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BRIEF COMMUNICATION

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Seizure duration and latency of hypermotor manifestations distinguish frontal from extrafrontal onset in sleep-related hypermotor epilepsy

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Summary

Sleep-related hypermotor epilepsy (SHE) is an epilepsy syndrome that is characterized by the occurrence of sleep-related hypermotor seizures of variable complexity and duration. Seizures usually arise in the frontal lobe, but extrafrontal seizure onset zones are well described. To identify clinically relevant ictal features of SHE that could distinguish a frontal from an extrafrontal onset zone, we conducted a retrospective analysis of seizure characteristics in 58 patients with drug-resistant SHE (43 frontal and 15 extrafrontal) who underwent video-stereo-electroencephalographic recordings and became seizure-free after epilepsy surgery. We found that the mean duration of electrographic seizures and clinically observable ictal manifestations were significantly shorter in frontal SHE compared to extrafrontal SHE. The mean latency between electrographic seizure onset and the onset of hypermotor manifestations was also shorter in frontal SHE. Accordingly, a latency > 5 seconds between the first video-detectable movement (eg, eye opening or a minor motor event) and the onset of hypermotor manifestations yielded a sensitivity of 75% and a specificity of 90% for an extrafrontal onset, thereby indicating that specific ictal features in SHE can provide clinically useful clues to increase diagnostic accuracy in this syndrome.

KEYWORDS

hypermotor seizures, nocturnal frontal lobe epilepsy, sleep, sleep-related hypermotor epilepsy, stereo-EEG

1 | INTRODUCTION

Sleep-related hypermotor epilepsy (SHE), formerly known as nocturnal frontal lobe epilepsy, is an epilepsy syndrome that is characterized by the occurrence of sleep-related hypermotor seizures of variable complexity and duration that occur mostly during non–rapid eye movement sleep.[1] Seizures in SHE have a frontal lobe semiology that consists of asymmetric tonic/dystonic postures and/or complex hypermotor behaviors.[2] These hypermotor seizures can nonetheless arise outside the frontal lobe in a significant proportion of cases[2-5] and therefore, distinguishing a frontal from an extrafrontal seizure onset zone (SOZ; ie, the cortical area from where seizures start and propagate) can be difficult, especially in magnetic resonance imaging (MRI)-negative cases.

In this study, we aimed to identify ictal features that could help differentiate frontal from extrafrontal SHE. To do so, we used clinical and stereo-electroencephalographic (EEG) data from our patient database at the Claudio Munari Center for Epilepsy Surgery.

2 | MATERIALS AND METHODS

We identified 135 patients with video-EEG–documented (confirmed) SHE[1] from a database of 1433 consecutive patients who underwent epilepsy surgery from October 1997 to July 2015. We then selected those who had undergone a stereo-EEG recording before epilepsy surgery and had a seizure-free outcome at a minimum follow-up of 2 years (Engel class I outcome). Enrolled patients were subdivided according to the location of the stereo-EEG–defined SOZ as frontal or extrafrontal.

To document interictal and ictal scalp EEG abnormalities, prolonged scalp video-EEG recordings were obtained in our epilepsy monitoring unit using Neurofax EEG-1100 (Nihon Kohden, Tokyo, Japan). To delineate the SOZ, stereo-EEG recordings were obtained by stereotactic placement of intracerebral multicontact electrodes to obtain a long-term EEG recording in a three-dimensional arrangement.[6] Individual stereo-EEG recordings were randomly assigned to experienced epileptologists (L.N., L.T., R.M., S.F.) who prospectively analyzed and detailed individual seizures. Seizure data were reviewed by a single interpreter (S.A.G.) who was blinded to the stereo-EEG results. The following data were analyzed: (1) the clinical and electrographic seizure duration based on video-stereo-EEG data, (2) the latency between electrical seizure onset and the first video-EEG detectable movement (eg, eye opening or minor motor event), (3) the latency between the electrical seizure onset and the onset of the hypermotor semiology, and (4) the latency between the appearance of the first video-EEG–detectable movement and the appearance of hypermotor semiology. For all these measurements, individual means were calculated for each patient to account for subject-specific differences. The number of recorded seizures during stereo-EEG varied greatly between patients (mean = 3.6 ± 3.1, range = 1-15). Considering the highly stereotypical features of ictal manifestations, only the first five recorded seizures for each patient were included in the analysis.

A group mean of patient-specific seizure characteristics was calculated for frontal and extrafrontal SHE. Unpaired two-tailed Student *t* tests with Welch correction or a Mann-Whitney *U* test (for non-normally distributed data) was used to compare variables between frontal and extrafrontal groups. Significant values were retained for $P < 0.05$. Receiver operator characteristic analysis was used to calculate the area under the curve values to identify clinically meaningful cutoff values related to ictal features. Statistical analysis was performed using SPSS statistics for Macintosh version 25.0 (IBM, Armonk, NY).

