Distinguishing Sleep Disorders From Seizures

Diagnosing Bumps in the Night

Christopher Paul Derry, MRCP; Margot Davey, FRACP; Murray Johns, FRACP; Katie Kron, BSc; Deborah Glencross, BSc; Carla Marini, PhD; Ingrid E. Scheffer, PhD; Samuel F. Berkovic, MD

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.” 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. 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]). 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, although such mutations are only identified in a minority of families with this condition. 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. These characteristics result in frequent misdiagnosis, with the events often being labeled as pseudo-seizures or parasomnias and some cases previously being designated as “paroxysmal nocturnal dystonia.” 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 appropri-
ate 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 fea-
tures have been described that may distinguish NFLE from
parasomnias, but the value of these features has not
been systematically assessed. As such, most authorities
recommend video EEG or video EEG–polysomnogra-
phy (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 ad-
mission to the hospital and are only practical if the noc-
turnal 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 investi-
gations are not available. In many cases, therefore, the
effective standard for diagnosis is the expert clinical in-
terview; 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 Para-
somnias (FLEP) scale to achieve this. Through valida-
tion 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 fol-
lowing 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 non-
rapid eye movement (NREM) arousal parasomnias, such as sleep
walking and night terrors, because these conditions are most
commonly confused with NFLE, 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 use-
ful 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 posi-
tively, 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 in-
terview and, when necessary, recording of events using video-
EEG monitoring). It was hypothesized that the total score, cal-
culated 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 pre-
dicting parasomnias.

##### Inclusion and Exclusion Criteria

The study population comprised patients who had been re-
ferred to a sleep physician or neurologist with a history of noc-
turnal 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 clini-
cal or electrographic evidence of nocturnal frontal lobe sei-
zures or a genetic mutation consistent with ADNFLE. In fami-
lies 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 with-
out recourse to video-EEG monitoring. In this group, the diag-
nosis was made on the basis of the history independently by 3
clinicians (a consultant adult epileptologist, a consultant pedi-
atric 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 un-
certainty on the basis of the history alone and in which the di-
agnosis 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 Hospi-
tal, Monash Medical Centre, and Epworth Hospital). Subjects
with NFLE and atypical parasomnias (confirmed by video-EEG
or PSG monitoring) were recruited retrospectively from a re-
view 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 dur-
ing a 2-year period. Subjects with typical parasomnias were re-
cruited 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 medi-
cal ethics committees of the Austin Health, Royal Children's,
Monash Medical Centre, and Epworth hospitals.

##### Scale Administration

Semistructured interviews were conducted twice for each sub-
ject by different researchers on separate occasions; the 2 inter-
views were at least 4 weeks apart. One researcher was a re-
search assistant with experience in taking epilepsy histories but
without medical training. The other was a physician experi-
enced in the diagnosis and treatment of sleep disorders and epi-
lepsy. The researchers were blinded to the patients’ identities and
diagnoses, as well as to each other’s interviews. During the in-

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 $\kappa$. $^{17}$

### 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 participants 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 $\kappa$ statistic of 0.97. The median FLEP score for the NFLE group was +5

