Pearls & Oysters: Diagnostic challenges in nocturnal frontal lobe epilepsy

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PEARLS

- Nocturnal frontal lobe epilepsy (NFLE) is best diagnosed by combined EEG-video recording.
- Clinical features of events can contribute to differentiation of NFLE and a parasomnia.

OY-STERS

- In many cases, the scalp EEG is unable to detect interictal and even ictal abnormalities, because the frontal lobe focus may be too deep to be detected.

CASE REPORT A 43-year-old man of normal intelligence consulted our outpatient clinic for nocturnal events that had started at age 32 years. These arise from sleep when he suddenly awakens, experiencing fear and the sensation of falling into a black hole or choking. He recalls raising his body and turning his head but does not recall what happens afterwards. His partner reported the events to be stereotyped, and occurring mostly after 1–2 hours of sleep. After rising, he falls backwards in the bed and jerks his arms and legs. He is unconscious for 3–5 minutes. Afterwards, he is confused and disorientated, and sometimes wanders through the house. These events occur once every 2 months and are debilitating. They affect his relationship and cause daytime sleepiness. Serial EEGs (including sleep deprivation), polysomnography, and MRI of the brain were normal. The individual was referred to our clinic for a 24-hour EEG video recording aiming to record an event. This EEG showed sporadic interictal epileptiform discharges (sharp waves, slow spike wave complexes), predominantly over the left frontotemporal area, but also over the right frontotemporal and frontal areas. During the night, 4 almost identical events occurred during non-REM (NREM) 1 and 2 sleep. In these events, the patient abruptly rose from the bed, looked around with an anxious expression, and went back to sleep after less than 20 seconds. In 2 events, an extension of the right hand was noted. The episodes were not followed by a phase of limb-shaking or by

disorientation. He did not call the nursing staff or remember the episodes afterwards. The EEG showed a K-complex at the beginning of each of these events, followed by a diffuse 11–12 Hz rhythm for several seconds, and was once followed by a short delta rhythm over the left frontotemporal region (figure). The episodes were accompanied by an acceleration of heart rate (from 54 to 72 bpm). After the event, when he closed his eyes again, a normal posterior dominant α rhythm was seen. As the events did not clinically resemble a physiologic arousal (due to the abrupt onset, marked stereotypy, and the tonic extension of the right hand), and in combination with the consistent (ictal) EEG findings, these episodes were considered to be of epileptic origin, and a diagnosis of NFLE was made (with paroxysmal arousals, sometimes with secondary generalization). Based on our findings during the EEG video recording, we speculated that the patient probably had more seizures than previously reported, which could also explain the excessive daytime sleepiness (EDS). Treatment was started with levetiracetam 1,000 mg twice daily and he became seizure-free. Moreover, EDS disappeared, confirming our hypothesis.

DISCUSSION Individuals with NFLE have seizures predominantly during sleep. The etiology can be genetic (e.g., autosomal dominant NFLE), lesional, or cryptogenic.¹ There is a male predominance and age at onset varies but is usually around adolescence.² Most seizures occur during NREM 2 sleep.³ It can be a debilitating disease as the seizures can also disrupt nocturnal sleep, resulting in EDS.³

Three different types of NFLE seizures can occur: paroxysmal arousals, nocturnal paroxysmal dystonia, and episodic nocturnal wandering.² Paroxysmal arousals, typically starting from NREM 2 sleep, are characterized by abrupt arousals during sleep, associated with stereotyped motor activity, and usually last less than 20 seconds. These seizures are the most frequent seizure type, comprising around 75% of all NFLE seizures. Nocturnal paroxysmal dystonia

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Figure EEG fragment in referential and bipolar montage during an event

Fragment of the EEG in referential montage common average (A) and bipolar montage (B) (time scale 20 seconds, amplitude scale 100 μ V/cm) during an episode of a sudden arousal accompanied by a fearful expression of the face and extension of the right hand. The EEG shows a K-complex (*), followed by diffuse α activity and left frontotemporal delta activity. Note the normal posterior dominant rhythm at the end of this fragment.

usually lasts less than 2 minutes, and seizures are characterized by dystonic/hyperkinetic features. Episodic nocturnal wandering can last up to 3 minutes, during which the individual leaves the bed and wanders around. Tachycardia and tachypnea often

accompany symptoms. It is possible for one person to have different NFLE seizure types, but the semiology at the onset of the seizure is usually stereotyped.

