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Sleep-related hypermotor epilepsy activated by rapid eye movement sleep

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ABSTRACT – Most sleep-related seizures occur during non-rapid eye movement (NREM) sleep, particularly during stage changes. Sleep-related hypermotor epilepsy (SHE) is a rare epileptic syndrome characterized by paroxysmal motor seizures, mainly arising from NREM sleep. Here, we report a patient with SHE who had seven seizures captured on video-EEG-polysomnography during REM sleep. Ictal semiology of this patient ranged from brief paroxysmal arousals to hypermotor seizures. On EEG-polysomnography, the spontaneous arousals were more frequent during REM than NREM sleep, with a considerably higher arousal index in REM sleep (20/hour). While the reason for seizures during REM sleep in this patient is unclear, we speculate that the threshold and mechanisms of arousal during different sleep stages may be related to the occurrence of seizures. [*Published with video sequences on www.epilepticdisorders.com*].

Key words: sleep-related hypermotor seizure, nocturnal frontal lobe epilepsy, paroxysmal arousal, REM sleep

It is well documented that seizures preferentially occur during non-rapid eye movement (NREM) sleep rather than rapid eye movement (REM) sleep, particularly in sleep-related hypermotor epilepsy (SHE), previously known as "nocturnal frontal lobe epilepsy" (NFLE) (Tinuper *et al*., 2016; Gibbs *et al*., 2016; Minecan *et al*., 2002; Provini *et al*., 1999). The diagnostic criteria and clinical features of SHE were recently revised by a group of international experts in the fields of epilepsy, sleep, and epidemiology. Diagnosis is primarily based on clinical history with the core clinical features of hypermotor events, using three different levels of diagnostic certainty:
– witnessed (possible);
– video-documented (clinical);
– and VEEG-documented (confirmed) (Tinuper *et al*., 2016).
In this report, we describe a case with confirmed SHE in which clusters of hypermotor seizures occurred exclusively during REM sleep during a 24-hour video-EEG-polysomnography (PSG) recording.

VIDEOS ONLINE

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Case study

A 21-year-old man presented with a six-year history of sleep-related episodes that were characterized by stereotyped hypermotor movements with vocalization lasting for 10-40 seconds. These events were nocturnal, causing the patient to wake from sleep with a feeling that he could only describe as "indescribable", without any emotional content. During the event, he would be aware of, but unable to control, his movements. These occurred nightly, about two to five times per night, always after the patient had been asleep for at least 1.5 hours. Poor sleep and increased stress exacerbated the frequency of the seizures. There was no known family history of epilepsy.

The patient was diagnosed with epilepsy at age 15, and pharmacological treatment with phenytoin was initiated with some initial success, but episodes reappeared. During the next six years, no further seizure remission was achieved with various antiepileptic drugs, such as phenobarbital, valproate and lamotrigine, as either mono- or polytherapy.

At our centre, a 24-hour video-EEG-PSG recording with a full 10-20 EEG montage captured seven nocturnal seizures, including four hypermotor seizures preceded by arousal and three paroxysmal arousals (PAs), all of which occurred exclusively during REM sleep. The spontaneous arousal index in REM and NREM sleep was 20 and 3.6 per hour, respectively. Hypermotor seizures were characterized by a predominance of repetitive rhythmic twisting of the trunk, from the left to the right side, accompanied by bizarre vocalization. All seizures were preceded by a PA which resembled physiological awakening, characterized by head turning and leg stretching (*see video sequences*). At the end of each attack, he was able to tell the nursing staff that he was fine and recalled what had happened. Interictally, the patient had occasional right frontal sharp waves, maximal at the Fp2-F4 electrodes (V1. *figure 1*). Preictal EEG-PSG showed low-voltage activity with rapid eye movement and loss of muscle tone, indicating that the seizures arose from REM sleep. Ictal EEG-PSG showed an increase in low-voltage fast beta activity, lasting about 5 seconds before arousal. Arousal was associated with awake-like alpha and beta activity, alongside EMG artefact. No clear-cut ictal epileptiform activity was identified at the onset of clinical seizures. During the hypermotor seizures, EEG was obscured by movement/EMG artefacts, making analysis of the EEG difficult, even with filtering. The postictal EEG showed right frontal slowing. Three isolated PAs were also identified during REM sleep. The ictal semiology was characterized by sudden head turning and some physical movements which resembled normal physiological awakening, and simultaneous EEG-PSG showed quasi-periodic sharp waves over the right frontal region, lasting for no more than 10 seconds (V2).

Neurological examination and 3T brain MRI were normal. A brain PET-CT was performed and interictal brain FDG-PET-CT showed focal hypometabolic zones in the right anterior temporal pole.

