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Editorial

The far side of sleep: Towards a deeper understanding of parasomnias and nocturnal seizures

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This issue of *Sleep Science* contains an article by Yeh and Schenck about behavioral dyscontrol during sleep emerging with sporadic (non-familial) nocturnal frontal lobe epilepsy (NFLE) [1]. A series of eight cases was reported, with video-polysomnography (vPSG) and sleep EEG documentation, and successful treatment outcome [1]. The sporadic form of NFLE is not as frequently reported and not as well understood compared to familial, autosomal dominant NFLE. Two notable findings in this case series are that (i) the spectrum of clinical features of sporadic NFLE, including its therapy, closely match the well-known clinical features and therapy of familial NFLE; and that (ii) the spectrum of clinical features of sporadic NFLE, including its therapy, in this first published series in Asian patients (from Taiwan), closely match the extensive published findings in Caucasian patients with NFLE, as cited in the article. The challenging issue of distinguishing NFLE from nocturnal temporal lobe epilepsy (NTLE), and from NREM sleep parasomnias is also addressed in this article, with the pertinent literature cited. There are overlapping features of behavioral dyscontrol in sleep with these three conditions, which very likely reflect overlapping activations of central (motor) pattern generators (CPGs) in the brainstem [2]. Sleep related nocturnal dissociative disorder (Noc DD) also shares behavioral features with these conditions, and activation of CPGs was strongly suggested in one reported case in which a 19 y.o. male engaged in prolonged (for several minutes) constant leg pedaling, both at home and in the sleep laboratory, with both episodes captured on video [3].

It is now known that abnormal ambulation during sleep can be a manifestation of sleepwalking (SW), NFLE, NTLE, REM sleep behavior disorder (RBD), or Noc DD [3–5]. Likewise, screaming during sleep can be a manifestation of these same conditions [6]. So in regards to similar abnormal complex sleep behaviors, there is a broad range of causes and usually separate therapies, which places a premium on establishing the proper diagnosis, which can then direct appropriate therapy. To this end, the validated Frontal Lobe Epilepsy Parasomnias (FLEP) scale, developed by Derry et al. [7], has been particularly useful in distinguishing NFLE from NREM sleep parasomnias, as utilized in the Yeh and Schenck report [1]. Nevertheless, controversial points are still being debated, as the recognized difficulties "in distinguishing nocturnal epileptic seizures from parasomnias reflect just one aspect of the intriguing issue of the pathophysiological relationships between all types of paroxysmal motor behaviors during sleep" [8]. The complexity of these pathophysiological relationships is highlighted by a study finding a greatly increased rate of NREM sleep arousal parasomnias in families of patients with NFLE [9]. Research on the cyclic alternating pattern (CAP), an EEG marker of arousal fluctuations during sleep, calls attention to the unifying role of pathological

arousals, originating in thalamocortical circuits, across epileptic, parasomnia and other abnormal motor events during sleep [10]. A recent study found different CAP characteristics in patients with NREM sleep arousal parasomnias compared to patients with frontal and temporal lobe epilepsies [11], which encourages further research on identifying different CAP profiles across patient populations with behavioral disturbances during sleep.

Update on sleepwalking and other NREM sleep parasomnias

Traditional knowledge regarding NREM sleep parasomnias as being exclusively disorders of slow-wave sleep (SWS) and disorders of arousal (DOA) from SWS, without either associated dreaming, any recall of NREM parasomnia events, or any daytime clinical concomitants, is giving way to an updated, data-based perspective and new pathophysiological hypotheses that are considered to represent a "paradigm shift" in understanding SW and other DOA [12]. For example, there is growing evidence suggesting that excessive daytime sleepiness is part of the SW phenotype that is linked to its underlying pathophysiology, and which cannot be explained by any comorbid sleep disorder or PSG evidence of nocturnal sleep disruption [13–15]. Also, in adult SW there can be substantial recall of specific elements of SW episodes and also recall of associated dream mentation, in striking contrast to childhood SW [13]. These findings also highlight current knowledge that SW is an expression of simultaneously activated states of (partial) sleep and (partial) wakefulness, a complex dissociated state, with clinical consequences [13]. These partially activated states of sleep and wakefulness reflect regional brain activity of "local sleep" or of local wakefulness. The concept of sleep as a whole-brain phenomenon has thus been radically reconsidered. In the new framework, parasomnias, as clinical dissociated states, result from coactivations of sleep and wakefulness across different brain regions [16]. As stated by Zadra et al. in regards to the pathophysiology of SW, "a broad and unifying view might implicate the simultaneous activation of localized cortical and subcortical networks that have roles in sleep and wakefulness [13]".

