

Nocturnal Frontal Lobe Epilepsy – An Update on Differential Diagnosis with Non-rapid Eye Movement Parasomnia

a report by

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Nocturnal frontal lobe epilepsy (NFLE) is a distinct paroxysmal sleep-related disorder covering a spectrum of presentations of presumed frontal lobe origin. NFLE starts in childhood and persists into young adulthood; is characterised by repetitive attacks with predominantly motor component, high frequency of attacks per night, inter-night repetition and stereotypy of the episodes; and displays uncommon electroencephalogram (EEG) ictal and interictal paroxysms during sleep.¹⁻⁴

NFLE is characterised by onset during infancy or childhood with persistence in adulthood, family history of similar NFL seizures and nocturnal episodes simulating non-rapid eye movement (NREM) parasomnias (sleep terrors or sleepwalking), general absence of morphological substrates based on clinical history and brain imaging, motor dystonic–dyskinetic attacks emerging from NREM sleep, repetitive and stereotypical features in the same patient and similar features among different patients, normal ictal and interictal EEGs without clear-cut epileptic paroxysms in more than 50% of the cases and general benefit from some antiepileptic drugs (AEDs), but occasional resistance to AEDs in some severe forms.

The different types of NFLE seizures may cause severe sleep disruption affecting both the macrostructure and microstructure of sleep and resulting in poor sleep quality, daytime tiredness and sleepiness. The movements may also be so severe that injuries resulting from striking hard objects can occur. One-third to half of patients also have occasional attacks during the day, not necessarily of the same type as those occurring at night-time, as well as secondary generalised tonic–clonic seizures. Neurological examination is generally normal.¹⁻⁴

Arousal Disorders

NREM parasomnias (arousal disorders) include confusional arousals, sleep terrors and sleepwalking. All are characterised by a motor component, autonomic activation, emotional involvement, poor memory or fragmented recalls of the episode, long duration (one to 20 minutes) and occurrence on emergence from deep NREM sleep, typically in the first third of the night with impairment in the ability to awake fully from

slow-wave sleep (SWS). They typically occur during the maturational age of life (childhood and adolescence), but may also persist in adulthood. Notwithstanding the sleep EEG characteristics of these arousal disorders as delta bursts or rhythmic delta activity preceding the episode, the slow-wave activity during the episodes and the polygraphic modification of heart rate, respiration and muscle tone, there is not, to date, a polysomnographic marker of these nocturnal phenomena.⁵⁻⁷

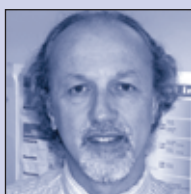
NFLE should be differentiated from parasomnias, in particular from NREM parasomnias such as arousal disorders. The clinical/anamnestic features are quite similar; however, the older age of onset, the high frequency of the episodes and their short duration, the partial preservation of consciousness and the tendency of the syndrome to persist in adulthood differentiate NFLE from arousal disorders. The motor pattern during sleep and the semiology of the attacks (stereotypy, dyskinetic and dystonic component, abrupt and sudden onset, dancing or jumping features for the more complex seizures) may be helpful, although the definite boundaries between the two types of episodes are still not completely understood. Differentiating paroxysmal arousal (PA) from confusional arousal (CA) is difficult because of the lack of paroxysmal EEG discharges in PA, and requires videopolysomnography (video-PSG).^{5,8}

The features that differentiate REM parasomnias from NFLE include later age of onset, motor episodes during the night enacting behaviour related to a dream, less stereotypical behaviour, polysomnographic characteristics of REM without electromyogram (EMG) atonia and an increase in EMG activity of the limbs.^{6,9} Other motor phenomena during sleep or sleep transitions, such as rhythmic movement disorder, hypnic myoclonus or physiological body movements, are easier to recognise. Nocturnal panic attacks are characterised by sudden awakening with complex autonomic activities and an unpleasant sensation of fear or imminent death, usually lasting longer than NFLE and, unlike in NFLE, not recurring. The presence of the same attacks during the day may also help to differentiate the syndrome from NFLE.^{3,4}

Differential Diagnosis – Clinical and Videopolysomnographic Findings

Notwithstanding the spread of video-PSG and the wide diffusion of the concept of NFLE, the differential diagnosis between some types of sleep-related seizures and paroxysmal non-epileptic motor events is still a challenge, and no definite guidelines have been approved for this field. Recently, groups in Melbourne (Australia)¹⁰ and Bologna (Italy)⁶ tried to delineate some practical points to differentiate or correlate NFLE and NREM parasomnias.

