

# Autosomal dominant nocturnal frontal lobe epilepsy

## A distinctive clinical disorder

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### Summary

The disorder of autosomal dominant nocturnal frontal lobe epilepsy has recently been identified, and is now delineated in detail. A phenotypically homogeneous group of five families from Australia, Britain and Canada, containing 47 affected individuals, was studied. The largest family contained 25 affected individuals spanning six generations. This disorder is characterized by clusters of brief nocturnal motor seizures, with hyperkinetic or tonic manifestations. Subjects often experienced an aura, and remained aware throughout the attacks. Seizures occurred in clusters (mean eight attacks/night) typically as the individual dozed, or shortly before awakening. The epilepsy usually began in childhood, and

persisted through adult life, with considerable intra-family variation in severity. Seizures were often misdiagnosed as benign nocturnal parasomnias, psychiatric and medical disorders. Interictal EEG studies were unhelpful. Ictal video-EEG studies showed that the attacks were partial seizures with frontal lobe seizure semiology. Neuro-imaging was normal. Carbamazepine monotherapy was frequently effective. This disorder showed autosomal dominant inheritance. Recognition of this entity is clinically important for diagnosis, appropriate therapy and genetic counselling. Moreover, this disorder now offers an opportunity to identify a gene for partial epilepsy.

**Keywords:** epilepsy; partial seizures; genetics

### Introduction

The epilepsies have been known to have an inherited component for many years, but for the common generalized and partial epilepsies a multifactorial mode of inheritance appears most likely (Andermann, 1982). Simple Mendelian inheritance occurs in certain rare epilepsies, predominantly of the generalized type. In four such disorders, this knowledge has led to successful genetic linkage analysis; benign familial neonatal convulsions linked to chromosomes 20q (Leppert *et al.*, 1989) and 8q (Lewis *et al.*, 1993), Unverricht-Lundborg disease to 21q (Lehesjoki *et al.*, 1991), juvenile

neuronal ceroid lipofuscinosis to chromosome 16 (Gardiner *et al.*, 1990), and hereditary dentatorubral-pallido-luysian atrophy to chromosome 12 (Koide *et al.*, 1994; Nagafuchi *et al.*, 1994). Regarding the partial epilepsies, a major genetic component occurs in the benign partial epilepsies of childhood (Bray and Wiser, 1964, 1965; Heijbel *et al.*, 1975), but the precise mode of inheritance remains elusive and may well be multifactorial (Doose and Baier, 1989). We recently recognized a partial epilepsy syndrome with clear-cut autosomal dominant inheritance (Scheffer *et al.*, 1994). Here we

present detailed clinical, electroencephalographic (EEG) and genetic data on this distinctive disorder, together with a consideration of its differential diagnosis. It appears that this disorder is not uncommon and has frequently been unrecognized due to difficulties in defining the epileptic nature of paroxysmal nocturnal events, and failure to appreciate the inheritance pattern.

## Methods

Five families containing 47 affected individuals were studied in Australia, Britain and Canada. Available living affected members and many unaffected family members underwent detailed clinical assessment. The Australian families were systematically studied using a validated questionnaire for clinical seizure diagnosis (modified after Reutens *et al.*, 1992), and by personal clinical examination. Electroencephalographic studies were carried out on all families, including sleep studies where possible. Ten individuals from four families had seizures documented by video-EEG recordings. All relevant past clinical history was reviewed, including investigations such as neuroimaging. Extensive pedigree information was obtained, and genetic analysis performed. This research study had been approved by the Austin Hospital Ethics Committee, and all participating individuals gave informed consent. Permission to publish photographs has been obtained.

This paper focuses on five families with a strikingly homogeneous phenotype. A sixth family (included in Scheffer *et al.*, 1994) was excluded as they presented a different electro-clinical picture.

## Results

### Clinical features

The five families presented a homogeneous clinical epilepsy syndrome, characterized by clusters of brief nocturnal motor seizures. Seizures began in childhood, usually persisting through adult life and, when recognized, were often readily controlled with appropriate anti-epileptic medication. A spectrum of severity was seen in affected individuals (*see Appendix for illustrative case histories*).

Age of seizure onset was known in 40 individuals. The mean age of onset was 11.7 years (median 8 years), ranging from 2 months to 52 years. Onset was during the first decade of life in 21 (53%) cases, and during the second decade in 14 (35%) cases (*see histogram, Fig. 1*).

Of 37 individuals where a history of seizure pattern was available, 28 (76%) described clustering of seizures when the condition was active. Clusters typically consisted of four to 11 attacks with a mean of 7.7 attacks (median six attacks) per night. Four patients commonly had more than 20 seizures per night, and one had 72 attacks recorded during one night of video-EEG telemetry (*see Appendix, case A:V-12*). Only

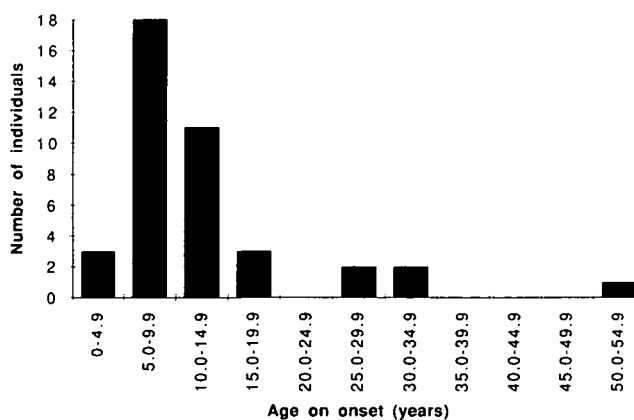


Fig. 1 Histogram of age of onset of seizure disorder.

nine (24%) of the 37 individuals reported a single attack per night.

Virtually all seizures arose from sleep. Thirty-three individuals gave a history of seizure timing. Seizures occurred most commonly as the person dozed; i.e. 19 (58%) cases described attacks very soon after falling asleep. Seizures also occurred in the early hours of the morning, with 16 (48%) cases having attacks after 04.00. Only three (9%) individuals reported attacks throughout the night. Ten (30%) subjects had seizures during a daytime nap, and nine (27%) described infrequent attacks when awake, although occurrence during light dozing could not be excluded.

Estimates of the seizure length were available from 38 subjects or their families. Seizures lasted an estimated mean of 74 s (median duration 60 s, range 5 s to 5 min). Generally attacks were brief, with 18 (47%) cases estimating their maximum seizure duration as <60 s. The mean timed length of ictal recordings of five patients was 20 s.

An aura was described by 28 (70%) of 40 individuals where a history was available, and included a wide variety of phenomena (*see Table 1*). The aura woke some individuals from sleep prior to the first attack of the night, while others were only aware of it after they had been woken. There was some intra-family similarity in the auras described: e.g. a father and daughter (*see Appendix, cases B:II-4 and B:III-4*) awoke with a cramp in their right leg, while a mother (*see Appendix, case A:IV-22*) and daughter heard a noise that built up and culminated as they lost consciousness.

