ORIGINAL CONTRIBUTION

Distinguishing Sleep Disorders From Seizures

Diagnosing Bumps in the Night

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Background: Abnormal paroxysmal events in sleep may be parasomnias or epileptic seizures. In nocturnal frontal lobe epilepsy (NFLE), the unusual seizure features often lead to diagnostic confusion with nonepileptic parasomnias; video-electroencephalography monitoring is usually required to make the diagnosis.

Objective: To examine the reliability of the clinical history in diagnosing NFLE, using the Frontal Lobe Epilepsy and Parasomnias (FLEP) scale.

Design: The FLEP scale, comprising specific questions reflecting the diagnostic features of NFLE and parasomnias, was developed by an expert panel following review of the literature. It was then validated in a sample of individuals with firmly diagnosed nocturnal events.

Setting: Patients were recruited after appropriate diagnostic workup in tertiary sleep and epilepsy referral centers in Melbourne, Australia.

Participants: Sixty-two patients (45 men) with paroxysmal nocturnal events.

Intervention: Two independent interviews were conducted in each case, with the patient and a witness, by researchers blinded to the diagnosis.

Main Outcome Measure: The diagnosis obtained from scores on the FLEP scale was compared with the confirmed diagnosis in each patient.

Results: Nocturnal frontal lobe epilepsy was correctly diagnosed from the FLEP score in 31 of 31 patients, with a sensitivity of 1.0 (95% confidence interval [CI], 0.85-1.00), specificity of 0.90 (95% CI, 0.73-0.97), positive predictive value of 0.91 (95% CI, 0.75-0.97), and negative predictive value of 1.00 (95% CI, 0.85-1.00).

Conclusions: A diagnosis of NFLE can be made reliably using the clinical features identified in the FLEP scale. This may reduce the requirement for tertiary referral and extensive inpatient monitoring.

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THE DIAGNOSIS OF ABNORmal paroxysmal motor events in sleep presents a particular challenge for the clinician. On the one hand, such events may be parasomnias, such as sleepwalking or sleep terrors; these are benign nonepileptic sleep disorders defined as "unpleasant or undesirable behavioral or experiential phenomena that occur predominantly or exclusively during the sleep period."[1] On the other hand, they may be epileptic seizures, requiring investigation and treatment. In many cases, distinguishing seizures and parasomnias by means of the clinical history is relatively straightforward.[2] However, a particular form of epilepsy that is increasingly recognized poses a diagnostic challenge. Seizures arising from the frontal lobes often occur during sleep and, in many patients, are entirely restricted to sleep. Nocturnal frontal lobe epilepsy (NFLE) occurs sporadically or as an inherited form with an established genetic basis (autosomal dominant NFLE [ADNFLE]).[3] Mutations in 2 genes that encode the α4 and β2 subunits of the neuronal nicotinic acetylcholine receptor (*CHRNA4* and *CHRNB2*) have been associated with ADNFLE,[4-6] although such mutations are only identified in a minority of families with this condition.[7] Seizures in NFLE may have bizarre clinical features, with vocalization, complex automatisms, and ambulation; investigation with electroencephalography (EEG) and magnetic resonance imaging often shows no abnormality.[8] These characteristics result in frequent misdiagnosis, with the events often being labeled as pseudoseizures or parasomnias and some cases previously being designated as "paroxysmal nocturnal dystonia."[9] Conversely, some parasomnias may be violent and con-

fused with NFLE. Such misdiagnoses are clearly to the detriment of the patient, who may be denied appropriate treatment or treated inappropriately.

While typical parasomnias are often not a significant clinical problem, individuals with severe or frequent events often seek medical attention. A number of historical features have been described that may distinguish NFLE from parasomnias,[8,10] but the value of these features has not been systematically assessed. As such, most authorities recommend video EEG or video EEG–polysomnography[10] (PSG) for the diagnosis of paroxysmal nocturnal events. These investigations are the "gold standard" in this situation; they involve monitoring patients in sleep through neurophysiological, cardiorespiratory, and video modalities and recording their nocturnal events. They are expensive and inconvenient investigations requiring admission to the hospital and are only practical if the nocturnal events are happening on a frequent, preferably nightly, basis. In those patients with less frequent events, it will often not be possible to capture an event during a monitoring period, in which case the investigation will not usually clarify the diagnosis. In addition, access to video-EEG and PSG monitoring services varies widely in different regions, and for many patients, these investigations are not available. In many cases, therefore, the effective standard for diagnosis is the expert clinical interview; in this situation, the history is vital and holds the key to arriving at the correct diagnosis.

