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Surgical treatment of drug-resistant nocturnal frontal lobe epilepsy

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Of the cases with nocturnal frontal lobe epilepsy (NFLE) ~30% are refractory to antiepileptic medication, with several patients suffering from the effects of both ongoing seizures and disrupted sleep. From a consecutive series of 522 patients operated on for drug-resistant focal epilepsy, 21 cases (4%), whose frontal lobe seizures occurred almost exclusively (>90%) during sleep, were selected. All patients underwent a comprehensive pre-surgical evaluation, which included history, interictal EEG, scalp video-EEG monitoring, high-resolution MRI and, when indicated, invasive recording by stereo-EEG (SEEG). There were 11 males and 10 females, whose mean age at seizure onset was 6.2 years, mean age at surgery was 24.7 years and seizure frequency ranged from <20/month to >300/month. Nine patients reported excessive daytime sleepiness (EDS). Prevalent ictal clinical signs were represented by asymmetric posturing (6 cases), hyperkinetic automatisms (10 cases), combined tonic posturing and hyperkinetic automatisms (4 cases) and mimetic automatisms (1 case). All patients reported some kind of subjective manifestations. Interictal and ictal EEG provided lateralizing or localizing information in most patients. MRI was unrevealing in 10 cases and it showed a focal anatomical abnormality in one frontal lobe in 11 cases. Eighteen patients underwent a SEEG evaluation to better define the epileptogenic zone (EZ). All patients received a microsurgical resection in one frontal lobe, tailored according to pre-surgical evaluations. Two patients were operated on twice owing to poor results after the first resection. Histology demonstrated a Taylor-type focal cortical dysplasia (FCD) in 16 patients and an architectural FCD in 4. In one case no histological change was found. After a post-operative follow-up of at least 12 months (mean 42.5 months) all the 16 patients with a Taylor's FCD were in Engel's Class Ia and the other 5 patients were in Engel's Classes II or III. After 6 months post-surgery EDS had disappeared in the 9 patients who presented this complaint pre-operatively. It is concluded that patients with drug-resistant, disabling sleep-related seizures of frontal lobe origin should be considered for resective surgery, which may provide excellent results both on seizures and on epilepsy-related sleep disturbances. An accurate pre-surgical evaluation, which often requires invasive EEG recording, is mandatory to define the EZ. Further investigation is needed to explain the possible causal relationships between FCD, particularly Taylor-type, and sleep-related seizures, as observed in this cohort of NFLE patients.

Keywords: epilepsy surgery; focal cortical dysplasia; nocturnal frontal lobe epilepsy; sleep-related seizures

Abbreviations: EDS = excessive daytime sleepiness; ENW = epileptic nocturnal wandering; EZ = epileptogenic zone; FCD = focal cortical dysplasia; FLE = frontal lobe epilepsy; NFLE = nocturnal FLE; SEEG = stereo-electroencephalography

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Introduction

It is well known that in frontal lobe epilepsy (FLE) seizures often occur during sleep (Crespel *et al.*, 1998; Herman *et al.*, 2001). The term nocturnal FLE (NFLE) has been adopted to indicate FLE patients who present seizures almost exclusively during sleep (Provini *et al.*, 1999). NFLE is characterized by sleep-related paroxysmal attacks of increasing complexity

and duration ranging from simple and brief stereotyped motor events to paroxysmal arousals and major attacks (Provini *et al.*, 1999). Some patients may show ictal deambulatory behaviours [epileptic nocturnal wanderings (ENWs)] (Montagna *et al.*, 1992; Plazzi *et al.*, 1995; Provini *et al.*, 1999). NFLE occurs sporadically or as an inherited form with an established genetic basis (autosomal dominant NFLE; Scheffer *et al.*, 1995; Oldani *et al.*, 1996, 1998) and it is considered a relatively benign clinical entity because seizures occur during sleep and in most of the cases a positive response to antiepileptic drugs is obtained. However, drug-resistant patients have been described; ~30% of cases are resistant to carbamazepine and to other antiepileptic drugs, particularly those with more complex motor attacks (Hirsch *et al.*, 1994; Provini *et al.*, 1999). Despite this relatively high rate of pharmaco-resistance, data about pre-surgical evaluation and surgical treatment in NFLE patients are limited to occasional case reports (Nobili *et al.*, 2003) and cannot be extrapolated from larger surgical series (Olivier, 1995; Jobst *et al.*, 2000; Schramm *et al.*, 2002). Here we describe the clinical, electrophysiological, neuroradiological and histological findings and the surgical results in 21 patients operated on for drug-resistant NFLE.