The seizure began with a gasp or grunt, or a vocalization which was either a prolonged moan or a single word. This often alerted the family to the attack. Eyes were usually open and staring during the attack, or sometimes rolled up. Oral and manual automatisms were uncommon.

The motor features of the attack varied from thrashing hyperkinetic activity in 16 cases, to tonic stiffening in 36, with superimposed clonic jerking in 23 individuals. Many individuals sat up or attempted to sit up during an attack. Some described forced hyperextension, where they would grab onto the headboard of the bed, and their head would be extended with eyes rolled upwards. Others found themselves

**Table 1** Auras

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Somatosensory	
Generalized shiver/tingling	(n = 6)
Cephalic	(n = 6)
Thoracic	(n = 1)
Epigastric	(n = 2)
Limb	(n = 5)
Special sensory	
Auditory	(n = 5)
Vertiginous	
Spinning/dizziness	(n = 2)
Falling	(n = 1)
Lifting	(n = 1)
Pushed	(n = 2)
Turning over and over	(n = 1)
Visual	(n = 3)
Olfactory	(n = 1)
Gustatory	(n = 1)
Psychic	
Fear	(n = 2)
Malaise	(n = 3)
Upset	(n = 1)
Altered awareness	(n = 1)
Déjà vu	(n = 1)
Dreaming activities	(n = 1)
Autonomic	
Difficulty breathing	(n = 3)

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(n) = number of individuals who described that aura type

prone in a crawling position; or felt pushed forwards or backwards, or were flung out of bed onto the floor, injuring themselves (see Appendix, case B:II-2).

Of 40 subjects, 28 (70%) believed that they remained aware through most of their seizures. They were unable to control their actions and were unable to respond, but could hear, and recount events later. Some perceived that if the attack could be altered, for example, someone held their head flexed rather than allowing it to hyperextend, they could modify or abort attacks. Thirteen (33%) individuals felt frightened during the attack, and some described fear of falling asleep while poorly controlled. During the attack, a subjective sensation of being unable to 'get one's breath' or choking (see Appendix, case C:IV-4) was described by 17 out of 28 subjects (61%), and, objectively, these individuals appeared to have difficulty breathing. Despite the retention of awareness, 13 (33%) patients described biting their tongue and 12 (30%) were incontinent during seizures. Loss of consciousness reflecting true secondarily generalized attacks occurred at some time in 23 (59%) individuals. Although post-ictal confusion was rare, most individuals were drowsy following attacks, and fell asleep again. Post-ictal headache was uncommon.

Seizures persisted through adult life, although they tended to peter out as patients approached their late forties or fifties. On close questioning, five subjects over 50 years of age described infrequent, brief attacks during sleep such as stiffening for 30 s. Two of these patients no longer received medication.

There was considerable intra-familial variation in the severity of the seizure disorder. Most affected family members had clusters of seizures intermittently, weekly or monthly. The more severely affected individuals tended to have earlier onset, and clusters of seizures every night. The most mildly affected individuals were two adolescent girls (see Appendix, cases A:V-33 and B:III-4) who had attacks for 3 months in the peri-pubertal period, and never received medication; they were only recognized as each had an affected parent. One man (see Appendix, case A:IV-31) was diagnosed during the systematic family study as he had stress-associated 'nightmares' approximately every 3 months, described by his wife, for which they had never sought medical attention.

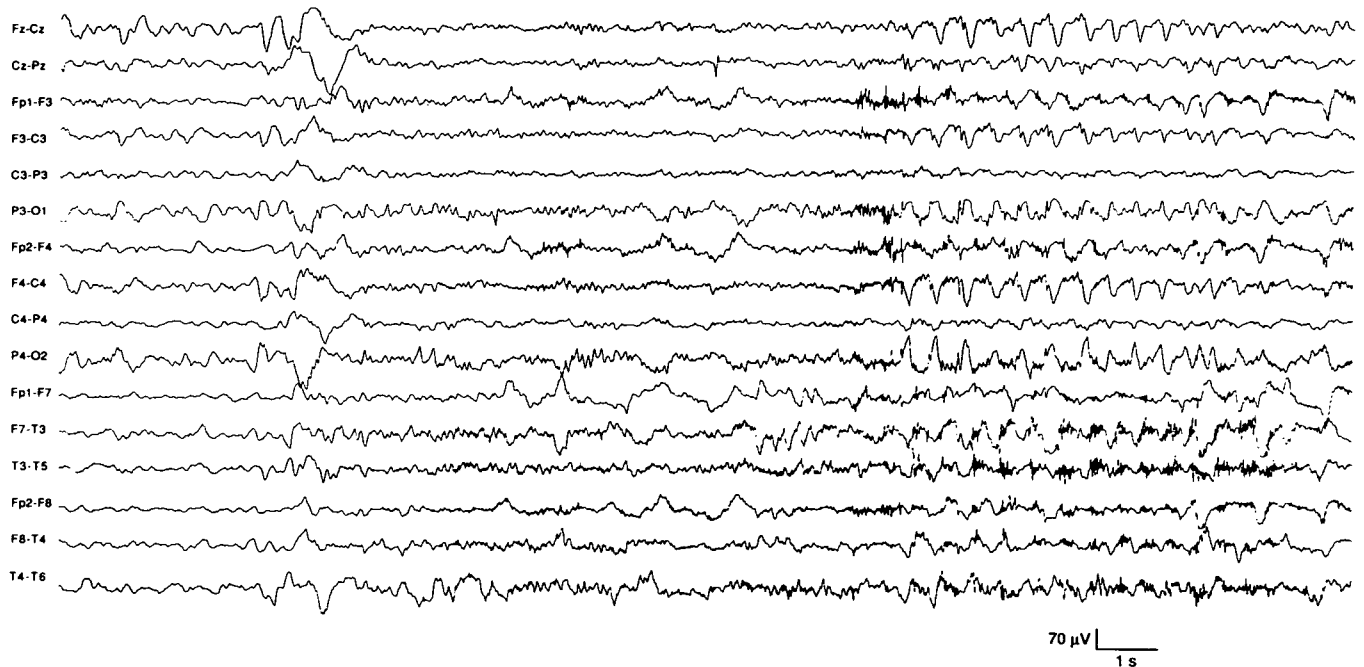
The principal seizure trigger factors were stress and fatigue. Four women had prolonged periods of remission with seizure recurrence after 10–20 years. A number of women (see Appendix, cases A:IV-22 and B:II-2) associated changes in seizure frequency, both increased and decreased, with menarche, pregnancy and menopause, but no consistent pattern was seen.