<table>
<thead>
<tr>
<th>Table. The Frontal Lobe Epilepsy and Parasomnias (FLEP) Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Feature</strong></td>
</tr>
<tr>
<td>Age at onset</td>
</tr>
<tr>
<td>At what age did the patient have their first clinical event?</td>
</tr>
<tr>
<td>$&lt;55$ y</td>
</tr>
<tr>
<td>$\geq 55$ y</td>
</tr>
<tr>
<td>Duration</td>
</tr>
<tr>
<td>What is the duration of a typical event?</td>
</tr>
<tr>
<td>$&lt;2$ min</td>
</tr>
<tr>
<td>2-10 min</td>
</tr>
<tr>
<td>$&gt;10$ min</td>
</tr>
<tr>
<td>Clustering</td>
</tr>
<tr>
<td>What is the typical number of events to occur in a single night?</td>
</tr>
<tr>
<td>1 or 2</td>
</tr>
<tr>
<td>3-5</td>
</tr>
<tr>
<td>$&gt;5$</td>
</tr>
<tr>
<td>Timing</td>
</tr>
<tr>
<td>At what time of night do the events most commonly occur?</td>
</tr>
<tr>
<td>Within 30 min of sleep onset</td>
</tr>
<tr>
<td>Other times (including if no clear pattern identified)</td>
</tr>
<tr>
<td>Symptoms</td>
</tr>
<tr>
<td>Are the events associated with a definite aura?</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Does the patient ever wander outside the bedroom during the events?</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No (or certain)</td>
</tr>
<tr>
<td>Does the patient perform complex, directed behaviors (eg, picking up objects, dressing) during events?</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No (or uncertain)</td>
</tr>
<tr>
<td>Is there a clear history of prominent dystonic posturing, tonic limb extension, or cramping during events?</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No (or uncertain)</td>
</tr>
<tr>
<td>Stereotypy</td>
</tr>
<tr>
<td>Are the events highly stereotyped or variable in nature?</td>
</tr>
<tr>
<td>Highly stereotyped</td>
</tr>
<tr>
<td>Some variability/uncertain</td>
</tr>
<tr>
<td>Highly variable</td>
</tr>
<tr>
<td>Recall</td>
</tr>
<tr>
<td>Does the patient recall the events?</td>
</tr>
<tr>
<td>Yes, lucid recall</td>
</tr>
<tr>
<td>No or vague recollection only</td>
</tr>
<tr>
<td>Vocalization</td>
</tr>
<tr>
<td>Does the patient speak during the events and, if so, is there subsequent recollection of this speech?</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Yes, sounds only or single words</td>
</tr>
<tr>
<td>Yes, coherent speech with incomplete or no recall</td>
</tr>
<tr>
<td>Yes, coherent speech with recall</td>
</tr>
</tbody>
</table>

Total score

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**PAROXSYMS**

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 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. However, while certain differences in the clinical histories in these conditions have previously been reported, 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. 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’s $\kappa$ 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, 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 parasymal 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. 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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**Correspondence:** Samuel F. Berkovic, MD, Epilepsy Research Centre, Department of Medicine (Neurology), University of Melbourne, Victoria, Australia (s.berkovic@unimelb.edu.au).

**Author Contributions:** Study concept and design: Derry, Davey, Johns, Marini, Scheffer, and Berkovic. Acquisition of data: Derry, Davey, Johns, Kron, Glencross, and Scheffer. Analysis and interpretation of data: Derry, Johns, Scheffer, and Berkovic. Drafting of the manuscript: Derry, Johns, Scheffer, and Berkovic. Critical revision of the manuscript for important intellectual content: Derry, Davey, Kron, Glencross, Marini, Scheffer, and Berkovic. Statistical analysis: Derry and Marini. Obtained funding: Berkovic. Administrative, technical, and material support: Johns, Kron, Glencross, and Berkovic. Study supervision: Davey, Johns, Scheffer, and Berkovic.

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**REFERENCES**

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. 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.”

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.

Barry Reisberg, MD  Rachelle Doody, MD, PhD  Frederick Schmitt, PhD  Steven Ferris, PhD

Correspondence: Dr Reisberg, William and Sylvia Silberstein Aging and Dementia Research and Treatment Center, New York University School of Medicine, 550 First Ave, New York, NY 10016 (barry.reisberg@med.nyu.edu).

Financial Disclosure: Dr Reisberg has received honoraria and travel support for lectures from Forest Laboratories, Merz Pharmaceuticals, and Lundbeck Pharmaceuticals, all manufacturers of memantine in various worldwide jurisdictions. He has also received grant support from Forest Laboratories and has served as a consultant to Merz Pharmaceuticals. Dr Doody has received compensation for consulting services and honoraria for lectures from Forest Laboratories. Dr Schmitt is a member of the speaker's bureau of Pfizer Inc and performs research consulting for Forest Laboratories and Pfizer Inc. Dr Schmitt also receives grant support from Pfizer Inc, Myriad, Sanofi-Synthelabo, and Forest Laboratories. Note that Dr Schmitt does not receive direct reimbursement for any of these activities; all of Dr Schmitt's honoraria and grant funds listed go to the University of Kentucky. Dr Ferris has previously been an investigator, consultant, and paid speaker for Forest Laboratories and a consultant and paid speaker for Merz Pharmaceuticals and Lundbeck Pharmaceuticals.


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).”