There is, therefore, a need to establish the reliability of historical features in distinguishing nocturnal frontal lobe seizures from parasomnias in those situations in which video EEG and PSG are impractical or unhelpful. We have developed the Frontal Lobe Epilepsy and Parasomnias (FLEP) scale to achieve this. Through validation of this scale in patients with established diagnoses, we have confirmed the value of the clinical history in the diagnosis of nocturnal events.

METHODS

SCALE DEVELOPMENT AND STRUCTURE

The FLEP scale (**Table**) was developed by an expert panel following review of the literature. The scale consists of a series of specific questions based on the clinical features of NFLE and parasomnias. Particular consideration was given to the nonrapid eye movement (NREM) arousal parasomnias, such as sleep walking and night terrors, because these conditions are most commonly confused with NFLE,[8,10] but the scale was designed to be broadly applicable. Questions were designed to address those features that, according to the medical literature and in the experience of the health care professionals involved, are useful in discriminating between the conditions (**Figure 1**). A choice of possible responses was assigned to each question, each with a score. Responses favoring epilepsy (such as events of brief duration, occurring multiple times per night) scored positively, and those favoring parasomnias (such as coherent speech without recall) scored negatively. Those features considered to be particularly strong indicators of either condition were given greater weighting based on the findings of a pilot study of 18 case histories. Cases used in the pilot study were not recruited into the formal validation study.

VALIDATION STUDY

Aims

The aim of the study was to compare the diagnosis made using the FLEP scale with the standard diagnostic test (ie, expert interview and, when necessary, recording of events using video-EEG monitoring). It was hypothesized that the total score, calculated by summing the individual scores on completion of the scale, would accurately predict diagnosis; an overall positive score should predict epilepsy, with a zero or negative score predicting parasomnias.

Inclusion and Exclusion Criteria

The study population comprised patients who had been referred to a sleep physician or neurologist with a history of nocturnal events of uncertain cause. Individuals with NFLE were eligible for the study if they had a history consistent with NFLE and at least 1 of the following: video-EEG monitoring with clinical or electrographic evidence of nocturnal frontal lobe seizures or a genetic mutation consistent with ADNFLE. In families with ADNFLE, no more than 2 family members from the same kindred were recruited.

Patients with parasomnias were recruited in 2 subgroups. The first group consisted of subjects who were referred to a sleep clinic for diagnosis of their nocturnal events but in whom a definite diagnosis of "typical" parasomnia was made by the specialist without recourse to video-EEG monitoring. In this group, the diagnosis was made on the basis of the history independently by 3 clinicians (a consultant adult epileptologist, a consultant pediatric epileptologist, and a consultant sleep pediatrician), none of whom were involved in the validation of the FLEP scale. The second group comprised cases in which there was diagnostic uncertainty on the basis of the history alone and in which the diagnosis was established by video-EEG or PSG monitoring. These cases were designated "atypical" parasomnias.

Recruitment

Patients with nocturnal events were recruited from 4 centers in Melbourne, Australia (Austin Health, Royal Children's Hospital, Monash Medical Centre, and Epworth Hospital). Subjects with NFLE and atypical parasomnias (confirmed by video-EEG or PSG monitoring) were recruited retrospectively from a review of existing medical databases and records covering a 10-year period. All patients with confirmed diagnoses who could still be contacted were approached regarding participation as well as all new cases identified during admission for investigation during a 2-year period. Subjects with typical parasomnias were recruited as a consecutive case series seen at a pediatric sleep clinic during a 2-year period. All subjects gave their written informed consent to the study protocol, which was approved by the medical ethics committees of the Austin Health, Royal Children's, Monash Medical Centre, and Epworth hospitals.

Scale Administration

Semistructured interviews were conducted twice for each subject by different researchers on separate occasions; the 2 interviews were at least 4 weeks apart. One researcher was a research assistant with experience in taking epilepsy histories but without medical training. The other was a physician experienced in the diagnosis and treatment of sleep disorders and epilepsy. The researchers were blinded to the patients' identities and diagnoses, as well as to each other's interviews. During the in-

