Nocturnal frontal lobe epilepsy
A clinical and polygraphic overview of 100 consecutive cases

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Summary
Nocturnal frontal lobe epilepsy (NFLE) has been delineated as a distinct syndrome in the heterogeneous group of paroxysmal sleep-related disturbances. The variable duration and intensity of the seizures distinguish three non-rapid eye movement-related subtypes: paroxysmal arousals, characterized by brief and sudden recurrent motor paroxysmal behaviour; nocturnal paroxysmal dystonia, motor attacks with complex dystonic–dyskinetic features; and episodic nocturnal wanderings, stereotyped, agitated somnambulism. We review the clinical and polygraphic data related to 100 consecutive cases of NFLE in order to define the clinical and neurophysiological characteristics of the different seizure types that constitute NFLE. NFLE seizures predominate in males (7 : 3). Age at onset of the nocturnal seizures varies, but centres during infancy and adolescence. A familial recurrence of the epileptic attacks is found in 25% of the cases, while 39% of the patients present a family history of nocturnal paroxysmal episodes that fit the diagnostic criteria for parasomnias. A minority of cases (13%) have personal antecedents (such as birth anoxia, febrile convulsions) or brain CT or MRI abnormalities (14%). In many patients, ictal (44%) and interictal (51%) EEGs are uninformative. Marked autonomic activation is a common finding during the seizures. NFLE does not show a tendency to spontaneous remission. Carbamazepine completely abolishes the seizures in ~20% of the cases and gives remarkable relief (reduction of the seizures by at least 50%) in another 48%. VideoEEG recordings confirm that NFLE comprises a spectrum of distinct phenomena, different in intensity but representing a continuum of the same epileptic condition. We believe that the detailed clinical and videoEEG characterization of patients with NFLE represents the first step towards a better understanding of the pathogenic mechanisms and different clinical outcomes of the various seizure types that constitute the syndrome.

Keywords: nocturnal frontal lobe epilepsy; paroxysmal arousal; nocturnal paroxysmal dystonia; epileptic nocturnal wanderings; parasomnias

Abbreviations: ADNFLE = autosomal dominant nocturnal frontal lobe epilepsy; ENW = episodic nocturnal wanderings; NFLE = nocturnal frontal lobe epilepsy; NPD = nocturnal paroxysmal dystonia; NREM = non-rapid eye movement; PA = paroxysmal arousals

Introduction
The widespread use of EEG recordings under audiovisual monitoring has disclosed several pathological conditions characterized by paroxysmal motor events during sleep. Two broad nosological categories with episodes of motor activity during non-rapid eye movement (NREM) sleep stages have been identified, namely the parasomnias such as sleep terror and sleep-walking, which are thought to represent disorders of arousal during sleep (Broughton, 1968), and the epileptic seizures arising during sleep (nocturnal or morpheic epilepsy). Among the latter, particular attention has been devoted in recent years to those seizures arising from epileptic foci located within the frontal lobe, so-called nocturnal frontal lobe epilepsy (NFLE). In past decades, the absence of clear-cut epileptic abnormalities on the scalp EEG, especially in epileptic children displaying nocturnal motor attacks, was thought to indicate that the episodes were parasomnias, even when they occurred in epileptic patients (Tassinari et al., 1972). Several isolated reports, however, documented epileptic abnormalities in patients with attacks clinically resembling sleep terrors or sleep-walking. In more recent
years, the clinical features of frontal lobe epilepsy have been elucidated, in particular the frequent absence of clear-cut epileptic abnormalities on the scalp EEG even during the ictal episodes, and the frequent onset of seizures during sleep (Tharp, 1972). Differentiating an epileptic from a parasomniasic attack by the EEG recording alone is not straightforward when the epileptic focus is located in the deep or mesial frontal regions and the attacks are restricted to NREM sleep. Over the last 20 years we have observed many patients complaining of nocturnal motor attacks. In 1981 we used the terms hypnogenic and later nocturnal paroxysmal dystonia (NPD) to label a syndrome characterized by recurrent motor attacks with dystonic–dyskinetic features arising from NREM sleep and usually lasting <2 min. The short duration, the stereotypic features of the episodes and the response to antiepileptic drugs, sometimes at low dosages, suggested an epileptic origin of this syndrome. However, the absence of ictal and interictal scalp EEG abnormalities and the extrapyramidal motor pattern could not exclude an undescribed paroxysmal movement disorder (Lugaresi and Cirignotta, 1981; Lugaresi et al., 1986). The epileptic nature of NPD subsequently was proved by us in three cases in which the use of special EEG electrodes (sphenoidal or zygomatic) disclosed epileptic EEG activity over the mesiotemporal regions (Tinuper et al., 1990). Meierkord and colleagues (Meierkord et al., 1992) subsequently demonstrated that the attacks in NPD patients not showing EEG epileptic abnormalities were clinically indistinguishable from those in which epileptic EEG activity was present. Meanwhile, it had been recognized that orbital and mesial frontal seizures, just like NPD, are characterized by complex bizarre motor patterns with bimanual/bipedal activity, rocking axial and pelvic movements and sometimes ambulation and by the frequent absence of epileptic abnormalities on routine scalp EEG and a frequent occurrence during sleep (Wada and Purves, 1984; Williamson et al., 1985). These epileptic seizures originate from deep frontal regions and for this reason routine scalp EEG is often inadequate to detect clear-cut epileptic abnormalities even during the episodes (Wada and Purves, 1984; Williamson et al., 1985). As more cases came to our notice over the years, we realized that it was impossible to group all NFLE patients together, as their nocturnal attacks had heterogeneous clinical features.

Paroxysmal arousal (PA) is the term we used to identify abrupt recurrent arousals from NREM sleep, associated with a stereotypic motor pattern, usually lasting <20 s. The epileptic nature of these episodes was documented by the finding of EEG epileptic activity during the attacks and by their response to antiepileptic drugs (Montagna et al., 1990). Patients displaying PA thus seemed to represent a group distinct from the usual NPD patients. However, PA and NPD could co-exist in the same case. That a relationship existed between PA and NPD was confirmed by our observation that PA could represent just the beginning of a full-blown NPD attack in those patients displaying both types of attacks (Montagna et al., 1990; Montagna, 1992; Sforza et al., 1993). Another feature of our patients was that both PA and NPD attacks were sometimes observed to recur quasiperiodically during long stretches of NREM sleep, especially during the light sleep stages, with the periodicity of 20–40 s typical of other physiological events of light sleep (Lugaresi et al., 1972), suggesting a modulation of the periodicity of epileptic attacks by the mechanisms involved in the organization of sleep microstructure. Later still, we documented the epileptic nature and the frontal lobe origin of the so-called episodic nocturnal wanderings (ENW) (Pedley and Guilleminault, 1977; Plazzi et al., 1995) in three cases with somnambulic agitated behaviour arising from NREM sleep. The epileptic origin of ENW had already been suggested (Pedley and Guilleminault, 1977), but had been refuted (Maselli et al., 1988; Oswald, 1989). Since PA, NPD and ENW can all occur together occasionally in patients, we deemed it likely that all of these attacks represented the spectrum of the NFLE syndrome (Montagna et al., 1990; Montagna, 1992; Plazzi et al., 1995).