Affected individuals were of normal intellect with no abnormalities on neurological examination. In family A, the proband and two of his three siblings had short stature, but only one of these two siblings had seizures.

Thirty-eight patients were taking anti-epileptic medication at the time of the study. Fifteen (39%) were on carbamazepine alone, and 12 (32%) were well controlled. Where known, the average adult daily dose of carbamazepine producing good control was 690 mg per day. Eleven (29%) of the more severely affected individuals were on more than one medication. Cessation of carbamazepine in adult life was associated with seizure recurrence. Some of the older patients had been taking phenytoin for many years with good control. Sodium valproate was generally not effective in controlling seizures, and when changed to carbamazepine, a dramatic improvement in seizure control was seen.

Interictal epileptiform abnormalities were sparse both in waking and sleeping records. Thirty-one (84%) of 37 patients had no interictal epileptiform activity. Six (16%) patients had epileptiform activity which was bifrontal (three), bifronto-central (one), left fronto-temporal (one), and left temporal (one). An excess of slow activity was found in eight (22%) patients; this was bilateral in three patients, and focal in five but without consistent localization, and in all cases was relatively mild.

Ictal video-EEG monitoring was successfully performed on 10 individuals. Three individuals showed bilateral sharp and slow wave activity which was frontally dominant, but not confined to the anterior quadrants (Fig. 2). One patient showed an arousal response followed by widespread rhythmic 9 Hz activity. In six subjects, no definite ictal discharges could be discerned. Attacks occurred most frequently in stage 2 of sleep, but were also seen in other stages of non-rapid eye movement (REM) sleep. Videos confirmed clinical descriptions as outlined above with individuals having prominent dystonic components (Figs 3 and 4).



**Fig. 2** Ictal EEG recording of a nocturnal seizure of a 7-year-old girl (family A:VI-13). The ictal EEG shows definitive epileptiform activity seen bilaterally with a complex electrical field over the frontal, central and parietal areas.

Neuro-imaging was performed in 14 patients. There were nine normal CT scans. Two had minor non-specific abnormalities (slightly enlarged right temporal horn; generalized ventricular enlargement). MRI brain scans were normal in five individuals.

Misdiagnoses were common in these patients (*see* Table 2), and included normal sleep behaviour or benign nocturnal parasomnias such as nightmares, night terrors, or somnambulism. Four individuals were thought to have psychiatric disorders such as hysteria and hyperactivity (*see* Appendix, cases A:V-12 and D:II-1). Other medical diagnoses entertained included sleep paralysis, startle disease, asthma and enuresis. Family C was diagnosed as having nocturnal paroxysmal dystonia (NPD) (Bhatia *et al.*, 1992).

### Genetic analysis

The five families studied were unrelated, and none had consanguinity. The ethnic origin was Anglo-Saxon in three, and French-Canadian in two. Family A was Australian and contained 25 affected members spanning six generations. Family B was also Australian, and had four affected individuals in two generations. Families D and E were French-Canadian, and contained two and nine affected members, spanning two and four generations, respectively. Family C was British, and contained seven affected cases spanning three generations (*see* Pedigrees, Figs 5 and 6).

Segregation analysis was strongly supportive of autosomal dominant inheritance. The male to female ratio was 0.62. Male to male transmission occurred in two families, excluding mitochondrial or sex-linked inheritance. Penetrance was 69% when all offspring of affected individuals were analysed.

However, only 56% of affected sibships had a parent known to be affected.