Table. The Frontal Lobe Epilepsy and Parasomnias (FLEP) Scale

Clinical Feature		Score
Age at onset		
At what age did the patient have their first clinical event?	<55 y	0
	≥55 y	–1
Duration		
What is the duration of a typical event?	<2 min	+1
	2-10 min	0
	>10 min	–2
Clustering		
What is the typical number of events to occur in a single night?	1 or 2	0
	3-5	+1
	>5	+2
Timing		
At what time of night do the events most commonly occur?	Within 30 min of sleep onset	+1
	Other times (including if no clear pattern identified)	0
Symptoms		
Are the events associated with a definite aura?	Yes	+2
	No	0
Does the patient ever wander outside the bedroom during the events?	Yes	–2
	No (or certaian)	0
Does the patient perform complex, directed behaviors (eg, picking up objects, dressing) during events?	Yes	–2
	No (or uncertain)	0
Is there a clear history of prominent dystonic posturing, tonic limb extension, or cramping during events?	Yes	+1
	No (or uncertain)	0
Stereotypy		
Are the events highly stereotyped or variable in nature?	Highly stereotyped	+1
	Some variability/uncertain	0
	Highly variable	–1
Recall		
Does the patient recall the events?	Yes, lucid recall	+1
	No or vague recollection only	0
Vocalization		
Does the patient speak during the events and, if so, is there subsequent recollection of this speech?	No	0
	Yes, sounds only or single words	0
	Yes, coherent speech with incomplete or no recall	–2
	Yes, coherent speech with recall	+2
Total score		

terviews, clinical information was obtained from the patient and a witness (usually the patient's partner, relative, or parent in the case of a child). Participants were reminded at recruitment and at the start of each interview not to discuss the nature of any investigations, the treatment, or the diagnosis they had received.

STATISTICAL ANALYSIS

For statistical analysis, the FLEP scale was treated as a diagnostic test for NFLE, with a total score of +1 or greater indicating a diagnosis of epilepsy and a score of zero or less indicating parasomnias. Sensitivity, specificity, and positive and negative predictive values were calculated, with 95% confidence intervals. Interrater agreement for the diagnosis was assessed using a Cohen κ.[17]

RESULTS

SUBJECTS

The study was undertaken between June 1, 2003, and June 1, 2005. Eighty-four subjects who met the entry criteria for the study were identified. Twenty-two subjects were not contactable or declined to participate in the study, leaving a total of 31 participants (15 men) with NFLE, 11 (8 men) with atypical parasomnias, and 20 (12 men) with typical parasomnias. All patients with atypical parasomnias and NFLE had undergone diagnostic video-EEG monitoring. The specific diagnoses for the participants were: 8, ADNFLE; 23, sporadic NFLE; 29, NREM arousal disorders (confusional arousals, sleepwalking, or sleep terrors); and 2, rapid eye movement sleep behavior disorder. In the NFLE group, the mean age of study subjects was 27.9 years, with a mean age at symptom onset of 8.1 years; in the NREM arousal parasomnia group, the mean age of subjects was 13.2 years, with a mean age at symptom onset of 5.8 years; and in the rapid eye movement sleep behavior disorder group, the mean age of study subjects was 69.1 years, with a mean age at onset of 64.0 years.

ANALYSIS

There was almost perfect interrater agreement in diagnosis based on the FLEP scale, with a κ statistic of 0.97. The median FLEP score for the NFLE group was +5

Age at Onset
Although NREM parasomnias tend to appear at a somewhat earlier age than frontal lobe seizures, both usually first are seen in the pediatric population, and there is considerable variability in age at onset for both conditions, limiting the usefulness of this feature in making a diagnosis. In contrast, however, REM sleep behavior disorder is a parasomnia that usually appears in men older than 50 years; it is rare for NFLE to appear at this age.

Duration of Events
Parasomnias can be brief or prolonged but typically last for several minutes or longer. The seizures of NFLE, however, are short, usually lasting for less than 1 minute and only infrequently longer than 2 minutes.[8] Occasional longer events may be reported in NFLE, but prolonged events are very rare.[11]

Clustering
The seizures of NFLE often cluster, with several on any given night and sometimes 20 or more.[8] In contrast, parasomnias infrequently occur more than once or twice per night.

Timing
The seizures of NFLE characteristically occur during stage 2 sleep.[8,12] As such, they may occur at any time of night, but in some individuals they may commonly occur very soon after falling asleep. Parasomnias, on the other hand, usually occur from deep NREM sleep (slow-wave sleep)[13,14]; they typically occur in the first half of the night but usually 1 or 2 hours after falling asleep.

Symptoms
The only definite semiological feature of NFLE thought to differentiate it from parasomnias is the presence of dystonic or tonic posturing.[8] However, although extensive wandering with the performance of complex-directed activities has been reported in NFLE,[15] in our experience this phenomenon is relatively uncommon. In 1 large NFLE series, such events constituted only 3% of all recorded seizures,[8] and when present, they are rarely the only (or the most troublesome) seizure type.[11] Most frontal lobe seizures with ambulation involve brief bursts of agitated running or jumping, usually confined to the bedroom, as opposed to sleepwalking, which usually involves walking around or even outside the house and often performing complex tasks such as dressing or even driving.[16]
Furthermore, while many patients with NFLE are unaware of many or all of their seizures, a significant number will be aware of at least a proportion. In such cases, they often report a distinct aura, typically a somatic sensation or a feeling that their "breath is stuck in their throat."[3,9] Although in parasomnias, vague and indistinct recollections of frightening or unpleasant feelings may be recalled after the event, clear recollections of auras are not reported.