3 | RESULTS

We identified 43 patients with frontal onset SHE and 15 patients with extrafrontal SHE. Clinical characteristics were similar in both groups, including etiology (Table 1). Seizure frequency in SHE was high and scalp EEG (routine and video-EEG) showed a large proportion of interictal and ictal abnormalities in both groups. However, less than one-half of scalp EEG abnormalities were helpful in localizing the SOZ to a particular brain region (Table 1).

3.1 | Stereo-EEG evaluation of SHE

A total of 107 seizures from frontal and 40 seizures from extrafrontal SHE were analyzed. We found that the mean electrographic seizure duration was significantly shorter in frontal SHE than in extrafrontal SHE (38.5 ± 40.0 seconds, median = 28.1, range = 10-233 vs 61.8 ± 25.4 seconds, median = 62.4, range = 24-125; $U = 103.5$, $P < 0.0001$; Figure 1A). Similar results were obtained when the mean

TABLE 1 Descriptive statistics of the 58 patients with SHE

	Frontal SHE, n = 43	Extrafrontal SHE, n = 15	*P*
Mean age at onset, y (range)	6.6 ± 4.1 (0.1-16)	6.2 ± 4.3 (0.25-13)	0.7
Mean duration of disease, y (range)	17.0 ± 8.8 (4-37)	18.0 ± 11.0 (3-40)	0.8
Hemisphere of SOZ, n (%)			
Right	27 (63)	11 (73)	0.5
Left	16 (37)	4 (27)	
Seizure frequency, n (%)			
Daily	32 (75)	10 (67)	0.7
Weekly	9 (21)	4 (27)	
Monthly	1 (2)	1 (6)	
Sporadic	1 (2)	0 (0)	
EEG, n (%)			
Interictal activity	35 (81)	13 (87)	1.0
Localizing	18 (42)	8 (53)	
Ictal activity	35 (81)	12 (80)	1.0
Localizing	20 (47)	7 (47)	
MRI-identifiable lesion, n (%)	25 (58)	7 (47)	0.6
Histopathology, n (%)			
FCD type I	3 (7)	1 (7)	0.6
FCD type II	36 (84)	12 (80)	
Gliosis	4 (9)	2 (13)	

EEG, electroencephalogram; FCD, focal cortical dysplasia; MRI, magnetic resonance imaging; SHE, sleep-related hypermotor epilepsy; SOZ, seizure onset zone.