The patient was started on oxcarbazepine and during the first year of follow-up, he reported that seizures were completely controlled except for when his medication was not taken properly.

Discussion

In this study, we report a case of confirmed SHE according to the new diagnostic criteria for sleep-related hypermotor seizures (Tinuper *et al.*, 2016). Video-EEG-PSG captured seven nocturnal seizures (four hypermotor and three PA), all occurring during REM sleep. The patient's history of seizures occurring after sleep, lasting for at least 1.5 hours, is also in agreement with seizures occurring during REM at home.

In our epilepsy and sleep disorder centre, this is the first case of SHE we have encountered which occurred during REM sleep. Seizures in this patient were always initiated by arousal at awakening, which is not uncommon for temporal and frontal seizures (Calandra-Buonaura *et al.*, 2012; Gumusyayla *et al.*, 2016). The spontaneous arousals were more frequent during REM than NREM sleep. We speculate that a lower arousal threshold during REM sleep is related to the patient's vulnerability to seizures during REM sleep. Three PA during REM sleep were identified on scalp EEG. The other arousals without synchronous epileptiform discharges were classified as physiological arousal. However, some of these arousals may be surface-negative seizures which would be apparent upon stereoelectroencephalography (SEEG) (Gibbs *et al.*, 2016).

Historically, the two main sleep stages, NREM and REM sleep, are reported to have different physiological components and contrasting effects on seizure threshold (Minecan *et al.*, 2002; Derry and Duncan, 2013). REM sleep has been postulated to have an antiepileptic effect (Minecan *et al.*, 2002; Ng and Pavlova, 2013). However, recent studies have found that REM sleep is associated with a low arousal threshold, allowing a rapid transition to wakefulness, which may decrease the threshold for PA (McNamara *et al.*, 2002; Montgomery-Downs *et al.*, 2006; Horne, 2013; Jung and St Louis, 2016).

It is difficult for us to ascertain the epileptogenic zone in the patient. As is typical in SHE, there was no clear-cut epileptic discharge at the onset of the seizures on scalp EEG, and the MRI did not show a lesion. Interictal