Developments thereafter occurred in the characterization of the genetics and molecular biology of NFLE. A familial clustering of NFLE had already been noted (Lee et al., 1985; Montagna, 1992; Vigevano and Fusco, 1993; Plazzi et al., 1995). More recently, Scheffer and colleagues (Scheffer et al., 1994a, 1995a) reported five families with NFLE inherited as an autosomal dominant trait, and introduced the term autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), the first partial epilepsy to show an autosomal dominant transmission. Linkage studies localized a gene for ADNFLF to chromosome 20q13.2 (Phillips et al., 1995) and later a mutation was identified in the neuronal nicotinic acetylcholine receptor α4 subunit in a single large Australian kindred (Steinlein et al., 1995). More recently still, a novel mutation in the M2 domain of the CHRNA4 gene was identified in a Norwegian family (Steinlein et al., 1997). Such mutations have not yet been confirmed in other families with NFLE (Berkovic et al., 1995; Mochi et al., 1997), indicating a genetic and probably also a clinical heterogeneity within ADNFLE. It is now necessary to characterize every case of NFLE as fully as possible, to specify any possible phenotypic variability. We describe here the clinical features of NFLE in a large population of patients, all studied in a uniform manner. Our twofold aim was to identify the differential features, if any, with the common parasomnias (sleep-walking and sleep terrors), still a frequent diagnostic challenge, and to see whether specific patterns disclose separate clinical entities within the larger NFLE family. This may be relevant to current clinical practice, since NFLE is found in 13% of all patients referred to our sleep laboratory for nocturnal motor disorders.

Material and methods
One hundred and twenty-six consecutive patients admitted to our Institute from 1972 to 1995 for nocturnal paroxysmal episodes suggestive of NFLE received a full neurological
examination (with particular emphasis on family history) and routine repeated EEG recordings during wakefulness. They subsequently underwent polysomnography which included in all cases standard bipolar EEG (according to the International 10–20 System), EOG, ECG, chin and limb (right and left deltoideus and tibialis anterior muscles) EMG, and chest and abdominal respiratory movements. Recordings were taken from bedtime to 1 h after awakening in the morning using closed circuit TV and continuous audiovisual split-screen monitoring. A physician and technicians were present throughout the recordings to assess vigilance and consciousness in case of seizures.

We placed additional sphenoidal or zygomatic electrodes (Sperling and Engel, 1986) in 37 of 55 (67%) patients with normal interictal scalp EEG.

Patients on antiepileptic drugs reduced or withdrew therapy 1–2 weeks before polysomnography. Patients were also asked to stop any sleep or psychoactive medication at least 1 week prior to the study. All of them had already undergone brain CT or MRI.

We screened all videopolysomnographic recordings for motor episodes, and, after selecting any motor event which had occurred during the recordings, we assembled those which could be defined as pathological. At the same time we examined the EEG tracings and then compared EEG patterns with the seizure semiology. We finally compared seizure semiology with the other clinical and demographic data.

Diagnosis of NFLE was straightforward when patients displayed one or more episodes associated with clear-cut ictal epileptic frontal activity during polysomnography. When ictal EEG was uninformative, we required the recording of more than one seizure with a stereotypic motor pattern, during one or more polysomnography recording. On the basis of the different intensity, duration and features of the motor pattern, we classified the epileptic seizures into three groups according to Montagna (Montagna, 1992). PA were the briefer (<20 s) episodes in which patients suddenly opened their eyes, raised their heads or sat up in bed with a bizarre posture of the limbs, staring around with a frightened or surprised expression and sometimes screaming; they then went back to sleep. NPD had a longer duration (20 s–2 min) and a more complex behaviour characterized by wide, often violent, sometimes ballistic movements, with dystonic posturing of the head, trunk and limbs such as head rotation, torsion of the trunk and choreo-athetoid movements of the arms and legs with vocalization. ENW were the longest episodes (1–3 min) in which the characteristic feature was stereotypic paroxysmal amnabulation during sleep, often agitated and accompanied by screaming and bizarre, dystonic movements. Finally, the presence of the CHRNA4 mutations [C→T transition at nucleotide 743 (Ser248Phe) and insertion at nucleotide 776 (776ins3)] was tested on DNA extracted from blood according to the method of Steinlein and colleagues (Steinlein et al., 1995, 1997) in 30 patients, 21 with NFLE and familial recurrence of nocturnal paroxysmal motor phenomena and nine sporadic cases.

Results

One hundred and ninety-eight polysomnography recordings were screened and 100 contained at least one paroxysmal episode. Thus 100 of 126 patients (70 males, 70%) manifested one or more nocturnal attacks during polysomnography and were analysed. The other 26 had uneventful recordings and were excluded from the analysis. At the time of our first observation, patients’ ages ranged from 6 to 65 years (mean 26 ± 12 years). The nocturnal paroxysmal episodes had appeared from 1 to 58 years (mean 12 ± 10) before our first observation. Patients were thereafter followed up by us for from 1 to 23 years (mean 3.5 ± 4 years).

Clinical data

Family history

Thirty-nine patients (39%) had at least one first degree relative with a probable primary parasomnia. The diagnoses, multiple in 17 patients, were made on clinical grounds without polysomnography, and included sleep-talking in 24 patients, sleep-walking in 21, primary enuresis in seven, sleep-terror in five, bruxism in four, head banging in one and REM-sleep behaviour disorder in another.

Twenty-five patients had a family history of epilepsy, eight of whom (belonging to six families) had NFLE (confirmed by polysomnography in three) with nocturnal episodes quite similar to those of the proband. In these cases, a pedigree study disclosed in all a transmission pattern consistent with autosomal dominant inheritance. In fact, five kindreds presented two or three affected members with a vertical transmission in two generations. The other family had four affected individuals in three generations. Six patients had a family history both for epilepsy and otherwise typical parasomnias.

