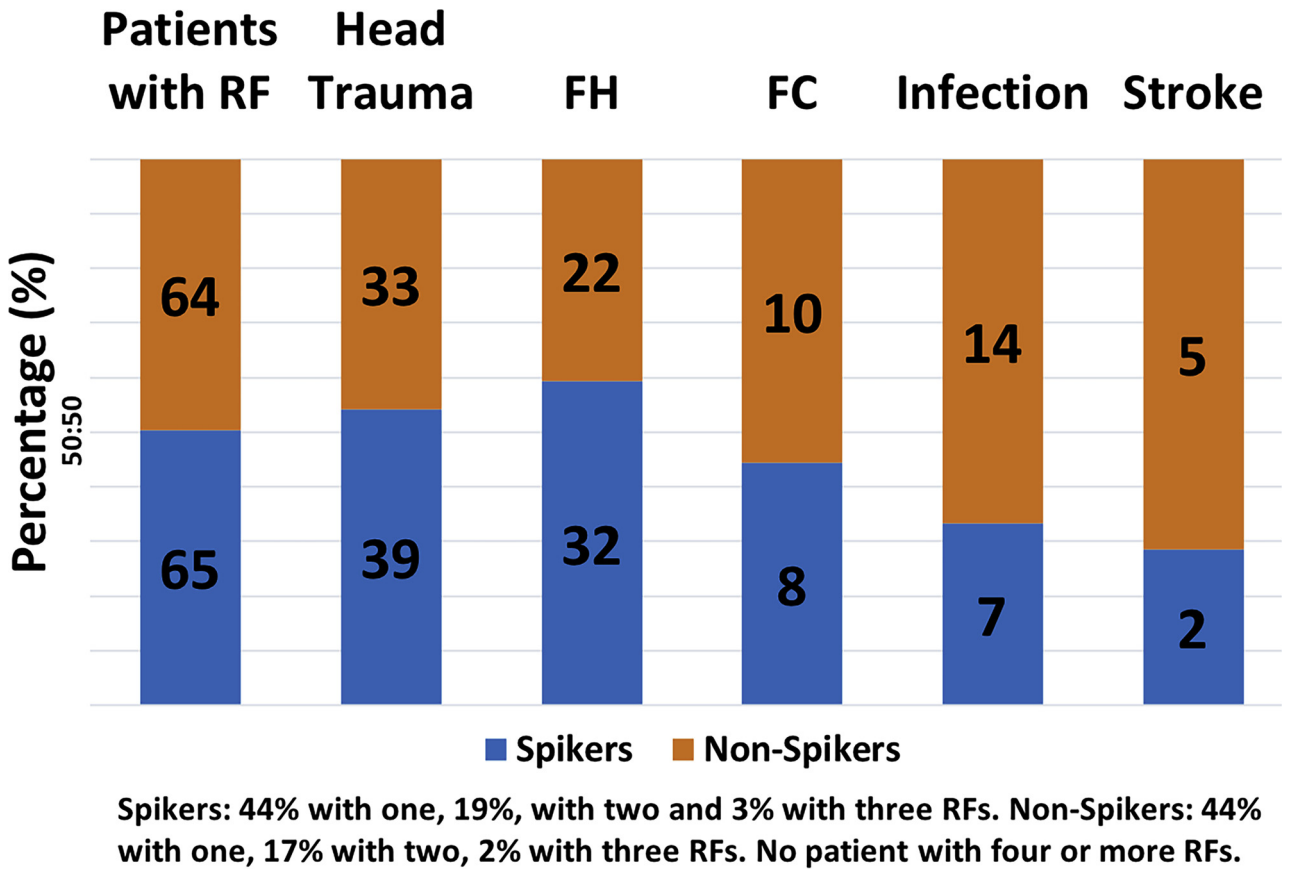

Fig. 3. Summary of epilepsy risk factors. Proportions of each category in spikers and non-spikers.