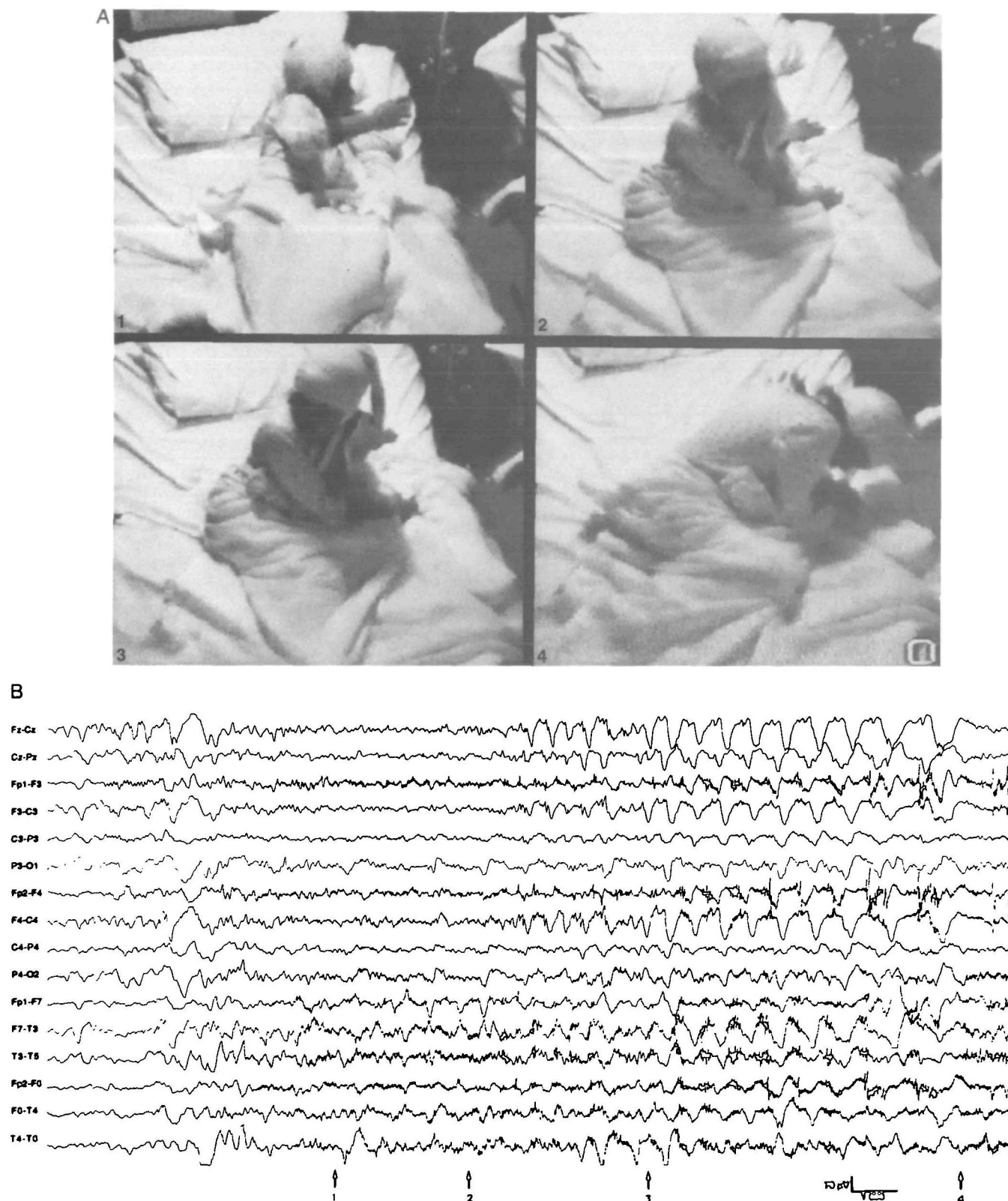
## Discussion

### Distinctive clinical disorder

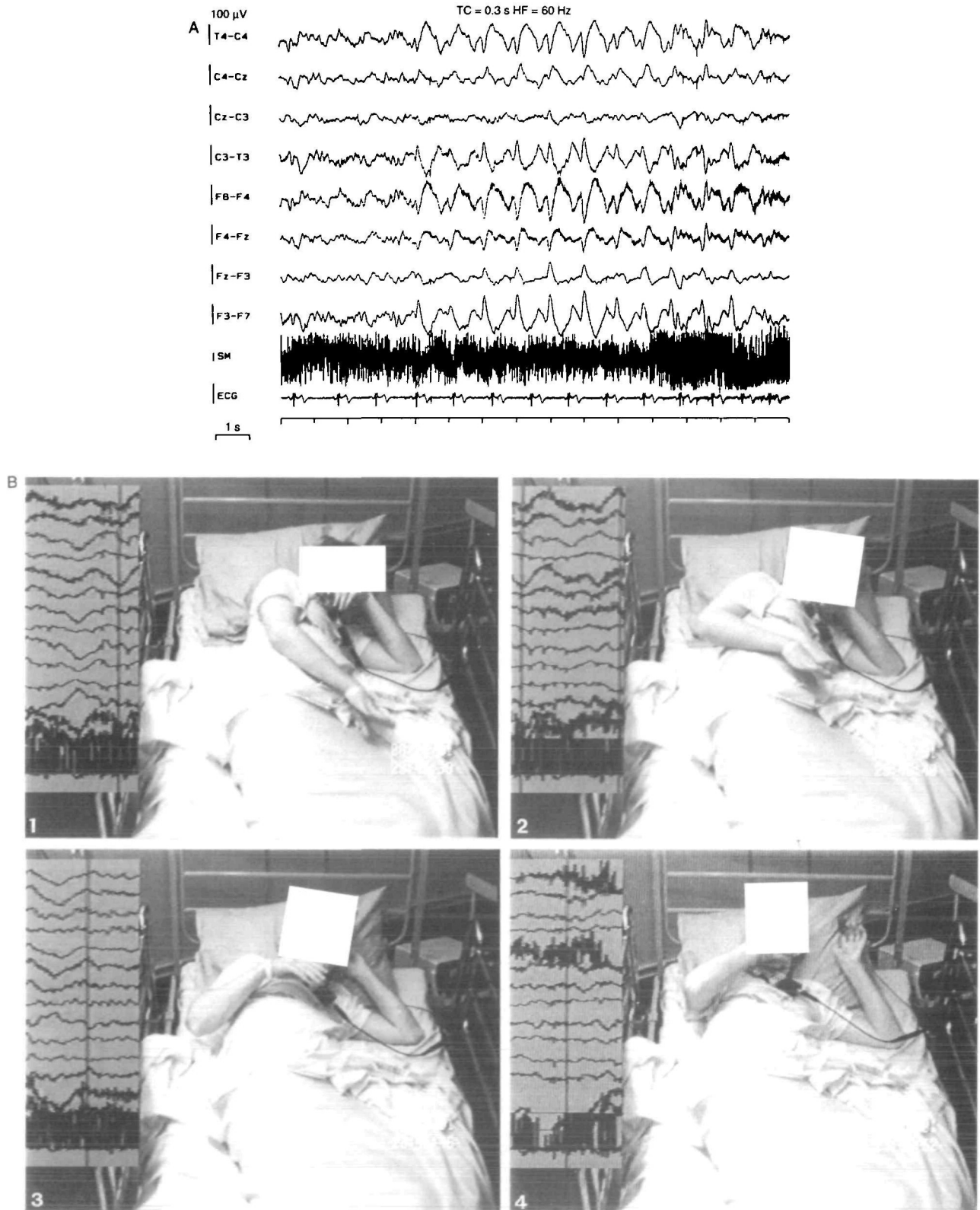
We describe a recognizable clinical syndrome of autosomal dominant nocturnal frontal lobe epilepsy in five families, containing 47 affected individuals (*see* Table 3). Onset of seizures varied from infancy to the sixth decade, but in 88% of cases was under age 20 years. Seizures occurred almost exclusively in sleep, usually as the subject dozed or in the few hours before awakening. Seizures typically began with a vocalization, with prominent motor manifestations of thrashing or tonic activity, and awareness was usually retained. They occurred in clusters of an average of eight attacks over a few hours. Affected individuals were of normal intellect with no neurological abnormalities, nor abnormalities on neuroimaging. Seizures often persisted through adult life. The clinical features were consistent with seizures of frontal lobe origin (*see* below).

### Electroencephalographic features

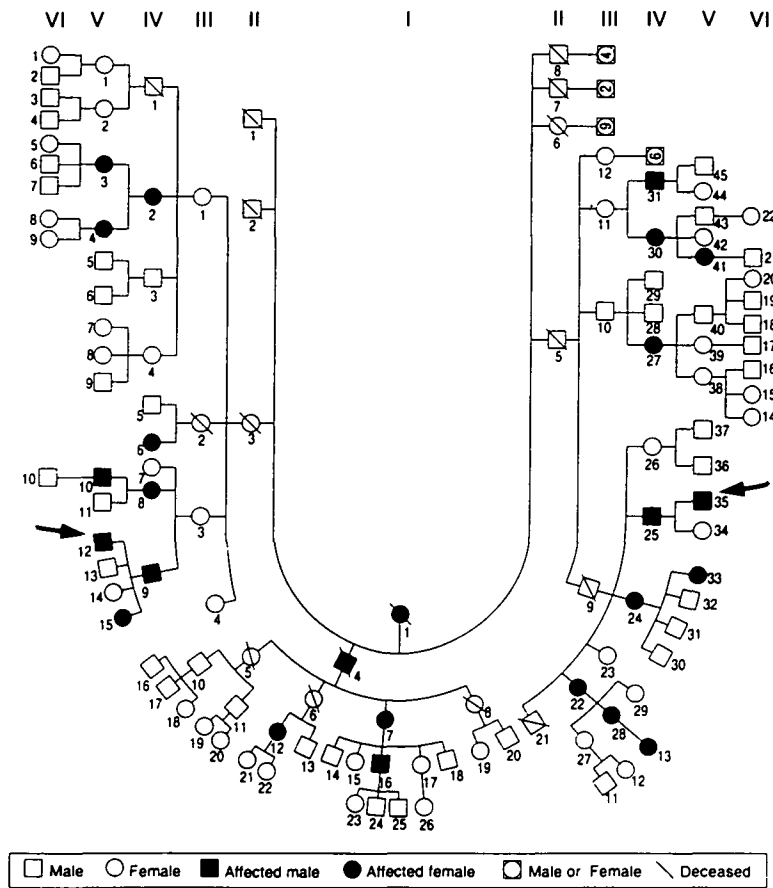
Interictal EEG recordings lacked epileptiform activity in 31 of the 37 (84%) subjects studied. Six individuals showed epileptiform abnormalities, most commonly localized to the anterior quadrant. Seizures occurred predominantly in non-REM sleep, most commonly in stage 2 on video-EEG telemetry. Ictal recordings were often obscured by movement artefact. Where ictal recordings were suggestive of an