Personal history

Thirty-four patients (34%) presented in their personal history, mostly in infancy, sleep disorders resembling sleep-talking, pavor nocturnus, enuresis, head banging and sleep-walking. A 1 to >30-year gap separated the last parasomniac manifestations from the onset of the NFLE seizure. Seven patients only had significant perinatal suffering, three had had febrile convulsions and three a mild head trauma preceding seizure onset (by age 16, 15 and 5 years).

Age at onset

Age at seizure onset ranged from 1 to 64 years (mean 14 ± 10 years).
Fig. 1 A typical PA seizure. An abrupt arousal during which the patient opens his eyes and raises his head, trunk and limbs with a fearful expression. The episode lasts 19 s. Polysomnograph: a K-complex precedes the seizure onset. Marked tachycardia and irregular breathing also occur.

**Reported frequency of nocturnal seizures**
Patients reported a mean of $20 \pm 11$ seizures per month. Sixty-one per cent of them reported $>15$ seizures per month. Patients with nightly seizures reported a frequency ranging from one to 20 seizures (mean $3 \pm 3$ attacks each night).

**Triggering factors**
In 78 cases (78%), no precipitating factors for the seizures were reported. Eighteen patients complained that psychological stress was a trigger for the nocturnal seizures, while in three cases seizures appeared after sleep deprivation and in one case peri-menstruation.

**Presence of secondarily generalized seizures**
Twenty-eight (28%) patients reported occasional nocturnal episodes different from the usual ones and clinically resembling secondarily generalized seizures with often prolonged tonic or vibratory and asymmetrical features.

**Sleep complaints**
Patients often complained of nocturnal sleep discontinuity, with sleep disrupted by repeated arousals. A remarkable number (72%), however, were not aware of their nocturnal motor manifestations. These were, in such cases, reported and described by their relatives, who instigated the medical consultation. In 18 cases, patients or relatives reported only episodes of duration and semiology suggesting PA, and in 47 cases they reported more complex behaviours with the characteristics of NPD, with six of them also reporting the association of briefer episodes like PA. Thirty-five patients referred stereotypic ambulatory behaviour suggesting ENW, eight of them associated with shorter episodes suggesting PA and/or NPD.

**Seizures during daytime wakefulness**
Thirty-four patients (34%) also had occasional seizures during daytime wakefulness, similar to the seizures during sleep. In 11 cases, daytime seizures had begun before the nocturnal episodes, in 15 cases they had appeared simultaneously and in eight cases after nocturnal seizure onset. In six cases, however, daytime seizures were sporadic, present for a few days or years, (in two cases, no more than five seizures in all, in one case seizures for a few days in a row only and in another case occasional seizures from age 10 months to 4 years).
Neurological examination
Neurological examination was normal in 92 cases (92%). We noted remarkable facial asymmetry in three patients; slight hemisomatic asymmetry in one case; slight mental retardation in two patients; and asymmetric tendon jerks in another two patients.

Neuroradiological examination
All patients underwent neuroradiological examination by means of enhanced brain CT and/or MRI. Abnormalities were disclosed in 14 cases (14%) and included frontal vascular malformation (two cases); ischaemic lesions (four cases: three frontal and one occipital); frontobasal arachnoid cyst (three cases); frontal cortical dysplasia (three cases); temporal atrophy (one case); and frontal gliosis (one case).

Videopolysomnographic data
We recorded two or more seizures with a stereotypic motor pattern in 93 of 100 patients, and in seven we recorded only a single episode but with clear-cut epileptic EEG activity upon polysomnography recording.

Seizure semiology
We recorded 495 PA episodes, lasting from 2 to 20 s (mean 9.8 s). Patients with PA had a mean of seven episodes per polysomnography recording. In 45% of the episodes, the first movement involved the upper limbs: the patients suddenly raised their arms while asleep, or assumed a dystonic posture of one hand or gesticulated with fingers or had massive jerks of the arms. In 21% of the attacks, the motor pattern subsequently spread to the lower limbs, with jerking, bending or rocking movements; in 15% of the episodes, the patients raised their heads and moved their hands to the face (5%) or arched their trunks (4%). In 26% of the episodes, the first movement was raising the head, then opening the eyes (7%) or moving the upper limbs (5%). In 12% of the episodes, however, the first movement occurred in the legs and then in the arms. As belated movements, the patients moved their backs or chewed and emitted sounds. After the attacks, all patients quickly went back to sleep. In the remaining 17% of the cases, seizure onset was characterized by the eyes opening (6%), swallowing (4%), shouting (4%) and pelvic movements (3%). In eight patients, seizures were characterized by asymmetric sustained posture of the limbs with choreo-athetoid movements such as vermicular movements of the fingers or of the feet (Fig. 1).
Fig. 3A and B.
Fig. 3 (A) An ENW seizure. The seizure is characterized by violent and complex ambulatory activity (2 min and 50 s). (B and C, opposite) Polysomnographs: after a spike and wave complex coinciding with arousal, a small amplitude fast activity appears over the anterior regions, more evident on the left. A paroxysmal EEG activity, partially masked by muscle artefacts, persists throughout the seizure. Tachycardia and irregular breathing accompany the episode.

We recorded 149 NPD episodes, lasting from 25 to 98 s (mean 33 s). There was a mean of three NPD episodes per polysomnography recording. In 32% of the episodes, the first movement involved the upper limbs followed by the lower limbs (14%), head (10%), trunk (3%) and eyes (opening) (3%). In 23% of the seizures, the first movement involved the lower limbs, with kicking or cycling and then the upper limbs (6%) or the trunk (rocking) (6%). In 20% of the episodes, the first movements involved the head, spreading then to the upper limbs (3%), the trunk (4%) or the eyes (7%). Finally, in only 15% of the episodes was the first movement opening of the eyes, then moving the lower limbs (4%) and the head (5%); in 4%, seizures began with pelvic movements; in 2% of the cases, patients had a facial grimace or swallowed (2%); in only 1% did the patient put the hands to the face and in another 1% the patient spoke or shouted. In nine patients, attacks displayed a violent ballistic pattern with flailing of the limbs (Fig. 2).

Compared with PA, these episodes were characterized by prolonged tonic or dystonic postures sometimes with superimposed clonic jerks of the involved limbs.