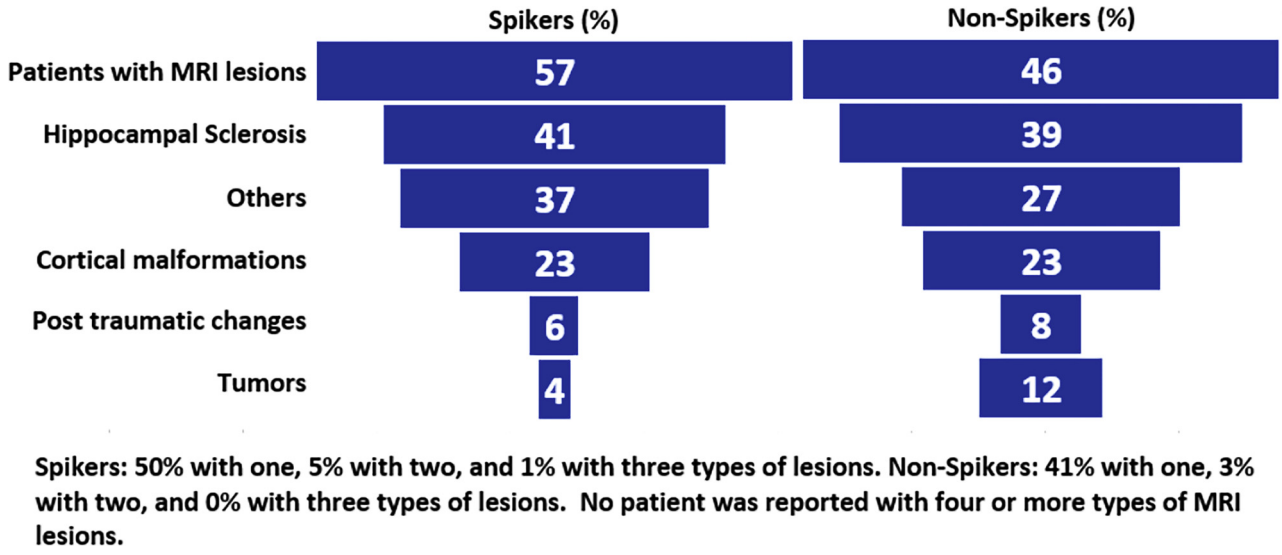

Fig. 4. MRI findings in spikers and non-spikers. Percentage of MRI lesion positives are shown in the top row and a breakdown of those lesions in the following rows.

determined by clinical data as well as presurgical assessments. Three patients had localized onset zones and two had regional onset zones. All five patients had IEDs in the SOZ and in the other areas on intracranial recordings.

4. Discussion

In this dataset, approximately one in six patients (17%) with proved focal epilepsy failed to show IEDs on prolonged scalp VEM. This was more common than we expected based on reports of routine EEG and short term VEM recording.(Lee et al., 2000; Marsan and Zivin, 1970; Narayanan et al., 2008) We do not think this is due to selection biases because our methodology focused on patients with demonstrated focal epilepsy, including all patients in the time frame of interest; additionally the entire 24-hour EEG tracings were reviewed daily for every patient, and the duration of scalp VEM was at least 3 days and nights. These measures could be expected to increase the likelihood of finding IEDs. Some of these patients were admitted to investigate the diagnosis of seizures after inconclusive outpatient assessments, and turned out to have focal epilepsy. However, a substantial number (182) already had diagnosis of drug-resistant epilepsy and were admitted for pre-surgical assessments. In any case, our findings emphasize the notion that the absence of IEDs on scalp EEG, even on prolonged VEM, is a weak argument against the diagnosis of focal epilepsy.