**Fig. 3** Ictal photographs (A) and EEG (B) of a different seizure in the same 7-year-old girl (family A:VI-13). Numbers 1–4 on the EEG correlate with frames 1–4 on the ictal photographs. The girl stirs from sleep at 03.30, holding her right hand in a tonic posture (frame 1); her EEG shows an arousal response from stage 2 of sleep shown by the sleep spindles preceding seizure onset. In frame 2, she is sitting, staring vacantly, with her arms on the left side supporting her body. The EEG shows high voltage rhythmic slow activity in the frontocentral region bilaterally 1.2 s after arrow 2. In frame 3, the girl's trunk, head and eyes are deviated to the right, and the EEG shows ongoing rhythmic delta. Rhythmic jerking of the girl's head and trunk are seen as she turns to the left and jerks towards the bed (frame 4). Her concurrent EEG shows cessation of the rhythmic ictal activity. Permission to publish the photographs of this patient was given by her mother.



**Fig. 4** EEG (A) and ictal photographs (B) of a 19-year-old man (family C:IV-4). The seizure occurs in slow wave sleep. The EEG changes precede the clinical seizure, and show high amplitude sharp and slow wave complexes at 1.5–2 Hz maximum in the fronto-central regions with equipotentiality at the midline lasting 11 s. During the seizure diagnostic EEG changes were not apparent (see frames 1–4). Clinically, the patient stirs from sleep and abducts both legs. Two seconds later, the man shows dystonic posturing of the right hand with spreading of the fingers (frame 1) and flexion of the right elbow a second later (frame 2). The man rolls on to his back and puts his left hand to the side of his face 6 s later (frame 3) and rubs his face. The attack lasts 10 s, and is finished by frame 4. The oximeter is on the man's left hand.



**Fig. 5** Pedigree of Family A. This Australian family was ascertained via the two probands indicated by arrows. Genealogical research later ascertained that they were related and formed part of a large family with 25 affected individuals.

**Table 2** Differential diagnoses and misdiagnoses made in our families

Normal sleep behaviour
Benign nocturnal parasomnias
Night terrors (pavor nocturnus)
Nightmares
Somnambulism
Psychiatric disorders
Hysteria
Hyperactivity
Neurological disorders
Nocturnal paroxysmal dystonia
Startle disease
Sleep paralysis
Paroxysmal dyskinesias
Other medical disorders
Asthma
Enuresis

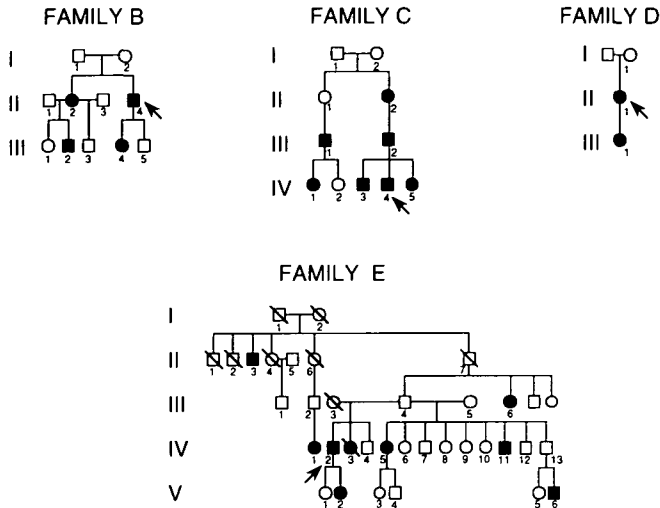
epileptiform disturbance, the predominant finding was of sharp and slow wave activity localized to the anterior quadrants bilaterally (Figs 2–4). More specific localizing

or lateralizing information was not obtained from EEG recordings.

Absence of surface interictal and even ictal EEG epileptiform activity in seizures of frontal lobe origin is well recognized (Niedermeyer and Walker, 1971; Rajna *et al.*, 1983; Williamson *et al.*, 1985; Quesney, 1986; Vigeveno and Fusco, 1993), and ictal recordings are often obscured by movement artefact (Fusco *et al.*, 1990). The lack of epileptiform activity may reflect the inaccessibility of the focus to scalp EEG recordings, and may only become apparent with highly specific depth electrode studies (Niedermeyer and Walker, 1971).

### Genetics

Segregation analysis of our families strongly supported autosomal dominant inheritance with a penetrance of 69%, when all offspring of affected individuals were analysed. The autosomal dominant inheritance pattern of this condition has not previously been appreciated, largely due to misdiagnosis, and also to under-recognition. Wide variability in severity of the seizure disorder was seen within families, and some



**Fig. 6** Pedigrees of Families B, C, D and E. Proband is indicated by arrows. See Fig. 5 for key to symbols.

**Table 3** Features of autosomal dominant nocturnal frontal lobe epilepsy

Childhood onset
Persistence through adult life
Clusters of seizures occurring in sleep
Partial seizures
Aura nonspecific
Vocalization at onset
Prominent motor features: hyperkinetic, tonic
Awareness retained
Occasionally secondarily generalized
Normal intelligence
Normal neurological examination
Interictal EEG usually normal
Ictal EEG bifrontal discharges in some
CT and MRI of the brain normal
Often responsive to carbamazepine monotherapy

mildly affected individuals were only identified by systematic family study (*see* case histories in Appendix). Many family members, particularly those in the older generations, were reluctant to admit to seizures, preferring to have occasional 'nightmares', than cope with the diagnosis of epilepsy, and the guilt they felt for transmitting a genetically determined disorder. Furthermore, reliable information on their childhood events, and on earlier generations, was not available.

### Misdiagnosis and differential diagnosis

Misdiagnoses were common in our families (Table 2) and included normal sleep behaviour, benign nocturnal parasomnias, and a wide variety of medical and psychiatric conditions.