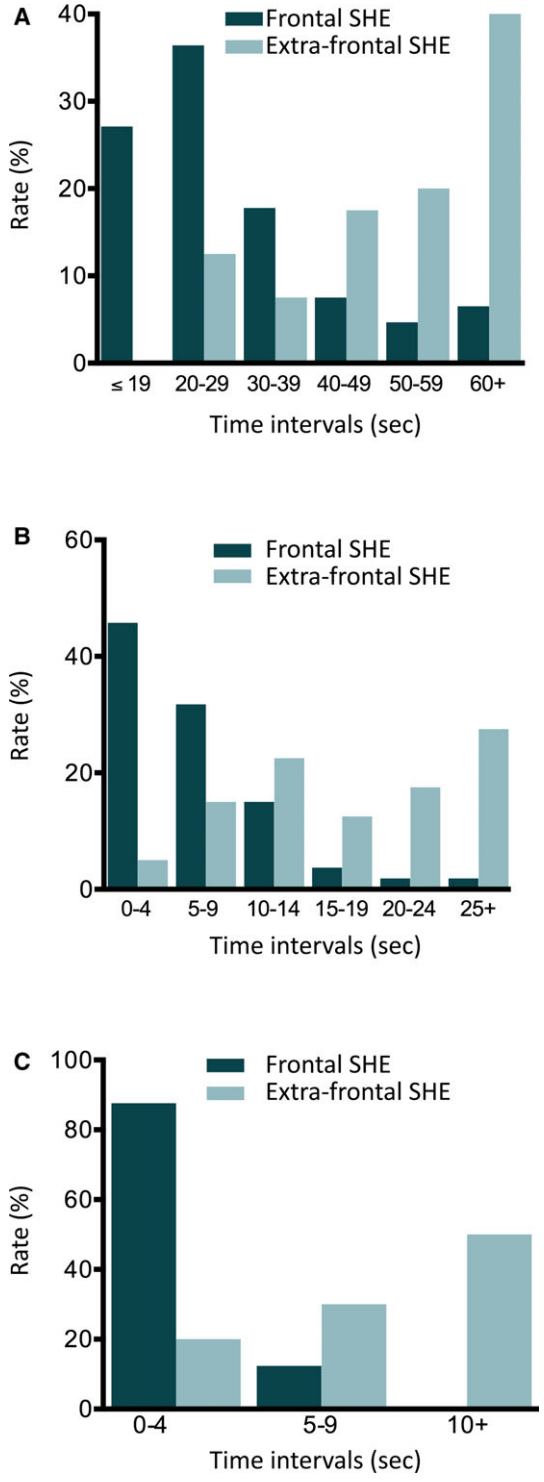

FIGURE 1 Stereo-electroencephalography (EEG)–recorded hypermotor seizures in frontal and extrafrontal sleep-related hypermotor epilepsy (SHE). A, Individual electrographic seizure duration from both groups divided into 10-second bins. B, Latency between stereo-EEG seizure onset and the start of the hypermotor manifestations, divided into 5-second bins. C, Latency between the first video-EEG detectable movement and the start of hypermotor manifestations divided into 5-second bins. Data presented are derived from 107 seizures in the frontal SHE group and 40 seizures in the extrafrontal SHE group

duration of clinical manifestations was measured (32.3 ± 34.7 seconds, median = 22.6, range = 5-174 vs 52.0 ± 20.5, median = 48.0, range = 20-117; $U = 103.0$, $P < 0.0001$). Moreover, a clinical seizure lasting >40 seconds yielded a sensitivity of 55% and a specificity of 90% for an extrafrontal onset (area under the curve = 0.85 ± 0.03, $P < 0.0001$). In all recorded seizures, clinical signs appeared after the emergence of the electrophysiological discharge. Five patients with frontal SHE had long clinical seizures (range = 63-174 seconds). The locations of the SOZ in these patients were frontopolar (n = 2), orbitofrontal (n = 1), fronto-opercular (n = 1), and frontal dorsolateral (n = 1).

The mean elapsed time from stereo-EEG seizure onset to the first video-detectable movement was significantly shorter in frontal SHE (4.3 ± 3.8 seconds, median = 3.8, range = 0-17 vs 9.5 ± 6.4 seconds, median = 7.0, range = 3-23; $U = 142.0$, $P = 0.003$). The same tendency was observed when the latency from electrographic seizure onset to the onset of hypermotor manifestations was measured (6.3 ± 4.1 seconds, median = 5.3, range = 1-20 vs 20.9 ± 10.3 seconds, median = 18.0, range = 8-41; $U = 34.5$, $P < 0.0001$; Figure 1B). In 80% of seizures occurring in the frontal SHE group, delay between seizure onset and hypermotor manifestations was <10 seconds, whereas the opposite was observed in the extrafrontal SHE group. Accordingly, the clinically observable delay between the first video-detectable movement and onset of hypermotor manifestations was very short in frontal SHE compared to extrafrontal SHE (2.2 ± 2.1 seconds, median = 1.6, range = 0-9 vs 11.4 ± 7.1 seconds, median = 9.8, range = 3-26, $U = 28.5$, $P < 0.0001$; Figure 1C). A latency > 5 seconds yielded a sensitivity of 75% and a specificity of 90% for an extrafrontal onset (area under the curve = 0.92 ± 0.03, $P < 0.0001$). Four frontal SHE patients exhibited a longer latency before the onset of hypermotor manifestations (range = 5-9 seconds). The locations of the SOZ in these patients were orbitofrontal (n = 2), frontopolar (n = 1), and fronto-opercular (n = 1). These patients were different from those reported above, who presented long clinical seizures with one exception.

4 | DISCUSSION

By means of stereo-EEG ictal recordings and with the assurance of postsurgical seizure-free outcome, our results provide simple but clinically relevant information for clinical practice, useful to differentiate frontal from extrafrontal onset SHE. We corroborate previous studies suggesting that seizures in SHE are longer when they begin outside the frontal lobe.[3,5] Although prolonged seizures (>60 seconds) were present in both groups, frontal onset hypermotor

seizures in our cohort tended to be significantly shorter than extrafrontal ones, frequently terminating in <30 seconds (Figure 1A). The duration of sleep-related frontal lobe seizures in our study is in line with previously published frontal lobe seizure data.[7] Also using stereo-EEG data, Bonini et al[7] observed latencies between electrographic seizure onset and clinical onset similar to what we observed in frontal onset SHE.