Given the time-consuming nature and the expense of executing a video-PSG for episodes that are often too infrequent to catch during



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a single night of recording, the Australian group tried to establish the reliability of anamnestic characteristics to distinguish NFLE from NREM when video-PSG is unavailable or unhelpful. On the basis of previous analyses and of practical experience, they developed a scale – Frontal Lobe Epilepsy and Parasomnias (FLEP) – with questions and possible answers determining a score. Responses favouring epilepsy score positively and those favouring parasomnias score negatively. These particular questions have been developed in a pilot subgroup of patients with a definite diagnosis, who were excluded from the application study.

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They compared the clinical diagnosis by FLEP scale with standard diagnostic tests – video-PSG and expert interviews – in a group of patients coming under observation for nocturnal episodes of uncertain definition. Three groups were defined – NFLE (31 patients), typical parasomnias (20 patients) and atypical parasomnias (11 patients).

The FLEP scale consists of 11 questions covering characteristics of the nocturnal attacks including age at onset, duration, clustering and timing of the episodes, symptoms, stereotypy, recall and vocalisation. According to the results, only three patients were erroneously classified by the non-medically trained, and two by the medically trained interviewer. In all cases, patients with atypical parasomnias with a low positive score were classified as having NFLE. The scale reached a sensitivity of 1 and a specificity of 0.9, with a Cohen k of 0.97 between different interviewers; notwithstanding the retrospective type of the study and the lack of video-PSG confirmation of typical parasomnias, the scale seems promising for the differential diagnosis of NFLE and parasomnias. However, the results need to be confirmed in a larger group of subjects and controlled in all the subjects with video-PSG.¹⁰

However, the weakness of the study is that the clinical features of the episodes are often neither completely nor well described by the bed partner, and the features of the attacks (stereotypy, repetitiveness, wandering or other characteristics) may belong both to parasomnias and seizures. This, in accordance with the theory that motor events may follow a stereotyped inborn fixed action pattern (motor central pattern generators), means that the syndrome is genetically determined and triggered by a common platform – the arousal network.¹¹ Thus, there may be a continuum between physiological movements in sleep, motor behaviour in parasomnia and some epileptic seizures. These considerations make clinical diagnosis intriguing but also difficult, and some concepts we have followed in the past years may not be completely applicable in this field.^{5,8,12}

Sometimes, sleep-related seizures similar to those observed in NFLE may arise from the temporal lobe rather than from orbitofrontal zones, in particular those characterised by affective symptoms and agitated and

deambulatory behaviours (known as epileptic nocturnal wanderings). They may involve large neuronal networks, sometimes with emergence from the frontal zone (orbitofrontal, anterior cingulate), but also with spreading to temporal limbic cortices.^{13,14} Moreover, some motor behaviours in this type of attack are not very different from some confusional arousals or sleepwalking episodes typical of NREM arousal parasomnias. The concept of the disinhibition of the innate motor pattern by central pattern generators may explain these similarities, as well as the possible co-existence in the clinical history (or in the familial tree) of parasomnia episodes in people affected by NFLE or seizures during sleep.^{3,6,8}

The guidelines for differentiating epileptic from non-epileptic motor phenomena during sleep provided by the Italian group article originated in some observed and verified statements. These were that behaviour patterns may be similar, semiological characteristics are not present in all the episodes – bearing in mind that the description by a witness may be not complete and adequate – and, finally, that clinically diagnostic tools – including EEG, video-PSG and video recording at home – are unreliable.

The authors reviewed the clinical aspects and features of the major motor phenomena during sleep and elaborated on remaining issues. They concluded that video-PSG analysis is of the utmost importance, but, due to lack of ictal and interictal scalp EEG abnormalities, is sometimes difficult to interpret. Furthermore, a debate is still open on the aetiopathogenesis of different epileptic and non-epileptic motor phenomena during sleep.²⁻⁴ The genetic form of NFLE – autosomal-dominant NFLE (ADNFLE) – has been linked to different mutations in the gene coding for neuronal nicotinic acetylcholine receptors (nAChR), but the exact mechanisms by which these mutations may modify the firing of neurons giving origin to seizures is not completely understood.¹⁵ Moreover, arousal disorders are often aggregated on a family basis and, in patients with NFLE, sporadic or genetic, we found co-existence of nocturnal parasomnic episodes or the presence of these attacks in family members.²⁻⁶

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Considering the central motor pattern generator theory, it is also possible that the genetic or sporadic alteration lies in the mechanisms controlling the arousal system, which explains why sometimes, or in some subjects, we can expect arousal disorders or epileptic seizures by the same activation but with different triggers – epileptic abnormalities or sleep-related dysfunctions.^{11,16} In support of this hypothesis, the authors collected data on familial aggregation of diagnosed NFLE patients and found, in comparison with a control population, a higher frequency of arousal parasomnias in NFLE probands and their relatives.⁶