### Benign nocturnal parasomnias

The most common misdiagnosis was of pavor nocturnus or night terrors: attacks where a child suddenly sits up during

the first 2 h of sleep, with a look of terror on his or her face. The child is inconsolable, confused, and amnesic for the event. Night terrors can readily be differentiated from the attacks in our patients by their longer duration of 5–10 min, absence of clustering of attacks, lack of motor activity, loss of awareness, and amnesia for the event. Other parasomnias, such as nightmares and somnambulism were misdiagnosed in our and other families (Godbout *et al.*, 1985; Montagna, 1992; Vigeveno and Fusco, 1993).

### Psychiatric misdiagnosis

Psychiatric misdiagnoses were made in four of our patients. In family D, a mother and daughter both had hysterical personalities, and pseudoseizures were suspected. Yet their unusual clinical pattern of sensory symptoms followed by tonic seizures with retained consciousness, and rare generalized seizures, made a learned or psychogenic behaviour very unlikely. Similar misdiagnosis of psychogenic events has been described in frontal lobe seizures (Williamson *et al.*, 1985; Commission, 1989; Fusco *et al.*, 1990; Vigeveno and Fusco, 1993) and in NPD (Lugaresi *et al.*, 1987).

One child was misdiagnosed as 'hyperactive' as the local doctor observed unusual behaviour which consisted of the boy springing from sleep into the crawling position and vocalizing, and this occurred many times over several hours.

### Nocturnal paroxysmal dystonia

Family C was initially thought to have NPD. Violent nocturnal motor attacks were described by Lugaresi and colleagues in 1981, who later named the condition 'Nocturnal Paroxysmal Dystonia', and described brief and long duration attacks (Lugaresi and Cirignotta, 1981; Lugaresi *et al.*, 1986). The brief attacks occurred in clusters on most nights, lasted 15–50 s, and clinically had prominent dystonic features, ballistic or choreic dyskinesias, often accompanied by vocalization. Some individuals had feelings of suffocation, and respiratory distress. Consciousness was not impaired and there was no post-ictal confusion. Diurnal attacks during wakefulness were rare. No interictal or ictal epileptiform EEG changes were seen. Response to carbamazepine was good, but drug withdrawal resulted in recurrence of attacks.

Attacks were initially regarded as a sporadic, non-epileptic, movement disorder, based on the lack of interictal and ictal EEG evidence, and the lack of response to phenytoin, and were thought to be related to paroxysmal kinesigenic choreoathetosis. Familial cases of NPD were subsequently identified, including autosomal dominant kindreds of NPD (Lee *et al.*, 1985), and NPD associated with benign nocturnal parasomnias (Godbout *et al.*, 1985).

More recently, opinion has shifted to the view that most or all of these events are epileptic seizures. Nocturnal paroxysmal dystonia is not uncommonly associated with unequivocal epileptic seizures (Lugaresi and Cirignotta, 1981; Lugaresi *et al.*, 1986). Comparison of patients with NPD,



daytime frontal lobe seizures and nocturnal motor attacks of known epileptic origin showed no distinguishing features between the three groups (Meierkord *et al.*, 1992). Study of classical NPD has shown progression to secondarily generalized seizures documented on EEG (Tinuper *et al.*, 1990). Various epileptic foci have been postulated in NPD including the mesial orbital frontal regions (Tinuper *et al.*, 1990; Montagna, 1992), the supplementary motor area (SMA) (Morris *et al.*, 1988) and the temporal lobe (Godbout *et al.*, 1985). Montagna (1992) has extrapolated further to suggest that NPD, episodic nocturnal wanderings and paroxysmal arousals represent a spectrum of sleep-related complex motor attacks which are epileptic in origin.

The attacks in our families with autosomal dominant frontal lobe epilepsy are indistinguishable from those described as NPD; e.g. the attacks of patient 1 of Lugaresi and Cirignotta (1981) are identical to those of our case A: VI-13 (*see* Figs 2 and 3). In our opinion, NPD is a misnomer implying an underlying movement disorder. As such, NPD is no longer an appropriate term for this condition, which deserves recognition as an epileptic disorder.

### *Familial dyskinesias*

The paroxysmal dyskinesias are a group of disorders with stereotyped attacks of choreoathetotic or dystonic movement, characteristically triggered by specific precipitants. Lance (1977) delineated the familial paroxysmal dyskinesias, and identified two distinct autosomal dominant dyskinesias which can be readily differentiated from our families by their clinical features. Paroxysmal kinesigenic choreoathetosis is the more common of the autosomal dominant dyskinesias, and is responsive to carbamazepine (Kato and Araki, 1969); however, attacks are diurnal, precipitated by sudden movement and of brief duration, usually <2 min. In contrast, attacks of paroxysmal dystonic choreoathetosis are prolonged, often lasting several hours; triggered by fatigue, alcohol, coffee, cold or emotion; are not influenced by phenytoin or barbiturates, and also occur in the waking state (Mount and Reback, 1940). Incontinence is not a feature.

Although the familial paroxysmal dyskinesias have some features in common with autosomal dominant nocturnal frontal lobe epilepsy such as an aura and the retention of awareness, the associated precipitants and diurnal nature of attacks makes them easy to differentiate.

### *Other medical conditions*

Other misdiagnoses made in our patients included asthma, enuresis and sleep paralysis. The misdiagnosis of asthma arose in some patients who experienced a feeling of difficulty breathing, and often panted during an attack. The description of respiratory distress could lead a physician to suspect respiratory disease in an unwitnessed attack. The misdiagnosis of enuresis in patients with unrecognized seizures is well known. Nocturnal seizures are not usually associated with

retained awareness as seen in our families. This led one woman with tonic seizures to be diagnosed as having sleep paralysis.

### *Characterization of the epilepsy syndrome* *Frontal lobe seizure semiology*

The nocturnal motor attacks in our families are partial seizures with frontal lobe seizure semiology. Frontal lobe seizures are characterized by prominent motor activity such as hyperkinetic thrashing activity, tonic contraction and, sometimes, dystonic posturing. They are usually brief without postictal confusion, and nocturnal clustering of attacks is common (Tharp, 1972; Williamson *et al.*, 1985; Waterman *et al.*, 1987; Commission, 1989; Vigeveno and Fusco, 1993).

Auras were described in 70% of our patients where details were available (*see* Table 1). Auras were heterogeneous and non-specific, the usual finding in seizures arising from a frontal lobe focus (Williamson *et al.*, 1985). The most commonly described auras were of a generalized tingling or shiver, auditory hallucinations, and somatosensory auras involving head or limb sensations. The shiver or generalized tingling described by six patients is a well recognized aura in proven frontal lobe epilepsy (Rasmussen, 1983; Williamson *et al.*, 1985; Quesney *et al.*, 1992; Vigeveno and Fusco, 1993). Seizures arising from the SMA may also be preceded by indefinable sensations, frequently non-lateralized, in the limbs, trunk or most of the body. These sensations have been described as pulling, pulsing, heaviness, numbness or tingling (Morris *et al.*, 1988; Morris, 1993). Seventeen of our subjects described a breathless feeling, which has been previously recognized in proven frontal lobe seizures (Williamson *et al.*, 1985).