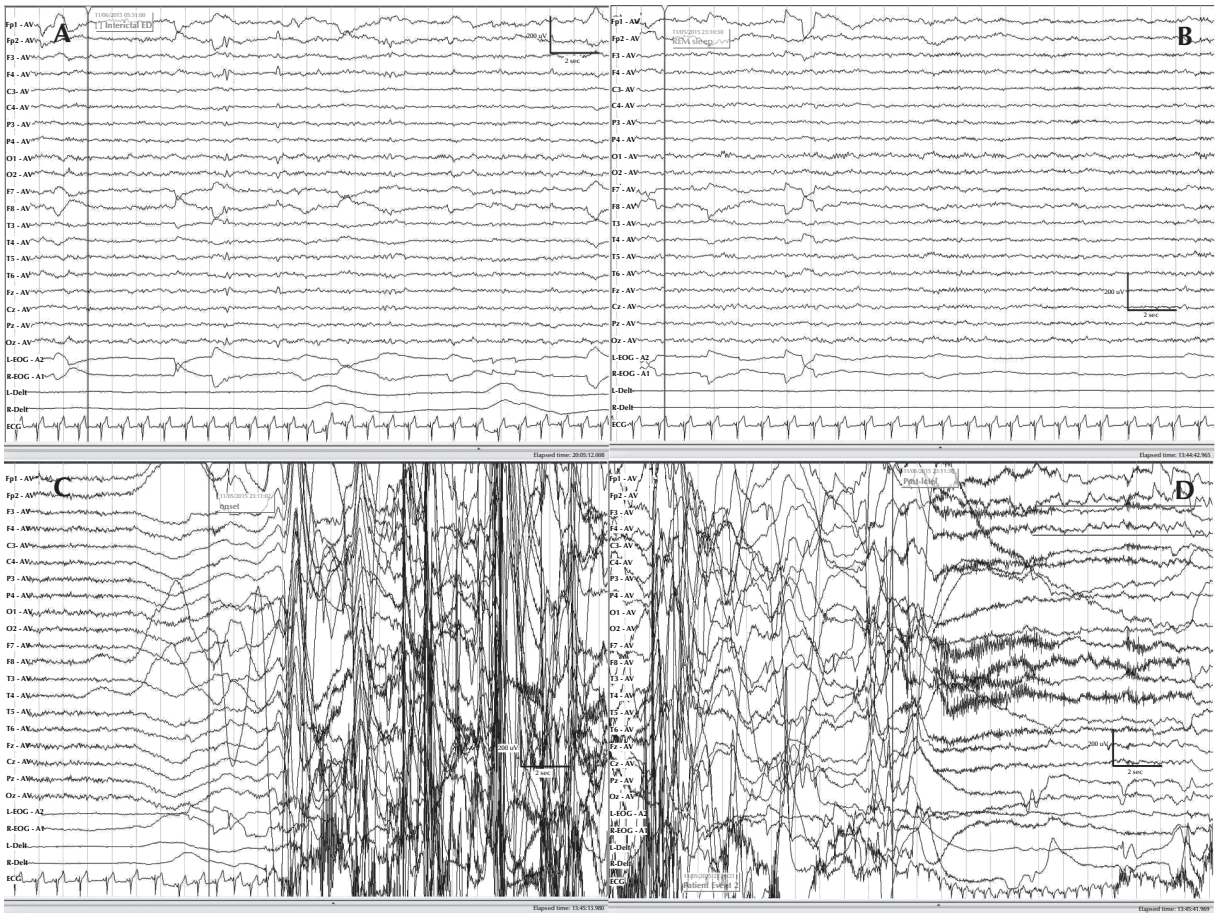

Figure 1. The interictal EEG (A) shows a focal abnormal sharp wave over the right frontal region during sleep, followed by the ictal EEG (B-D) revealing a seizure during REM sleep; no abnormal epileptic discharge was found at the onset of the seizure, which was marked only by movement/EMG artefact. Postictal EEG shows focal slowing located in the right frontal area.
AV: average montage; L-Delt: left deltoid; R-Delt: right deltoid.

FDG-PET showed a focal hypometabolic zone located in the right anterior temporal pole. The PET findings are somewhat discordant with the interictal findings which showed epileptiform potentials from the right frontal area. Given the patient's good response to oxcarbazepine, the patient declined intracranial EEG recording to elucidate more precisely the seizure onset zone.

In recent years, SEEG has been used as a clinical tool to gather information on seizure onset, particularly when the onset is difficult to fully lateralize and localize with scalp electrodes. Interestingly, most cases of sleep-related hypermotor seizures investigated using SEEG seem to have had an insular or temporal onset (Arain *et al*., 2016; Proserpio *et al*., 2011a). Contrary to decades of belief that SHE is of frontal origin, it is now well recognized that in a significant proportion of patients affected by SHE, seizures originate outside the frontal lobe (Proserpio *et al*., 2011b; Arain *et al*., 2016; Tinuper *et al*., 2016).

In our patient, we hypothesize that the seizure onset region may be the hypometabolic zone in the right anterior temporal pole, with the first sensation of an indescribable feeling being a temporal lobe sensation (Perven and So, 2015).

Only one 24-hour VEEG-PSG recording is a limitation of our study, and repeating the monitoring would confirm whether seizures only occur during REM.

The incidence of SHE during REM is currently unknown, and it may be under-reported, as many epilepsy centres do not perform concurrent PSG, and EEG, ECG, oculogram/EOG, and EMG may help to confirm the sleep stage. We propose concurrent EEG and PSG, as well as careful documentation of seizures, sleep stages, and arousals, will aid in our understanding of the relationship between sleep and seizures.

This understanding has the potential to lead to new avenues for investigation and treatment.

Supplementary data.
Summary didactic slides are available on the www.epilepticdisorders.com website.

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None of the authors have any conflict of interest to declare.

Legends for video sequences

Video sequence 1

This video demonstrates the semiology of two seizures captured by video-EEG-PSG. Seizures were all preceded by a paroxysmal arousal (PA) which resembled normal awakening, characterized by manual automatisms, head turning, and leg stretching. Shortly afterwards, the patient opened his eyes with abnormal major motor behaviour and bizarre vocalization, characterized by repetitive twisting of the trunk from the left to the right side, associated with chaotic hypermotor activity involving the arms and legs.

Video sequence 2

This video shows PA from REM sleep. Ictal semiology is characterized by sudden head turning and some physical movement which closely resembles normal physiological awakening. The EEG shows quasi-periodic sharp waves over the right frontal region lasting for no more than 10 seconds.

Key words for video research on www.epilepticdisorders.com

Phenomenology: hypermotor seizures with a paroxysmal arousal onset
Localisation: focal
Syndrome: sleep-related hypermotor epilepsy (SHE)
Aetiology: unknown

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TEST YOURSELF

(1) What is the relationship between REM sleep and seizures?

(2) Is paroxysmal arousal (PA) a type of seizure?

(3) What is the relationship between arousal and the occurrence of seizures in epilepsy patients?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".