We recorded a total of 16 ENW episodes which lasted from 31 to 180 s (mean 87 s), characterized by raising the head (60%), opening the eyes (53%), moving the trunk (40%), sitting on the bed, stretching out the legs, leaving the bed and then moving around the bed and the room (100%). The patients often vocalized or spoke unintelligibly (75%), or screamed with a terrified expression (Fig. 3).

Intraindividual stereotypy was remarkable in all types of attack and in all patients. In fact, attacks, whether PA, NPD or ENW, were remarkable for their conserved temporal and motor pattern which remained constant from one attack to another. Such a high degree of phenotypic stereotypy was confirmed by us in those patients who underwent several polysomnography recordings: in one case of PA, up to 52 identical episodes were recorded, and 11 NPD and 14 ENW episodes in other individuals.

Whenever possible, patients were interviewed during the seizures. Twenty-seven patients were interviewed during PA episodes. Patients were in contact immediately at the end of the episode and 12 out of the 27 also during the PA episode: when interviewed, the patient answered promptly and relevantly, and in some cases reported an undefined sensation (such as falling, sudden arousal, imminent death).

Out of the 59 cases interviewed during NPD episodes, 26 (44%) were in contact at the end of the episode and 10 also during the episode (sometimes the patients voluntarily tried to stop the involuntary movements, for instance by holding firm the moving limb); 19 patients during and four at the end of the NPD episodes were not in contact.

During the ENW, all of the four patients interviewed were not in contact, but they correctly answered questions immediately at the end of the seizure.

In 12 patients, a typical NPD seizure developed into a full-blown secondarily generalized seizure. All of these
patients had reduced or withdrawn antiepileptic drugs before polysomnography.

Periodicity
In 25 patients (25%), seizures of different intensity recurred periodically every 20 s to 2 min during sleep. In most (72%) of these cases, such a periodicity had become evident since the first stage 2 NREM sleep, in 14% during stage 3–4 and in 14% during the first REM sleep stage. In all patients, the periodic movements mimicking those observed during the seizure involved the legs (the feet in 15, the legs in five), whereas only five displayed movements of the arms.

Sleep stages during which seizures appeared
Seizures appeared between 1 and 558 min after sleep onset (mean 207 ± 133 min). Ninety-seven per cent of the attacks appeared during NREM sleep: 69% of the cases during light (stage 1–2) and 28% during deep (stage 3–4) sleep. Only three percent of seizures occurred during REM sleep.

Interictal wake EEG
Fifty-five patients (55%) had a normal wake scalp EEG. In 33 patients (33%), EEG showed clear-cut focal epileptic abnormalities: frontal (six cases), frontotemporal (seven cases), frontoparietal (one case), temporal (11 cases), occipital (one case) and, in seven cases, only by sphenoidal leads. Aspecific focal EEG theta activity was recorded in 12 patients. Right and left hemispheres were affected equally.

Interictal sleep EEG
In 51 patients (51%), sleep EEG was completely normal. Forty-five patients (45%) showed focal epileptic abnormalities: frontal (12 cases), frontotemporal (nine cases), frontoparietal (three cases), centroparietal (two cases) and temporal (10 cases). In nine of these 45 cases, the focal abnormalities were detected only on sphenoidal leads. Four patients showed focal slow activity.

Ictal polysomnography
EEG recordings during the attacks failed to disclose ictal epileptic activity in 44 cases (44%). In such cases, EEG was often masked by muscular artefacts or characterized by an abrupt transition to wake activity or light sleep, often preceded by a K-complex. The first EEG modifications were either a diffuse (14 cases) or focal (five cases) flattening of background activity, or focal theta activity (15 cases), or a rhythmic delta activity (six cases). In eight patients only, ictal EEG was characterized by spikes and spike-wave activity and in eight cases by a small amplitude fast activity.

In 42 patients, ictal EEG displayed a clear-cut focal pattern: 21 cases frontal, six frontotemporal, one vertex and one temporal; in 13 patients, rhythmic theta activity or epileptic (spike and spike waves) abnormalities were confined to the sphenoidal and/or zygomatic leads. In 21 cases, the abnormalities affected the right-sided regions, in 21 those on the left.

Autonomic modifications were remarkable in most of the cases: tachycardia (88 cases), sustained tachypnoea (40 cases) and irregular respiratory rhythm (37 cases) appeared synchronously with seizure onset or preceding the movement artefact. We also recorded the photoplethysmogram in 13 patients: polysomnography recordings displayed abrupt flattening of the photoplethysmogram at the beginning of the seizure, sometimes preceding the motor attack and the other autonomic modifications (Fig. 4).

The videopolysomnographic data of the different type of seizures are summarized in Tables 1 and 2.

Follow-up and response to antiepileptic drugs
Based on our earlier experience (Lugaresi et al., 1981; Lugaresi et al., 1986), carbamazepine was the drug of our choice in these patients. Eighty patients received carbamazepine at a dosage varying from 200 to 1000 mg/day in monotherapy (59 cases) or polytherapy (21 cases), associated with one or more of these drugs: clonazepam nine cases, phenobarbital seven, clobazam three, lamotrigine three, vigabatin three, phenytoin one, valproic acid one, primidone one). Only one patient had to stop carbamazepine because of somnolence and ataxia. In 16 cases (20%), carbamazepine controlled the nocturnal seizures completely, in 19 cases (24%) it reduced nocturnal seizures by at least 75% and abolished any occasional diurnal attack and in 19 cases (24%) it reduced seizures by half. In 25 cases (32%), carbamazepine did not modify seizure frequency at all.

The one patient who had to withdraw carbamazepine obtained a 98% reduction of seizures with phenytoin. In five cases, carbamazepine was withdrawn because it was ineffective, and phenytoin (in two) or clobazam (in three, in one case associated with valproic acid) were instituted, without any significant efficacy. An analysis of the cases with seizures resistant to carbamazepine showed that most (72%) had >25 seizures per month. Of these patients, only one had PA, 20 PA + NPD and four PA + NPD + ENW.

One patient did not receive carbamazepine but underwent neurosurgery for a vascular right frontal malformation, with total disappearance of the seizures.

Only two patients were not put on carbamazepine. One had received clonazepam and another phenytoin, phenobarbital and valproate in other institutions.

Seventeen patients refused any drug because their seizures were not disturbing, or because they had a spontaneous reduction of seizure frequency (two cases).

Genetic findings
Of the 30 patients investigated, nine sporadic and 21 with positive family history, all tested negative for the CHRNA4 mutations.
Fig. 4 NPD seizure: the ictal polysomnograph showed a marked autonomic activation with tachycardia, abrupt flattening of the plethysmogram and irregular breathing.