Stereotypy
Video studies of NFLE have revealed the extremely high degree of stereotypy of seizures within patients, with many individuals having multiple brief attacks identical in appearance to the onset of their longer seizures.[8] Parasomnias, on the other hand, usually show a degree of variability from attack to attack, although they will often be broadly similar in a given individual. It is important to take a detailed history in this regard because marked stereotypy may significantly favor a diagnosis of NFLE over parasomnias.

Recall
Although not always present, lucid recall of a proportion of events is relatively common in NFLE. Patients with parasomnias occasionally have vague recollection of some of the events, particularly if they wake toward the end, but lucid recall is exceptional.

Vocalization
Vocalization is very common in both parasomnias and NFLE. When restricted to shouts, groans, or single words such as "mum" or "help," this vocalization is of no discriminatory value. When present, however, more complex intelligible speech is significant. In NFLE, this speech is often a reflection of retained awareness and will usually be remembered; this is in marked contrast to the complex speech of parasomnias, which, by definition, occurs when the patient is not fully conscious and is not remembered the next day.

Figure 1. Clinical features that may be useful in distinguishing nocturnal frontal lobe epilepsy (NFLE) from parasomnias. These features were included in the scale based on their discriminatory value. NREM indicates nonrapid eye movement; REM, rapid eye movement.

(range, +1 to +11). The median score for the complete parasomnia group was –4 (range, –12 to +3); for the typical parasomnias, –4 (range, –9 to –1); and for the atypical parasomnias, –4 (range –12 to +3). The distribution of scores according to diagnosis is given in **Figure 2**.

For interviewer 1 (nonmedically trained), sensitivity was 1.00 (95% confidence interval [CI], 0.86-1.00), specificity was 0.90 (95% CI, 0.73-0.97), positive predictive value was 0.91 (95% CI, 0.75-0.97), and negative predictive value was 1.00 (95% CI, 0.85-1.00). For interviewer 2 (medically trained), sensitivity was 1.00 (95% CI, 0.86-1.00), specificity was 0.93 (95% CI, 0.79-0.98), positive predictive value was 0.94 (95% CI, 0.78-0.98), and negative predictive value was 1.00 (95% CI, 0.85-1.00).

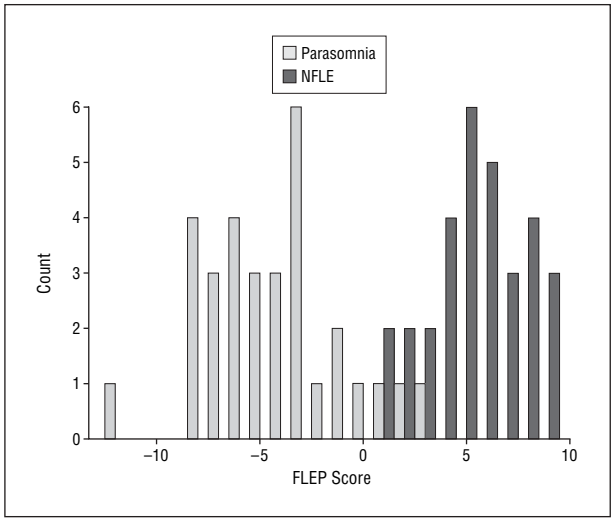

Figure 2. Frequencies of Frontal Lobe Epilepsy and Parasomnias (FLEP) scale scores generated by the nonmedically trained interviewer, color-coded according to actual diagnosis. Of the 62 patients interviewed, 3 had their conditions incorrectly diagnosed using the scale; these were all patients with parasomnias who generated low positive scores. The graph generated by the medically trained interviewer is very similar, but with only 2 misdiagnoses. NFLE indicates nocturnal frontal lobe epilepsy.