Furthermore, the intracerebral recording techniques have not elucidated the problem. They helped to confirm the increasing

complexity and duration of different motor seizures due to the spread and propagation of the discharges within the frontal lobe in NFLE patients with drug-resistant seizures.¹⁷ However, deep electrode recordings showed that short-lasting minor motor events two to four seconds in duration – often related to brief intracerebral epileptic discharges – are not differentiated from physiological behaviours from a clinical and video-PSG point of view. The epileptic discharges may increase sleep fluctuations and possible physiological phenomena, as well as parasomnic episodes or periodic leg movements in sleep (PLMS), and arousal instability may increase the epileptic discharges. The result is that normal motor behaviours or periodic small movements (PLMS, bruxism, sleep-talking), whether or not accompanied by ictal discharges, are indistinguishable.^{18,19}

The frequency and stereotypy of the attacks during sleep – often considered a hallmark of NFLE diagnosis – are not completely explained by the morphology or distribution of the epileptic discharges. They may vary depending on the sleep stage, the level of arousal during which the discharges emerge and, sometimes, the body position of the patient.^{17,18} In general, minor episodes, if not accompanied in the same recording by more complex attacks, are difficult to differentiate from normal arousals/awakenings or parasomnias, and only the presence of a high number of these events together with a clinical suspicion of NFLE may be useful in discriminating between a sleep disorder and epilepsy.^{5,6,8,16} In any case, it remains to be explained why, with this form of epilepsy, seizures occur during sleep and rarely in wakefulness. It has been hypothesised that the genetic basis may facilitate the appearance of seizures during the synchronising state (NREM sleep), which activates oscillations between thalamocortical loops and brainstem-activating systems.²⁰ These very slow oscillations may manifest in the EEG as different forms of graphoelements – delta waves, K-complex, spindles or arousal fluctuations as in cyclic alternating pattern (CAP) – all of them with major expression on the frontal lobe. These oscillations may activate epileptogenic foci or, alternatively, arousal disorders, and may explain similar motor behaviours since they share a common pathway of the central motor pattern generator.^{11,20}

A recent observation using deep electrodes in nocturnal hyperkinetic seizures demonstrated that pre-seizure sleep spindles were longer than and different from interictal ones. This bore no relation to wake activity (12 hours as alpha activity) or the spatial relationship of the ictal onset, suggesting and emphasising the thalamic role and the importance of the thalamocortical circuit in generating seizures in NFLE.²¹ This thalamocortical loop dysfunction may again imply genetic alteration at the nicotinic receptor level, since defects at this level have been demonstrated in family members with NFLE. The dorsal thalamus

has the highest density of nicotinic receptors in the brain, and these receptors are probably involved in the arousal regulation.²² The same positron emission tomography (PET) study showed a reduction of these receptors in the prefrontal cortex. The shift of the pathogenetic mechanism to thalamocortical circuits is, to date, a hypothesis that needs to be confirmed in more patients. However, it may explain the preponderance of seizures during NREM sleep and the lack of classically interictal scalp EEG epileptiform abnormalities.

On the other hand, experimental studies in animals found an involvement of nAChR in the regulation of sleep microstructure, in particular of arousal oscillation.²³ This confirms that arousal oscillation, increase in micro-arousals, periodic instability of sleep microstructure (as measured by CAP rate increase) and the relationship of the nocturnal motor attacks with phase A of the CAP are more than an epiphenomenon of NFLE or ADNFLE. Thus, it is conceivable that a genetic alteration observed in NFLE might be the route of both epileptic susceptibility and arousal instability, giving origin to both parasomnias and frontal lobe seizures during sleep.¹⁶

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Conclusions

Despite standardised semiological and video-PSG criteria, guidelines to differentiate nocturnal frontal lobe seizures from arousal disorders are lacking, and critical or intercritical EEG are not useful. However, deep electrode research studies have allowed us to gather more information to define the border of the two disorders better. We are still a long way from evidence-based diagnosis for many sleep episodes. Video-PSG examination, although expensive and not always available in all clinical settings, remains the gold standard for diagnosis. Detailed clinical interviews, with bed partners where available, is a valid supportive instrument, and home video-recording of the episodes at night is to be encouraged. Further research in the genetic and epidemiological fields together with elucidation of the motor component of the nocturnal attacks by video-PSG, not only in sleep disorders but also in normal subjects, may help to define the border between these two interesting phenomena. ■

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