Table 1 Videopolysomnographic data

<table>
<thead>
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<th>PA</th>
<th>NPD</th>
<th>ENW</th>
<th>Total</th>
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<tr>
<td>Number of seizures recorded</td>
<td>495</td>
<td>149</td>
<td>16</td>
<td>660</td>
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<tr>
<td>Seizure duration (s)</td>
<td>9.8</td>
<td>33</td>
<td>87</td>
<td>18</td>
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<td>Seizure onset after sleep onset (min; mean ± standard deviation)</td>
<td>195 ± 125</td>
<td>217 ± 140</td>
<td>262 ± 144</td>
<td>207 ± 133</td>
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<tr>
<td>Sleep stages during which seizures appeared (%)</td>
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<td></td>
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<td></td>
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<tr>
<td>Stage 1</td>
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<td>11</td>
<td>20</td>
<td>9</td>
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<td>Stage 2</td>
<td>62</td>
<td>62</td>
<td>27</td>
<td>60</td>
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<tr>
<td>Stage 3–4</td>
<td>28</td>
<td>23</td>
<td>53</td>
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<td>Autonomic modifications</td>
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<td>Tachypnoea/modification of respiratory rhythm</td>
<td>78</td>
<td>80</td>
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Table 2 Interictal and ictal EEG

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<th>PA</th>
<th>NPD</th>
<th>ENW</th>
<th>Total</th>
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<tr>
<td>Number of patients</td>
<td>9</td>
<td>51</td>
<td>40</td>
<td>100</td>
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<td><strong>Interictal wake EEG</strong></td>
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<tr>
<td>Normal</td>
<td>7 (78%)</td>
<td>20 (39%)</td>
<td>28 (70%)</td>
<td>55</td>
</tr>
<tr>
<td>Focal non-specific abnormalities</td>
<td>2 (22%)</td>
<td>6 (12%)</td>
<td>4 (10%)</td>
<td>12</td>
</tr>
<tr>
<td>Focal epileptic abnormalities</td>
<td>0</td>
<td>25 (49%)</td>
<td>8 (20%)</td>
<td>33</td>
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<tr>
<td><strong>Interictal sleep EEG</strong></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Normal</td>
<td>7 (78%)</td>
<td>18 (35%)</td>
<td>26 (65%)</td>
<td>51</td>
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<td>Focal non-specific abnormalities</td>
<td>0</td>
<td>0</td>
<td>4 (10%)</td>
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<tr>
<td>Focal epileptic abnormalities</td>
<td>2 (22%)</td>
<td>33 (65%)</td>
<td>10 (25%)</td>
<td>45</td>
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<td><strong>Ictal EEG</strong></td>
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<tr>
<td>Normal</td>
<td>4 (44%)</td>
<td>17 (33%)</td>
<td>23 (58%)</td>
<td>44</td>
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<td>Theta activity</td>
<td>4 (44%)</td>
<td>6 (12%)</td>
<td>5 (13%)</td>
<td>15</td>
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<td>Focal or diffuse flattening</td>
<td>1 (12%)</td>
<td>12 (23%)</td>
<td>6 (15%)</td>
<td>19</td>
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<td>Delta activity</td>
<td>0</td>
<td>5 (10%)</td>
<td>1 (2%)</td>
<td>6</td>
</tr>
<tr>
<td>Fast activity</td>
<td>0</td>
<td>6 (12%)</td>
<td>2 (5%)</td>
<td>8</td>
</tr>
<tr>
<td>Epileptic abnormalities</td>
<td>0</td>
<td>5 (10%)</td>
<td>3 (7%)</td>
<td>8</td>
</tr>
</tbody>
</table>
Analysis of seizure types

Upon analysis of the combination of the different types of seizures, three categories of patients could be distinguished: patients with only PA (PA group, nine cases); patients with NPD possibly associated with PA (NPD group, 51 cases); and patients with ENW associated with both or either PA and NPD (ENW group, 40 cases). In particular, in the NPD group, 19 patients had only NPD seizures and 32 patients had NPD and PA. In the ENW group, 31 patients had PA and ENW, two patients had NPD and ENW, and seven patients had PA, NPD and ENW. No patient had ENW alone. In all the patients with at least two seizure types, the attack onset was characterized by the same stereotypic movement.

Within the PA group, all of the patients had a normal personal history and normal neurological and neuro-radiological examinations. None of these patients had seizures during the daytime or during wakefulness, or secondarily generalized seizures. Only three such patients accepted treatment, and carbamazepine was effective in two of them, reducing seizures by 75%.

Twenty-four per cent of the patients belonging to the NPD group had a structural brain abnormality; 57% of the patients presented seizures also during wakefulness and 49% had secondarily generalized seizures. In 24% of the cases, carbamazepine controlled seizures completely and in 14 cases (31%) it reduced seizures by at least 50%.

Five per cent of patients with ENW had focal abnormalities on brain CT and/or MRI. Thirteen percent of patients presented seizures also during the daytime. Carbamazepine controlled seizures completely in five patients (16%); there was a seizure reduction of at least 50% in 22 patients (71%).

Statistical analysis ($\chi^2$ test) disclosed a significance for several associations of clinical characteristics with the three types of seizures (PA, NPD and ENW). In particular, in the PA group, the normal personal history ($P = 0.008$) and the absence of daytime and secondarily generalized seizures ($P < 0.001$), and in the NPD group, the family history for epilepsy ($P < 0.001$) and the higher frequency of night time ($P = 0.022$) and daytime and secondarily generalized seizures ($P < 0.001$) were statistically significant. In the ENW group, the family history positive for parasomnias ($P < 0.001$) and the personal history of sleep-walking ($P = 0.008$) were statistically significant. Furthermore, these patients significantly displayed a normal wake and sleep interictal EEG ($P = 0.005$). The clinical data for these different groups are reported in Tables 3 and 4.

Discussion
Clinical features

In our series of 100 patients with NFLE, age at onset of the nocturnal seizures varied, but centred during infancy and adolescence, at around puberty ($14 \pm 10$ years as a mean), a finding also typical of other partial epilepsies (Hauser, 1998). However, the wide range (1–64 years of age) certainly reflects a degree of heterogeneity in the causative mechanisms.

We also found a high male prevalence ($7 : 3$), a finding not universal for all of the partial epilepsies, and typically encountered instead in some parasomnias such as the REM sleep behaviour disorders, in which the male predominance is even higher ($9 : 1$).