The frontal lobe is the biggest lobe and covers 40% of the brain. It can be roughly subdivided into 3 parts: the dorsolateral, mesial, and basal parts. Epileptiform activity from these sites is often hidden from detection by scalp EEG. It is suggested that seizures arising from the dorsolateral convexity produce abnormalities on EEG, ictally as well as interictally, but those from the mesial frontal and basal areas do not.^{4,5} Muscular artefacts can also mask ictal activity. In one study, around 50% of individuals had normal interictal wake and sleep EEGs.² Furthermore, only 56% of ictal registrations showed EEG changes, which can include diffuse or focal flattening of the background, focal theta or rhythmic delta activity, spike and waves complexes, or small amplitude fast activity.

The differential diagnosis of NFLE includes NREM parasomnias. NREM parasomnias include confusional arousals, somnambulism (sleepwalking), and sleep terrors. There are some clinical characteristics that may help to differentiate NFLE from NREM parasomnias (table). While the onset of NFLE and

Table Clinical characteristics favoring nocturnal frontal lobe epilepsy (NFLE) or non-REM parasomnia

Event characteristic	NFLE	Non-REM parasomnia
Timing of event	Anytime during sleep period	First third of sleep period
Duration	<30 seconds	>1 minute
No. events per night	Multiple	0-1
Awakening after event	Yes	No
Clear offset of event	Yes	No
Tonic/dystonic posturing	Possible	No
Stereotyped behavior	Yes	No
Violent behavior during event	Possible	No
Recollection of event	Possible	No
Interaction with environment	None to mild degree	High degree
Course on frequency of events during adulthood	Stable or increased	Decreased or disappearance

NREM parasomnias is usually in childhood, NFLE seizures are usually stable or increase in frequency during the course of the disease, while NREM parasomnias decrease or disappear during adolescence or adulthood.^{2,6} The number of events per month in NFLE is much higher than in NREM parasomnias, with a mean of 36 seizures compared to less than 1 to 4 attacks in parasomnias.^{2,6} The motor pattern of the attack can also give a clue to the diagnosis; dystonic or tonic posturing is thought to be seen only in NFLE.² Furthermore, stereotyped movements are suggestive of NFLE. The duration of NFLE is usually less than 1 minute, while NREM parasomnias can last for several minutes. Behavior in NFLE can be violent, as opposed to NREM parasomnias.^{2,6} A high degree of interaction with the environment (conversation/complex behavior such as opening drawers) is uncommon in epilepsy.⁷ Recollection of the attack is suggestive of NFLE, but no recollection may occur in both NFLE and NREM parasomnias.⁷ Patients with NFLE usually fully arouse after an event and the event has a clear offset, in contrast to patients with NREM parasomnias.⁸ More than half of seizures in NFLE arise from NREM 2 sleep, while NREM parasomnias often arise from NREM 3 sleep.^{2,6} NREM parasomnias therefore usually occur in the first third of the night, whereas NFLE can occur at any time during the night.^{2,6}

In 2006, the frontal lobe epilepsy and parasomnias scale was designed and validated.⁹ It was claimed to discriminate accurately between NFLE and parasomnias. In 2008, the scale was reassessed in a clinical setting, and was found to have a 6% risk of a false diagnosis; in a third of cases, the scale did not allow a definite diagnosis.¹⁰

EEG video recording is important in diagnosing NFLE. The EEG is sometimes unable to detect an ictal rhythm but additional video footage of the signs during the events may facilitate diagnosis.

AUTHOR CONTRIBUTIONS

F.M.E. Cox: drafting/revising the manuscript, study concept or design, accepts responsibility for conduct of research and final approval. G.J.

Lammers: drafting/revising the manuscript, accepts responsibility for conduct of research and final approval. R.D. Thijs: drafting/revising the manuscript, accepts responsibility for conduct of research and final approval. G.H. Visser: drafting/revising the manuscript, accepts responsibility for conduct of research and final approval.

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