Vocalization occurred in 76% of our patients, often indicating seizure onset, and included moaning, calling out a prolonged word, gasping or grunting. Bizarre vocalization is well recognized in seizures emanating from the medial frontal lobe and ranges from continuous sounds such as prolongation of a word, to rhythmic, interrupted vocalizations, crying, moaning, grunting, shouting, snorting, blowing, humming, swearing, repetitive vowel sounds and gibberish (Penfield and Jasper, 1954; Williamson *et al.*, 1985; Fusco *et al.*, 1990).

Motor activity in our patients' seizures varied from thrashing hyperkinetic attacks to tonic extension with clonic movements. Motor behaviour is a prominent feature of mesial frontal lobe or SMA seizures and consists of bimanual and bipedal activity, axial movements including disorganized thrashing movements (Waterman *et al.*, 1987), tonic posturing of the extremities sometimes associated with clonic movements (Penfield and Jasper, 1954; Niedermeyer and Walker, 1971; Morris *et al.*, 1988, 1993; Commission, 1989; Quesney *et al.*, 1990). Similar clusters of brief tonic motor seizures to those in our patients, were seen in the hypnic postural seizures of frontal lobe origin in Vigeveno and

Fusco's paediatric series (1993). These authors compared video-telemetry records of their cases with those of Lugaesi's NPD patients, and felt that there were some differences in the motor behaviour. However, the clinical features of the two groups were very similar. Our family study clarifies this conflict by delineating the spectrum of autosomal dominant nocturnal frontal lobe epilepsy; ictal motor behaviour varies from the dystonic-choreic description of NPD to tonic postural seizures (Vigevano and Fusco, 1993).

Seventy percent of our patients remained aware through most of their seizures, which is well recognized in mesial frontal lobe (Fusco *et al.*, 1990) or SMA seizures (Morris *et al.*, 1988; Morris, 1993). Postictal confusion is absent or minor in mesial frontal lobe seizures (Williamson *et al.*, 1985), a similar finding to our patients who denied confusion and usually settled back to sleep.

Studies of patients with frontal lobe epilepsy have shown that a significant number of patients have a family history of epilepsy (Fusco *et al.*, 1990; Vigevano and Fusco, 1993). Indeed, studies of frontal lobe epilepsy (Vigevano and Fusco, 1993) and NPD (Lugaesi and Cirignotta, 1981; Godbout *et al.*, 1985; Lee *et al.*, 1985; Tinuper *et al.*, 1990) have described pedigrees with multiple generations affected. We suspect that a number of these kindreds had unrecognized autosomal dominant nocturnal frontal lobe epilepsy, as seen in our families.

It is likely that there are other forms of inherited partial epilepsy. We have examined other kindreds with a different electroclinical picture of diurnal partial seizures and active epileptiform discharges on interictal EEG studies. These families are phenotypically different from the distinctive homogeneous phenotype described here. Molecular genetic analysis will clarify whether these other patterns of familial partial epilepsy represent allelic or locus heterogeneity.

### *Relationship to the benign partial epilepsies of childhood*

The idiopathic localization-related epilepsies are defined as, childhood partial epilepsies with focal EEG abnormalities (Commission, 1989). They include benign childhood epilepsy with centrotemporal spikes, and childhood epilepsy with occipital paroxysms; and, by definition, occur in children of normal intellect and neurological examination, where no anatomical lesion is demonstrable. These epilepsy syndromes are age-related, remit spontaneously by adult life, and have a recognized genetic component. It has been anticipated that benign partial epilepsy syndromes localizing to other cortical regions will be identified and reports of apparently benign frontal lobe epilepsy have been described (Beaumanoir and Nahory, 1983; Vigevano and Fusco, 1993).

The seizure disorder described in our families does not fulfil the criteria of a 'benign' epilepsy syndrome (Lerman and Kivity, 1991) in that seizures persist through adult life. However, in other ways, this syndrome satisfies many

'benign' criteria: childhood onset, partial seizures generally amenable to treatment, seizures occurring more frequently in sleep, and no underlying neurological abnormality. Furthermore, this syndrome has an unequivocal genetic aetiology. Carbamazepine produced good control in many of our patients and in many of the children in the paediatric series, in contrast with a number of other anti-epileptic drugs. In Vigevano and Fusco's (1993) series, five out of six children had seizure recurrence following withdrawal and required re-institution of carbamazepine suggesting this entity is not benign. Our patients required long-term medication.

Genetic studies of benign childhood epilepsy with centrotemporal spikes have shown an increase in epileptiform abnormalities in the EEGs of relatives of probands (Bray and Wiser, 1964). Clinical studies alone are not suggestive of a monogenic inheritance pattern, but when the EEG trait is analysed, an autosomal dominant pattern with variable age-dependent penetrance has been hypothesized (Bray and Wiser, 1965; Heijbel *et al.*, 1975). By comparison, the partial epilepsy syndrome described here follows clear-cut single gene inheritance based solely on clinical information.

### *Neurobiology and animal models*

An animal model correlate of inherited partial epilepsy exists in the El mouse which has seizures arising in the hippocampus (Seyfried and Glaser, 1985; King and LaMotte, 1989; Mutoh *et al.*, 1993), where there is gliosis without neuronal loss (Brigande *et al.*, 1989). The major gene responsible for the El mouse epileptic phenotype has been mapped to mouse chromosome 9 (Rise *et al.*, 1991), which may allow identification of a human epilepsy candidate gene on the basis of conserved synteny with human chromosome 3. El mouse seizure susceptibility appears to be inherited as a partial dominant trait, modified by other genes (Rise *et al.*, 1991). Our families, however, do not manifest typical complex partial seizures of hippocampal origin, so it is not surprising that molecular genetic studies of our families have excluded linkage to the human chromosome regions syntenic to the El-1 mouse locus (Lopes-Cendes *et al.*, 1994).

Although a variety of pathogenetic mechanisms have been hypothesized for the idiopathic generalized epilepsies, the mechanism of a genetic partial epilepsy is more difficult to explain. Presumably, the product of the abnormal gene would be exclusively or preferentially expressed in the frontal lobes. A genetically determined localized disorder of neuronal migration is one hypothesis, but we have been unable to confirm this by MRI studies. Clarification should come with linkage studies currently underway, ultimately leading to identification of the gene for this condition.