A familial recurrence of the attacks was found in 25% of our cases, a rate which is again comparable with that found in most partial epilepsies (Ottman, 1989). However, detailed pedigree analysis of our cases demonstrated clear genetic, probably autosomal dominant, transmission in relatively few patients (only eight cases belonging to six families), a surprisingly low rate compared with that reported by others (Oldani et al., 1997). This discrepancy reflects the restrictive criteria we adopted in our study (we required at least two generations affected, and not just one affected relative) compared with others, and probably also some variation in the selection of the clinical material.

We acknowledge, however, that our criteria could be unnecessarily restrictive, especially in the light of the recent demonstration of a dominantly inherited epilepsy with variable foci and, therefore, variable clinical manifestations (Scheffer et al., 1994b, 1995b; Berkovic and Scheffer, 1997).

Even within the cases which conformed to an autosomal model of genetic transmission (ADNFLE), we confirmed the genetic heterogeneity of the syndrome, since none of our patients tested positive for the mutations found in previously described families with ADNFLE.

A high percentage of our NFLE cases (39%) presented a family history of nocturnal paroxysmal episodes that fits the diagnostic criteria for parasomnias (International Classification of Sleep Disorders, 1990). This much higher frequency of parasomnia in our material compared with that reported for large control populations [in which prevalence for sleep terrors and sleep-walking ranges from 1 to 6% of the entire population (Partinen, 1994; Hublin et al., 1997)] compares also with the higher prevalence of parasomnias in the personal history of our patients (34%). These findings can be explained in several ways: they could reflect an ascertainment bias, since we placed special emphasis on the family and personal history of sleep disturbances, and the lack of a comparable normal population in our study; or instead they could be due to errors in the diagnosis of the attacks, which were mistaken for parasomnias and instead were true epileptic seizures. In this second case, the familial recurrence in our material would be much higher and would compare well with that reported by other authors (Oldani et al., 1997). We feel uneasy, however, in attributing all of the paroxysmal events, whether present in the familial or in the personal history of our patients, to epilepsy. We interpreted the anamnestic episodes as parasomnias because of their age-dependent course, rarity of episodes and their being not violent and often not disturbing for the patient. The episodes fulfilled the diagnostic criteria put forth for parasomnias (International Classification of Sleep Disorders, 1990) and,
Table 3 Clinical data

<table>
<thead>
<tr>
<th></th>
<th>PA</th>
<th>NPD</th>
<th>ENW</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>9</td>
<td>51</td>
<td>40</td>
<td>100</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>6</td>
<td>31</td>
<td>33</td>
<td>70</td>
</tr>
<tr>
<td>Females</td>
<td>3</td>
<td>20</td>
<td>7</td>
<td>30</td>
</tr>
<tr>
<td>Age at observation (years; mean)</td>
<td>26</td>
<td>28</td>
<td>25</td>
<td>26 ± 12</td>
</tr>
<tr>
<td>Age at onset (years; mean ± standard deviation)</td>
<td>15 ± 9</td>
<td>15 ± 12</td>
<td>13 ± 6</td>
<td>14 ± 10</td>
</tr>
<tr>
<td>Family history positive for parasomnias</td>
<td>6</td>
<td>9</td>
<td>24</td>
<td>39</td>
</tr>
<tr>
<td>Family history positive for epilepsy</td>
<td>2</td>
<td>17</td>
<td>6</td>
<td>25</td>
</tr>
<tr>
<td>Personal history of perinatal suffering/febrile convulsions</td>
<td>0</td>
<td>7</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Personal history of parasomnias</td>
<td>4</td>
<td>8</td>
<td>22</td>
<td>34</td>
</tr>
<tr>
<td>Abnormal neurological examination</td>
<td>0</td>
<td>6</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Abnormal neuroradiological examination (CT/MRI)</td>
<td>0</td>
<td>12</td>
<td>2</td>
<td>14</td>
</tr>
<tr>
<td>Response to carbamazepine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seizures completely controlled</td>
<td>0</td>
<td>11</td>
<td>5</td>
<td>16</td>
</tr>
<tr>
<td>Reduction by at least 75%</td>
<td>2</td>
<td>10</td>
<td>7</td>
<td>19</td>
</tr>
<tr>
<td>Reduction by half</td>
<td>0</td>
<td>4</td>
<td>15</td>
<td>19</td>
</tr>
<tr>
<td>Seizures unmodified</td>
<td>1</td>
<td>20</td>
<td>4</td>
<td>25</td>
</tr>
</tbody>
</table>

Table 4 Seizure features

<table>
<thead>
<tr>
<th></th>
<th>PA</th>
<th>NPD</th>
<th>ENW</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>9</td>
<td>51</td>
<td>40</td>
<td>100</td>
</tr>
<tr>
<td>Seizure frequency/month (mean ± standard deviation)</td>
<td>16 ± 12</td>
<td>23 ± 11</td>
<td>16 ± 10</td>
<td>20 ± 11</td>
</tr>
<tr>
<td>Seizure frequency/night (mean ± standard deviation)</td>
<td>2 ± 1</td>
<td>3 ± 2</td>
<td>3 ± 3</td>
<td>3 ± 3</td>
</tr>
<tr>
<td>Daytime seizures</td>
<td>0</td>
<td>29</td>
<td>5</td>
<td>34</td>
</tr>
<tr>
<td>Secondarily generalized seizures</td>
<td>0</td>
<td>25</td>
<td>3</td>
<td>28</td>
</tr>
</tbody>
</table>

Table 3 Clinical data

moreover, they often ended well before the onset of the clearcut epileptic seizures. Relatives often could clearly distinguish between the two different types of attack. However, we have no direct proof, since these earlier episodes usually were not monitored electrophysiologically and, therefore, we cannot exclude that they too represented some kind of epileptic seizures in infancy or childhood, with somewhat differing clinical patterns. A third explanation is that they were true parasomniac episodes, and this entails the possibility that NFLE and arousal disorders share some common pathogenic mechanism, present in both the acquired and the genetic cases. Such an intriguing possibility was not excluded even in the works which established the genetic linkage and mutations in families with ADNFLE (Scheffer et al., 1995a), since in those studies the diagnosis of NFLE was anamnestic for most familial cases and not confirmed by electrophysiological means. The peculiar functional organization of the frontal lobes and the well documented involvement of some mesial orbital frontal areas in sleep regulation (Sterman and Wyrwicka, 1967) are not against such a possibility.