In addition to seizure duration, we found that the latency between the stereo-EEG seizure onset and the start of hypermotor manifestations was much longer in extrafrontal SHE. During this period, extrafrontal SHE patients were either asleep or lying motionless in bed with their eyes open. This delay in behavioral manifestations was >15 seconds in two-thirds of extrafrontal SHE (10/15 patients), whereas this was only observed in 7.5% of frontal SHE (3/40 patients). This phenomenon suggests that hypermotor manifestations appear once the ictal discharge spreads to or disrupts frontal lobe networks, confirming previous observations in a small cohort of patients.[3,5,8] Interestingly, the observed delay between the ictal onset and the first video-detectable movement, usually coinciding with an awakening of the patient, suggests that it is not the hypermotor behavior itself that provokes an arousal in SHE but the organizing and possibly spreading of ictal activity.[2] Although an in-depth analysis of seizure semiology was not performed in this study, once the hypermotor manifestations began, no visually observable differences in seizure phenotype were observed between the groups, supporting the hypothesis of a seizure-induced frontal release of innate behavioral automatisms.[9]

The most clinically relevant finding of our study is the longer latency between the first video-detectable movement and the onset of the hypermotor manifestations in extrafrontal SHE. This time interval can represent a valuable clinical clue to diagnose a SHE with extrafrontal onset, especially considering that this feature is obtainable through noninvasive video analysis of seizures. Although some hypermotor manifestations did occur rapidly after awakening in extrafrontal SHE patients, a latency of >5 seconds provided a specificity of 90% for an extrafrontal onset. This finding, coupled with a longer seizure duration, may be helpful during presurgical planning and for MRI data interpretation. Moreover, in MRI-negative cases, these findings could help tailor stereo-EEG implantations to include extrafrontal sampling in the presence of extrafrontal clinical features and conversely, minimize the risk of overimplantation in the absence of such features.

It remains to be seen whether the seizure characteristics observed in this study are applicable to genetic forms of SHE and to drug-sensitive SHE, but in light of recent findings that drug-sensitive SHE cases have a poor long-term seizure control outcome, it is conceivable that an underestimated proportion of patients with MRI-negative SHE in the general population are carriers of an undetected focal cortical dysplasia.[10-12] Finally, a prospective confirmation of our findings will be of interest, because our analysis, although blinded to the stereo-EEG conclusions, was open to occasional group classification inferences because of electrode labeling.

In conclusion, our study indicates that specific features, such as seizure duration and latency between the first video-detectable movement and the onset of the hypermotor manifestations, should be considered to increase diagnostic accuracy in SHE.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to report. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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REFERENCES

1. Tinuper P, Bisulli F, Cross JH, et al. Definition and diagnostic criteria of sleep-related hypermotor epilepsy. Neurology. 2016;86(19):1834–42.
2. Gibbs SA, Proserpio P, Terzaghi M, et al. Sleep-related epileptic behaviors and non-REM-related parasomnias: insights from stereo-EEG. Sleep Med Rev. 2016;25:4–20.
3. Nobili L, Cossu M, Mai R, et al. Sleep-related hyperkinetic seizures of temporal lobe origin. Neurology. 2004;62(3):482–5.
4. Ryvlin P, Minotti L, Demarquay G, et al. Nocturnal hypermotor seizures, suggesting frontal lobe epilepsy, can originate in the insula. Epilepsia. 2006;47(4):755–65.
5. Proserpio P, Cossu M, Francione S, et al. Insular-opercular seizures manifesting with sleep-related paroxysmal motor behaviors: a stereo-EEG study. Epilepsia. 2011;52(10):1781–91.

6. Cardinale F, Cossu M, Castana L, et al. Stereoelectroencephalography: surgical methodology, safety, and stereotactic application accuracy in 500 procedures. Neurosurgery. 2013;72(3):353–66.
7. Bonini F, McGonigal A, Trebuchon A, et al. Frontal lobe seizures: from clinical semiology to localization. Epilepsia. 2014;55 (2):264–77.
8. Proserpio P, Cossu M, Francione S, et al. Epileptic motor behaviors during sleep: anatomo-electro-clinical features. Sleep Med. 2011;12(suppl 2):S33–8.
9. Tassinari CA, Rubboli G, Gardella E, et al. Central pattern generators for a common semiology in fronto-limbic seizures and in parasomnias. A neuroethologic approach. Neurol Sci. 2005;26 (suppl 3):S225–32.
10. Nobili L, Cardinale F, Magliola U, et al. Taylor's focal cortical dysplasia increases the risk of sleep-related epilepsy. Epilepsia. 2009;50(12):2599–604.
11. Harvey AS, Mandelstam SA, Maixner WJ, et al. The surgically remediable syndrome of epilepsy associated with bottom-of-sulcus dysplasia. Neurology. 2015;84(20):2021–8.
12. Licchetta L, Bisulli F, Vignatelli L, et al. Sleep-related hypermotor epilepsy: long-term outcome in a large cohort. Neurology. 2017;88(1):70–7.

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