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## Appendix of illustrative case histories

### *Severely affected individuals*

#### *Family A: V-12*

A 26-year-old man was the proband of one half of family A. He startled excessively as a newborn infant, and at age 4 years, he was found prone in the crawling position in bed, and diagnosed as hyperactive. A 4 h cluster of attacks at 6 years led to the diagnosis of epilepsy. Seizures began with a grunting noise, he sprang onto all fours and rocked back and forth, sniffing and snorting. His seizure disorder was most poorly controlled at 16 years when multiple seizures occurred nightly. Episodes of status epilepticus have occurred several times. During one night of monitoring, 72 seizures were recorded.

During his twenties, seizures occurred after 1.5 h of sleep, typically in clusters of two to 15 attacks/night, every fortnight. He felt a numb feeling across his face, tried to sit up, and pressed his right hand to his eyes. He felt frightened, could not get his breath and gasped. He was stiff and shook all over, with head extended and eyes elevated. He remained aware throughout the attack. Milder attacks lasted 20–40 s, while more severe ones lasted 90 s, and seizures occurred every second minute. He bit his tongue and was rarely incontinent. He had only had one secondarily generalized tonic-clonic seizure (GTCS) when taken off medication in hospital. Current medication was carbamazepine 600 mg nocte and sodium valproate 2000 mg/day. His other medical problem was short stature.

#### *Family A:IV-22*

A 50-year-old woman had experienced two distinct types of seizures arising from sleep, each confined to a particular period of her life

with an intervening seizure-free period of 11 years. Seizures began at 7 years with an aura of feeling as if she were falling down a well, associated with a screaming noise, and culminating in loss of consciousness as she reached the bottom of the well. The seizure was then secondarily generalized with urinary incontinence, and occasional tongue-biting. Seizures occurred one to two times nightly and lasted 1 min. This seizure pattern persisted until her third pregnancy at 28 years, with exacerbation during pregnancy.

She was seizure free on no treatment from 28 years until menopause at 39 years. Seizures had been poorly controlled since, occurring in clusters of up to 10/night, beginning 10 min after she fell asleep or dozed during an afternoon nap. These seizures began with gasping noises. She felt unable to breathe, and felt and appeared frightened. She attempted to sit up, but her limbs were rigid, with trembling hands; her eyes were open and staring. Awareness was preserved but she was unable to respond. Seizures lasted 20–30 s. There was no post-ictal confusion but she had a 30 s headache, and was tired the following morning. Seizure control had slowly deteriorated. She was receiving 600 mg carbamazepine/day.

#### *Family B:II-2*

A 46-year-old woman had seizure onset at 32 years. Up to four seizures occurred in a series 15 min after falling asleep. Seizures began with an aura of a warm feeling in her head. She sat up and grabbed on to the bed, otherwise she would fall out, injuring herself. Her legs extended and thrashed around, and she often developed painful leg cramps unless she could dorsiflex her ankles at the onset of the seizure. She hyperventilated through the seizure, and appeared

flushed. She remained fully aware, crying out, 'help me' and able to respond, albeit with slow speech. These seizures lasted 1 min without post-ictal confusion or drowsiness, although sometimes she would be shaky and unsteady.

She also described less frequent, more unpleasant seizures not preceded by an aura. These occurred at any time during sleep, including on awakening, and in clusters of up to three attacks. Her arms and legs extended, and she felt unable to get her breath. She remained aware, but could only respond with a moan. These attacks lasted up to 5 min. She never had a generalized convulsion. These seizures began between her second and third pregnancy associated with the stress of marital separation. Her only period of complete seizure remission had been during her third pregnancy. She was receiving 700 mg sodium valproate/day and 4 mg flunitrazepam at night, and had one cluster of seizures/week.

#### *Moderately affected individuals*

##### *Family B:II-4*

A 43-year-old man developed seizures at 28 years. He woke up from sleep with an aura of a cramp in his right leg and a feeling of *déjà vu*, followed by frantic movements with kicking, jerking and extension of his lower limbs, and noisy breathing. He recalled some of his seizures and there was no post-ictal confusion or drowsiness. Seizures lasted 30–60 s, and occurred in clusters of 3–12 seizures/night between 05.00 and 07.00. Secondarily generalized seizures occurred rarely. The combination of 600 mg carbamazepine and 2 mg clonazepam/day produced complete seizure control over the next 6 years.

##### *Family C:IV-4*

A 19-year-old music student developed nocturnal attacks from 7 years. He would awaken from sleep with a feeling that his breath was stuck in his throat. This feeling could be preceded by paraesthesia over the face, and sometimes over the entire body for a few seconds. During a 20 s seizure, he remained aware and would get out of bed to reach an open window. He also reported longer episodes with loss of awareness lasting up to 1 min. During these seizures, his neck and trunk arched backwards and his legs thrashed around, but there was no incontinence or tongue-biting. His attacks always occurred in sleep in clusters of 15–20 seizures/night.

##### *Family D:II-1*

A 35-year-old woman developed seizures at age 16 years. Her seizures began with an aura of numbness or tingling in the left toes that moved quickly up the leg to the groin, followed by a shock-like feeling as if part of her 'was stuck in an electric socket'. She stiffened and assumed an opisthotonic posture, and vibrated, remaining partially aware, although unable to talk. Most attacks occurred at night, either waking her or as she fell asleep. She had rare daytime attacks while relaxing, and would sit or lie down. Her seizures lasted 20–30 s, and she never had generalized convulsions. Her attacks improved spontaneously in her third decade, but recurred when her daughter developed similar seizures. Past medical history included surgical repair of a patent ductus arteriosus, and endocarditis. She was immature with a histrionic personality and was of normal intelligence.

#### *Mildly affected individuals*

##### *Family A:V-33*

A 17-year-old girl had seizures at 12 years for 3 months. These attacks occurred as she dozed, with up to six each night. She would awaken with a startled scream, and thrash around in the bed for 30 s. There were oral and manual automatisms, and she appeared frightened afterwards. She never received treatment, and the attacks ceased spontaneously. Her father recognized the attacks as similar to her mother's seizures. There were no secondarily GTCS.

##### *Family A:IV-31*

A 47-year-old man had not been diagnosed as having seizures until he was interviewed for the study. He described stereotyped 'nightmares' from the age of 5 years that began with a sensation of a visual hallucination such as a truck falling or backing onto him, and feeling scared. He screamed out, sat up in bed with his arms above his head, and was not aware. His wife described this as 'climbing the wall', and felt attacks were triggered by stress. The seizures lasted <1 min, with only one per night, approximately 3 monthly. There were no secondarily GTCS.

##### *Family B:III-4*

A 14-year-old girl developed seizures at age 12 years, and described an identical aura to her father of a cramp in her right leg. She only had three secondarily generalized attacks and was fully controlled by carbamazepine.