Personal antecedents typically found in the focal lesional epilepsies (such as birth anoxia, febrile convulsions, neuropsychological defects indicating encephalopathy, etc.) were shown in a minority of our cases (only 13%), and the same was true for focal brain CT or MRI abnormalities, reported in only 14% of our patients. This rather low prevalence of lesional factors in our NFLE material is unlike most partial epilepsies, and suggests a ‘functional’ mechanism for most, though not all, of the cases.

Seizure semiology

VideoEEG recordings demonstrated that NFLE comprises a spectrum of distinct phenomena, different in intensity but representing a continuum of the same epileptic condition, since seizures of different intensity could co-exist in the same patient. Moreover, when PA, NPD and ENW were present in the same patient, the semiology at the start of the attack was similar, and brief seizure fragments represented the beginning of the more prolonged episodes. This feature (Sforza et al., 1993), besides confirming the continuity of the different clinical manifestations (PA, NPD and ENW), also represents a strong indicator of the epileptic nature of the attacks, since it may be explained by spreading of the epileptic discharge to progressively wider areas of the cortex (Talairach et al., 1973).

This takes us to the reason for distinguishing between PA, NPD and ENW as different clinical aspects of one heterogeneous syndrome, or for just lumping all these differing manifestations together in one broad nosological definition, as other authors have done (Oldani et al., 1996; Ambrosetto, 1997). We believe that detailed dissection of the features of each patient and group of patients with NFLE, e.g. phenotypic characterization, represents the first necessary
step towards a better understanding of the pathogenic mechanisms, especially when searching for acquired or genetic causes of the heterogeneity of NFLE. Our results show how the different groups of patients seem to have different causations and prognosis and, therefore, we advocate maintaining this semeiologic distinction.

PA are underestimated on clinical grounds alone, since they are reported by patients only if especially frequent and violent. In some patients with PA only, daytime tiredness, fatigue and sleepiness were not rare and were often the main complaint, which seemed to correlate with the frequency of the PA. This has been noted before, daytime somnolence being the only symptom reported by patients with paroxysmal awakenings (Peled and Lavie, 1986). Patients with PA alone seem to be rare (9% in our material), but this group of patients is characterized by a total absence of daytime seizures and a lack of brain lesions on neuroradiological studies. The most usual motor pattern of the PA was a more or less sudden jerk of the upper limbs and trunk. The stereotypic repetition of the same pattern, sometimes tens of times for long stretches during sleep, and the presence of choreoathetoid and dystonic postures of the limbs help to differentiate the PA from the physiological hypnic jerks or sleep starts upon purely visual inspection alone, even when EEG epileptic activity is not recorded.

NPD attacks also begin with a paroxysmal arousal, but go on to display the pattern typical of a seizure originating in the supplementary motor areas, with extension of the ipsilateral limb, flexion of the contralateral limbs and rotation of the head; other attacks instead display rhythmic or ballistic movements, or the rocking pelvic and body movements of the mesial frontal orbital seizures.

ENW remain more difficult to record because of their lower frequency. Since, however, all of our patients with ENW also showed PA and/or NPD attacks during polysomnography, the latter represent a useful means of documenting NFLE in these patients too. The striking feature of ENW, and one which has been described since their first documenting of NFLE in these patients too. The striking feature of polysomnography, the latter represent a useful means of NFLE also showed PA and/or NPD attacks during lower frequency. Since, however, all of our patients with mesial frontal orbital seizures.

The diagnosis of NFLE may thus represent a diagnostic dilemma. A marked autonomic activation is a common finding during the seizures (tachycardia in 88% and modifications of respiratory rhythm in 77% of the cases), but it cannot distinguish the epileptic attacks from disorders of arousal.

**Differential diagnosis**

A diagnosis of parasomnia—pavor nocturnus or somnambulism—is often made prior to or even after the videopolysomnography recordings, especially in children (Pedley and Guilleminault, 1977; Maselli et al., 1988; Oswald, 1989; Vigevano and Fusco, 1993; Plazzi et al., 1995). The differential features of these parasomnias with NFLE, shown in Table 5, include the different time course of the parasomnias, somnambulism rarely occurring for the first time in adulthood (Hublin et al., 1997) and usually setting in between 4 and 6 years of age (Cirignotta et al., 1983), while more than half the cases have a remission before the age of 18 years (Rottersman, 1946; Cirignotta et al., 1983). The mean lifetime duration of somnambulism is 7 years (Sours et al., 1963), compared with 20 ± 12 years in the case of our patients with NFLE. Seizure frequency and semiology are also important clinical criteria to distinguish epilepsy from disorders of arousal. Though the latter can show up in clusters, they are mainly sparse, the mean frequency of episodes being once every 1–4 months (Sours et al., 1963), quite unlike the nightly occurrence of NFLE. In fact, it is extremely unusual for pavor nocturnus or somnambulism to reach such a high frequency as the 2–3 episodes per night we recorded as a mean in our patients. The motor pattern during the seizures represents a very helpful differential feature, since parasomnias do not present the ‘extrapyramidal’ patterns (such as dystonic posturing, tremor, choreo-athetosis) of NFLE, or the violent agitated motor behaviour of ENW. The intra-individual stereotypy of the attacks remains the most useful clinical clue to NFLE, especially when several episodes of PA and NPD are recorded in a single or in subsequent polysomnography sessions. Careful analysis of the motor features of the attacks is therefore required.

REM sleep behaviour disorders are another type of parasomnia which, however, can be differentiated more easily from NFLE because of their later onset (~60 years of age), their clinical polymorphism and association with a dream-like experience after the attack and their polygraphic features of REM sleep without atonia (Schenck et al., 1986).

Nocturnal panic attacks should also be differentiated from NFLE. They are defined as sudden awakenings from sleep in a state of panic with somatic sensations of sympathetic arousal such as tachycardia, pressure and constriction around the chest and neck, and intense subjective fear (Craske and Barlow, 1989). Sensations of derealization and imminent death are also common. The onset of panic attacks is in adolescence (15–19 years) or middle age (Von Korff et al., 1985). These attacks sometimes resemble NFLE (Plazzi et al., 1998), but are usually vividly recalled and rarely recur more

**EEG findings**

In many patients, ictal (44%) and interictal wake (55%) and sleep (51%) EEGs were uninformative, being either normal or masked by muscular artefacts. Only in some of our cases did sphenoidal EEG electrodes prove useful, as shown by the fact that 13 patients had ictal epileptic EEG activity detected only by these electrodes.