COMMENT

PRINCIPAL FINDINGS

Paroxysmal events in sleep may pose a significant diagnostic challenge to the clinician. While a number of conditions are associated with motor activity in sleep, particular confusion can arise when trying to differentiate between NREM arousal parasomnias and NFLE. This confusion arises through the similarities in the clinical features of these conditions and the fact that in both conditions magnetic resonance imaging and interictal EEG results are often normal.[8,18] While certain differences in the clinical histories in these conditions have previously been reported,[8,10] the usefulness of these features has not previously been examined in a systematic way. As a result, video-EEG or PSG monitoring is considered essential to confirm the diagnosis in difficult cases.[10] In this study, however, we have demonstrated that data from the clinical history alone are usually sufficient to accurately discriminate between NFLE and parasomnias, even in difficult cases. We have also shown that the FLEP scale is a valid and reliable instrument for facilitating this process and may, therefore, be a useful diagnostic tool for health care professionals with limited experience with NFLE.

STRENGTHS AND WEAKNESSES OF THE STUDY

The sensitivity of 1 and specificity of 0.9 are good for a test of this kind, and a Cohen κ of 0.97 indicates almost perfect interrater reliability. While both individuals conducting the interviews had some experience in taking epilepsy histories, the fact that the scores of the physician and the research assistant (who is not medically trained) were very similar suggests that specialist epileptological or sleep training is not required to reliably use this scale.

The main weakness of the study is the retrospective nature of recruitment for the monitored group of patients. These factors reflect the fact that NFLE is not common and parasomnias, although reported in around 15% of the pediatric population,[19] are usually mild and do not require tertiary referral for diagnosis and management. In the group of severely affected patients, recording events during video-EEG monitoring may still be difficult or impossible owing to the unpredictable nature of the attacks. Because of the relatively small numbers of patients with confirmed video monitoring findings per year, it was not practical to administer the FLEP scale prospectively (ie, before the diagnosis was confirmed by video monitoring).

A further potential criticism relates to the absence of confirmatory video-EEG monitoring in the consecutive series of typical parasomnias. While from a scientific perspective such supportive data would be desirable, in reality it is impractical to obtain them. If a secure diagnosis of parasomnias has been made by an expert on the basis of the history, it is rarely justified, clinically or economically, to admit a child for prolonged monitoring, and the investigation may well be fruitless for episodic attacks. We therefore only had video-EEG or PSG data on those patients with atypical parasomnias, in whom the diagnosis was regarded as uncertain.

COMPARISON WITH OTHER STUDIES

To our knowledge, this is the first study to systematically assess the reliability of salient historical features in the diagnosis of paroxysmal events in sleep. While a number of authors have described clinical features that are suggestive of NFLE, the majority have emphasized the need for confirmatory PSG.[8,10,18] We have demonstrated, in patients referred to tertiary centers for diagnostic review, that if the important features of the history are elicited and weighted according to the FLEP scale, the correct diagnosis will be reached in most cases.

MEANING OF THE STUDY AND USE OF THE SCALE

Using the clinical features we have identified in the FLEP scale, an accurate assessment of the likelihood of epilepsy may be made at the initial consultation, even when the clinician has limited experience with these conditions. Appropriate reassurance and treatment strategies may be given to those individuals with parasomnias, avoiding the need for specialist referrals and unnecessary anxiety and expense. Likewise, prompt investigation and treatment will be possible in those individuals with epilepsy.

From a practical perspective, there was a small degree of overlap in the FLEP scores for the 2 groups. We would conclude that, on the basis of this study, any patient with a score of zero or less is very unlikely to have epilepsy, and any patient with a score of greater than +3 is very likely to have epilepsy. In those with a score of +1 to +3, there is a relatively high chance of epilepsy, and further investigation would be required in these individuals. However, in our sample, such patients made up less than 20% of the total group, indicating that a rigorous clinical history (weighted according to the FLEP scale) may significantly reduce the need for tertiary referral and extensive investigation of paroxysmal nocturnal events.

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served," referred to the patient group that initially received placebo in the double-blind phase, not the patients initially randomized to memantine as Dr Schneider states.[1(p52)] *Also, Dr Schneider states in quotation 5 that we, "suggest[ed] a disease-modifying effect." Our actual statement on this matter was that "definitive conclusions . . . require prospective, randomized, double-blind trials."*[1(p53)]

We hope our report is not only informative and useful for clinicians and the families of patients, but also is useful in providing benchmarks for further achievements in the investigation of treatments for this progressive and prevalent disease.

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Correction

Errors in Abstract, Text, and Table. In the Original Contribution by Derry et al titled "Distinguishing Sleep Disorders From Seizures: Diagnosing Bumps in the Night," published in the May issue of the ARCHIVES (2006;63:705-709), subjects were incorrectly referred to as "men" instead of "males" in the "Participants" section of the Abstract on page 705 and in the "Subjects" subsection of the "Results" section on page 707. Also, the response to the row "Does the patient ever wander outside the bedroom during the events?" in the Table on page 707 should read "No (or uncertain)."