It is not entirely clear why some patients with epilepsy have IEDs and others do not. One explanation could be that IEDs and seizures are independent phenomena, and patients can have epilepsy without having IEDs. We think this is an unlikely explanation. In day to day practice, intracranial EEG very often demonstrates IEDs in areas of the cerebral cortex which do not correspond to any IEDs on scalp EEG. Five patients in the non-spiker group in our study had intracranial EEG monitoring during which IEDs were directly recorded from the cerebral cortex in the seizure onset zone as well as some adjacent areas. Furthermore, magnetoencephalography can record IEDs from some areas of the cerebral cortex, such as the insula, temporal or frontal neocortex, which are not detectable on scalp EEG, and can be explained at least in part by the dipole orientation of the spikes (Kakisaka et al., 2013). It is unlikely that antiseizure medications supress IEDs. It was previously shown that anti-seizure medications do not have significant effects on interictal epileptiform discharges (Gotman and Marciani, 1985). Most of our patients (74% of non-spikers and 82% of spikers) were off antiseizure medications or on reduced dosages. Janszky et al (Janszky et al., 2001) showed that the rate of IEDs can increase after seizures. Yet, our non-spiker population failed to show IEDs even after they had seizures. In one study (Janszky et al., 2005) the authors reviewed 303 patients with TLE and demonstrated that the seizure frequency and duration of epilepsy were independently associated with IEDs frequency. Similarly, in another study (Clemens et al., 2005), 38 patients with TLE were analysed and a significant correlation between spiking rates and duration of epilepsy was reported. We did not see any significant difference in duration of epilepsy and the frequency of focal or bilateral convulsive between spiker and non-spiker groups. This discrepancy with previous studies could be due to heterogeneity of our patients with various type of focal epilepsy rather than TLE only.

We believe that IEDs do occur in the epileptogenic cortex (Ball et al., 1977; Bishop, 1949; Creutzfeldt and Houchin, 1974; Gloor, 1983), but they are not detected by scalp EEG electrodes for a number of reasons, which clinicians should keep in mind. The scalp acts as a spatial average of electrical activity, requiring IEDs to have a high signal to noise ratio to be seen on scalp EEG (Cooper et al., 1965; Delucchi et al., 1962). Factors affecting the size of the signal include the area of the cerebral cortex generating the IEDs. By using a piece of fresh cadaver skull, a pulse generator connected to saline-soaked cotton balls placed on the inside of the skull, an artificial dura made from a polyethylene sheet, and EEG recording electrodes on the exterior surface of the skull bone, Cooper et al concluded that at least 6–10 cm of cerebral cortex is needed to generate synchronized cortical activities detectable by scalp electrodes (Cooper et al., 1965). A more recent study by using simultaneous scalp and intracranial electrodes in epilepsy presurgical assessments demonstrated that an area of 10–20 cm^2 of synchronized spiking is more likely necessary to generate IEDs recordable on scalp EEG (Tao et al., 2007).

A second factor is the distance of the IED generator to the recording electrodes. The amplitude of the IEDs is inversely related to the radius of the distance between the IED generator and the recording electrodes (Alarcon et al., 1994; Rush and Driscoll, 1969). A third factor which is usually often more important than distance (Gloor, 1983), is the orientation of the electrical field/dipole of the IED-generating cerebral cortex in relation to the recording electrodes (i.e., the solid angle of volume conduction) (Gloor, 1985). IEDs with vertical dipoles (i.e., perpendicular to the scalp) are more likely to be detected by scalp electrodes than IEDs with horizontal/tangential dipoles (i.e., parallel to scalp), such as spike generators in the wall of a sulcus (Gloor, 1985). Lastly, the degree of synchronization of the discharging neurons determines its amplitude on scalp EEG.

Of note, our data failed to demonstrate any statistically significant

differences between spikers and non-spikers in clinically relevant variables, such as age, gender, duration of epilepsy and VEM, seizure activation methods, frequency of seizures, seizure focus locations, epilepsy risk factors and brain MRI lesions. This supports our argument that physiological variance, rather than distinct clinic-pathological subgroups explains the absence of IEDs on scalp EEG. Admittedly, a small sample size could contribute to the lack of statistical significance, and analyses of larger patient groups may yield further insights.

In conclusion, approximately one in six patients with proven focal epilepsy failed to show IEDs on prolonged VEM. Therefore, lack of IEDs on scalp EEG, even with long term video-EEG monitoring, by itself does not mitigate against the presence of focal epilepsy. We hypothesise that a number of factors may be responsible for the lack of IEDs in non-spikers, including the size of the IED cortical generator, its proximity to the recording electrodes, its orientation, and the degree of synchrony of neuronal discharges. These factors are amenable to investigation with simultaneous scalp and intracranial EEG recordings.

Disclosure

None of the authors has any conflict of interest to disclose.

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