A study on intracerebral EEG recording during sleep documented a dissociation of regional EEG activities during a parasomnia episode, illustrating how the brain phenomenon of "local sleep" can be the substrate for clinical dissociated states [17]. In this study, a young adult male with refractory focal epilepsy had a CA recorded by vPSG and intracerebral EEG. The dissociated state underlying the CA episode consisted of local arousal of the motor and cingulate cortices that contrasted with simultaneous increased slow waves in the frontoparietal associative cortices. These findings were present before the onset of the CA episode and throughout the CA. Therefore, this carefully documented CA episode was not a global sleep phenomenon, but rather a phenomenon of coexisting and contrasting local states of sleep and wakefulness.

A new clinical frontier for achieving a deeper understanding of NREM sleep parasomnias and other sleep disorders has been opened up by the use of high-density (256 electrode channels) sleep EEG monitoring during vPSG studies, developed by the Tononi group. In a recent study utilizing high-density sleep EEG in six healthy subjects [18], a total of 141 falling-asleep periods were analyzed to assess changes in slow-wave and spindle activity during this transitional state. The major finding was that the number and amplitude of slow waves followed two dissociated, intersecting courses during the wake-sleep transition: slow wave number increased slowly at the beginning and rapidly at the end of the falling-asleep period, whereas amplitude at first increased rapidly and then decreased linearly. Most slow waves occurring early in the transition to sleep had a large amplitude, a steep slope, and involved broad regions of the cortex. Most slow waves occurring later had a smaller amplitude and slope, and involved more circumscribed parts of the cortex. Spindles were initially sparse, fast, and involved few cortical regions, then became more numerous and slower, and involved more areas. The two types of slow waves identified in the wake-sleep transition had distinct cortical origins and distributions. The authors hypothesized that these two types of slow waves result from two distinct synchronization processes: (1) a subcortico-cortical, arousal system-dependent, process that predominates in the early phase and leads to "type I slow waves", and (2) a "horizontal", cortico-cortical synchronization process that predominates in the late phase and leads to "type II slow waves". The authors concluded that the dissociation between these two slow-wave synchronization processes in time and (brain) space suggests that they could become pathologically disturbed with sleep disorders – including NREM sleep parasomnias that emerge from slow-wave sleep.

Other promising future research areas that could lead to a deeper understanding of NREM sleep parasomnias include various brain imaging techniques (including SPECT, PET, transcranial magnetic stimulation), and familial, genetic, and molecular studies that should provide additional critical information on the neurobiological substrate of NREM sleep parasomnias [13].

Update on RBD

The "RBD odyssey" [19] continues at an accelerated pace while covering ever-expanding territories of research. The literature on RBD has continued to grow exponentially, both in breadth and depth since the exponential growth of RBD publications was first quantified [20]. The most compelling research, conducted by numerous international investigators, concerns the strong associations of RBD with neurodegenerative disorders, especially the alpha-synucleinopathies, viz. Parkinson disease (PD) dementia with Lewy bodies (DLB), and Multiple System Atrophy (MSA) [21,22]. There are two perspectives for considering this strong association. First, RBD can be the first clinical manifestation of future alpha-synucleinopathy neurodegeneration. Data from our center and from the Barcelona group have recently documented 81% and 82% "conversion rates", respectively, from idiopathic RBD (iRBD) to a parkinsonian disorder, with a mean interval of approximately 12–14 years from onset of iRBD to the clinical