The diagnosis of NFLE may thus represent a diagnostic
Table 5 Comparative features of parasomnia versus NFLE

<table>
<thead>
<tr>
<th></th>
<th>Parasomnias (sleep-walking/sleep terrors)</th>
<th>NFLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset (mean ± standard deviation)</td>
<td>Usually &lt;10 years</td>
<td>14 ± 10</td>
</tr>
<tr>
<td>Family history positive for parasomnias</td>
<td>62–96%</td>
<td>39%</td>
</tr>
<tr>
<td>Episode frequency/month (mean ± standard deviation)</td>
<td>From &lt;1 to 4</td>
<td>20 ± 11</td>
</tr>
<tr>
<td>Episode frequency/night (mean ± standard deviation)</td>
<td>1</td>
<td>3 ± 3</td>
</tr>
<tr>
<td>Clinical course through the years</td>
<td>Tend to disappear</td>
<td>Increased frequency</td>
</tr>
<tr>
<td>Disease duration</td>
<td>7 years</td>
<td>20 ± 12 years</td>
</tr>
<tr>
<td>Episode duration</td>
<td>From 15 s to 30 min</td>
<td>From 2 s to 3 min</td>
</tr>
<tr>
<td>Movement semiology</td>
<td>Complex, non-stereotypic</td>
<td>Violent, stereotypic</td>
</tr>
<tr>
<td>Triggering factors</td>
<td>Yes: sleep deprivation, febrile illness, stress, alcohol consumption</td>
<td>None in 78%</td>
</tr>
<tr>
<td>Ictal EEG</td>
<td>High amplitude slow waves</td>
<td>Normal in 44%; epileptic activity in 8%</td>
</tr>
<tr>
<td>Autonomic activation</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Episode onset after sleep onset</td>
<td>First third of the night</td>
<td>Any time</td>
</tr>
<tr>
<td>Sleep stages during which episodes appear</td>
<td>3–4 NREM</td>
<td>2 NREM in 60%</td>
</tr>
</tbody>
</table>

than once per night. Their duration is also rather prolonged, 24 min as a mean (Von Korff et al., 1985). In these respects, nocturnal panic attacks can be differentiated from NFLE.

Finally, differential diagnosis of NFLE must include attacks that we originally described under the terms NPD of intermediate or long duration (Lugaresi and Cirignotta, 1984; Montagna, 1992; Montagna et al., 1992). In particular, we named NPD with intermediate duration, those attacks occurring during sleep triggered by arousals and also during wakefulness after protracted exercise. These attacks were observed in two children and lasted 3–5 min. The epileptic origin of attacks was contradicted by the peculiar motor pattern, characterized by asynchronous jerks of the head, trunk and limbs, resembling a puppet on a string, the absence of ictal and interictal EEG epileptiform abnormalities, the inefficacy of anticonvulsants and, above all, the triggering effect of prolonged exercise. Such characteristics resembled the features of a paroxysmal motor disorder (Montagna et al., 1992).

NPD with long-lasting attacks was the term we used to describe dystonic–dyskinetic attacks lasting for 2–50 min arising from light NREM sleep in two patients, one of whom developed familial Huntington’s disease 20 years after onset of the nocturnal attacks. These motor episodes recurred several times per night and did not respond to any treatment, including antiepileptic drugs. The long duration of the attacks, the absence of response to anticonvulsant therapy and the onset in a patient later affected by Huntington’s disease suggested basal ganglia involvement (Lugaresi and Cirignotta, 1984).

**Natural history and treatment**

NFLE does not show a tendency to spontaneous remission. In our cases responding to treatment, withdrawal of the antiepileptic drugs was always followed by the reappearance of the seizures. Carbamazepine completely abolished the seizures in ~20% of the cases, and gave remarkable relief (reduction of the seizures by at least 50%) in another 48%. In nearly a third of the cases, however, the seizures proved resistant to any antiepileptic drug treatment. These percentages are comparable with those observed in many types of partial epilepsy and do not support the concept that NFLE is always a benign epilepsy (Oldani et al., 1997).

Some degree of benignity is of course afforded by the fact that seizures occur during the night and are thus relatively better tolerated. Some patients of ours in fact, suffering from rare and brief attacks (PA or NPD), chose not to undergo therapy because they did not feel incapacitated by the seizures.

**Pathophysiological conclusions**

NFLE has a peculiar relationship to the physiology of sleep. Polygraphic recordings show that a mesiofrontal epileptic focus is often activated during NREM sleep. A K-complex often coincided with or even preceded the ictal EEG and autonomic modifications on the recordings. K-complexes are characteristic sleep figures arising in the prefrontal cortex and are characterized by ample hyperpolarization–depolarization sequences. That the K-complexes may represent an important factor in the onset of NFLE seizures is also suggested by the fact that seizures tend to cluster with a quasi-periodic repetition at a rate similar to that of the K-complexes and other periodic physiological phenomena during light sleep (Lugaresi et al., 1972). We envisage that the epileptic discharges thus triggered may then diffuse to limbic cortical and subcortical circuits, provoking sudden vigilance and autonomic changes, and peculiar motor patterns.

**Conclusion**

NFLE is a not such a rare variant of epilepsy, accounting for 13% of our polysomnography recordings for nocturnal motor disorders run in our laboratory over 20 years.
Its clinical relevance has been and still is underestimated, and many cases, especially in children, are misdiagnosed as arousal disorders. NFLE is, however, heterogeneous, and ADNFLE is a genetic variant which is itself both clinically and biologically heterogeneous. NFLE is not always a benign condition, many patients being resistant to any antiepileptic drug therapy. The diagnosis of NFLE, even when employing advanced EEG techniques and videopolysomnography recordings, remains a powerful challenge. NFLE should always be suspected in the presence of paroxysmal nocturnal motor events characterized by a high frequency of same-night or inter-night repetition, persistence into post-puberty adulthood, ‘extrapyramidal’ features or agitated behaviour and remarkable stereotypy of the attacks.

Acknowledgements
We wish to thank Dr Mirella Mochi and Dr Lucia Valentino for genetic analysis, Professor P. L. Lenzi and Nino Bertozzi for their contribution to the statistical analysis, Carlo Grassi for photographic assistance, and Elena Zoni and Alessandra Laffi for technical assistance in preparing the manuscript. This work was 40% supported by a MURST grant in 1997.

References
Phillips HA, Scheffer IE, Berkovic SF, Hollway GE, Sutherland GR, Mulley JC. Localization of a gene for autosomal dominant nocturnal frontal lobe epilepsy to chromosome 20q13.2 [see
NFLE: a clinical and polygraphic overview


Received July 29, 1998. Revised December 21, 1998. Accepted February 3, 1999