Material and methods

We performed a retrospective review of 522 patients who received resective surgery in our centre from 1996 to 2005 for drug-resistant focal epilepsy, and we identified 21 cases (4%) who met the following criteria:

(i) More than 90% of seizures occurring during sleep since initial epileptic manifestations, based on questionning of patients and their relatives. This distribution of seizures was confirmed by seizure diaries filled over a time period for at least one year and by subsequent long-term video-EEG recordings.
(ii) Evidence from presurgical evaluation of a frontal lobe onset of the seizures.
(iii) Surgical resection performed within the anatomical limits of the frontal lobe.
(iv) A postoperative follow-up period of at least 12 months.

The presurgical evaluation included:

(i) Accurate analysis of historical data, with particular attention to type and chronology of ictal clinical subjective and objective manifestations and the possible post-ictal deficits;
(ii) Screening for excessive daytime sleepiness (EDS) measured by a validated questionnaire [Epworth Sleepiness Scale (Johns, 1991; Vignatelli *et al.*, 2003)];
(iii) Long-term monitoring with scalp video-EEG, including at least one video-polysomnographic (PSG) recording of nocturnal sleep;
(iv) High-resolution MRI, customized according to main electroclinical information employing a 1.5-tesla ACS-NT unit (Philips Medical Systems, Best, The Netherlands). Since in this population of patients the electroclinical data pointed to a frontal lobe origin of the seizures, the images were acquired parallel with and perpendicular to the anteroposterior commissure line, according to a previously reported protocol (Colombo *et al.*, 2003);
(v) Full neuropsychological testing, for patients with non-conclusive anatomo-electro-clinical data as to the localization of the epileptogenic zone (EZ), stereo-electro-encephalography (SEEG) with stereotactically placed intracerebral electrodes was performed (Munari *et al.*, 1994; Cossu *et al.*, 2005), for a better definition of the EZ. An individualized arrangement of electrodes (exploration) was employed, according to a predefined localization hypothesis based on non-invasive findings. Following recording of spontaneous seizures, intracerebral electrical stimulations were used, when needed, to provide a functional mapping of eloquent structures and to induce seizure or parts of seizure, with the aim to better define the EZ.

The occurrence during sleep of motor manifestations of different complexity was separately assessed, distinguishing among (Provini *et al.*, 1999):

(i) minor events, represented by short-lasting (2–4 s) stereotyped movements involving the limbs, the axial musculature and/or the head (Fig. 1);
(ii) paroxysmal arousals, characterized by abrupt arousals lasting ~5–10 s, accompanied by stereotyped movements (trunk and head elevation) often associated with vocalization and frightened expression (Fig. 2);
(iii) major attacks, previously defined as 'nocturnal paroxysmal dystonia', consisting of stereotyped movements such as asymmetric tonic or dystonic posturing or other bizarre behaviours (choreoathetoid and ballistic movements of the limbs) lasting ~20–30 s (Fig. 3), which were categorized according to the International League Against Epilepsy (ILAE) classification (Blume *et al.*, 2001);
(iv) ENWs, consisting of paroxysmal ambulation, often associated with fear and bizarre behavioural manifestations (Fig. 4).

Two patients with sleep-related seizures, with a suspicion of NFLE, underwent a presurgical evaluation but were excluded from epilepsy surgery: in the first case heavy psychiatric disturbances contraindicated a SEEG study for possible harmful behaviour; the other patient was excluded after bilateral SEEG investigation which failed to clearly lateralize the EZ.

Resective micro-surgery was conducted according to the results of the anatomo-electro-clinical investigations, and it was aimed at removal of the EZ, taking into account potential functional constraints to avoid new neurological deficits.

All the surgical specimens were routinely processed to obtain a histological diagnosis. Focal cortical dysplasias (FCD) were categorized according to a recently proposed classification (Tassi *et al.*, 2002). Seizure outcome was assessed according to Engel's classification (Engel *et al.*, 1993).

Tapering of preoperative antiepileptic drug regimen was not considered before 12 months following surgery.

Results

The main demographic and anamnestic features of the 21 patients are summarized in Table 1. There were 11 males and 10 females, whose mean age at seizure onset was 6.2 years (SD 5.2; range 0.5–17 years); mean age at surgery was 24.7 years (SD 8.5; range 11–41 years); and mean duration of epilepsy was 18.2 years (SD 8.9, range 4–38 years). Seizure frequency was <20/month in 1 case, 20–60/month in 7 cases

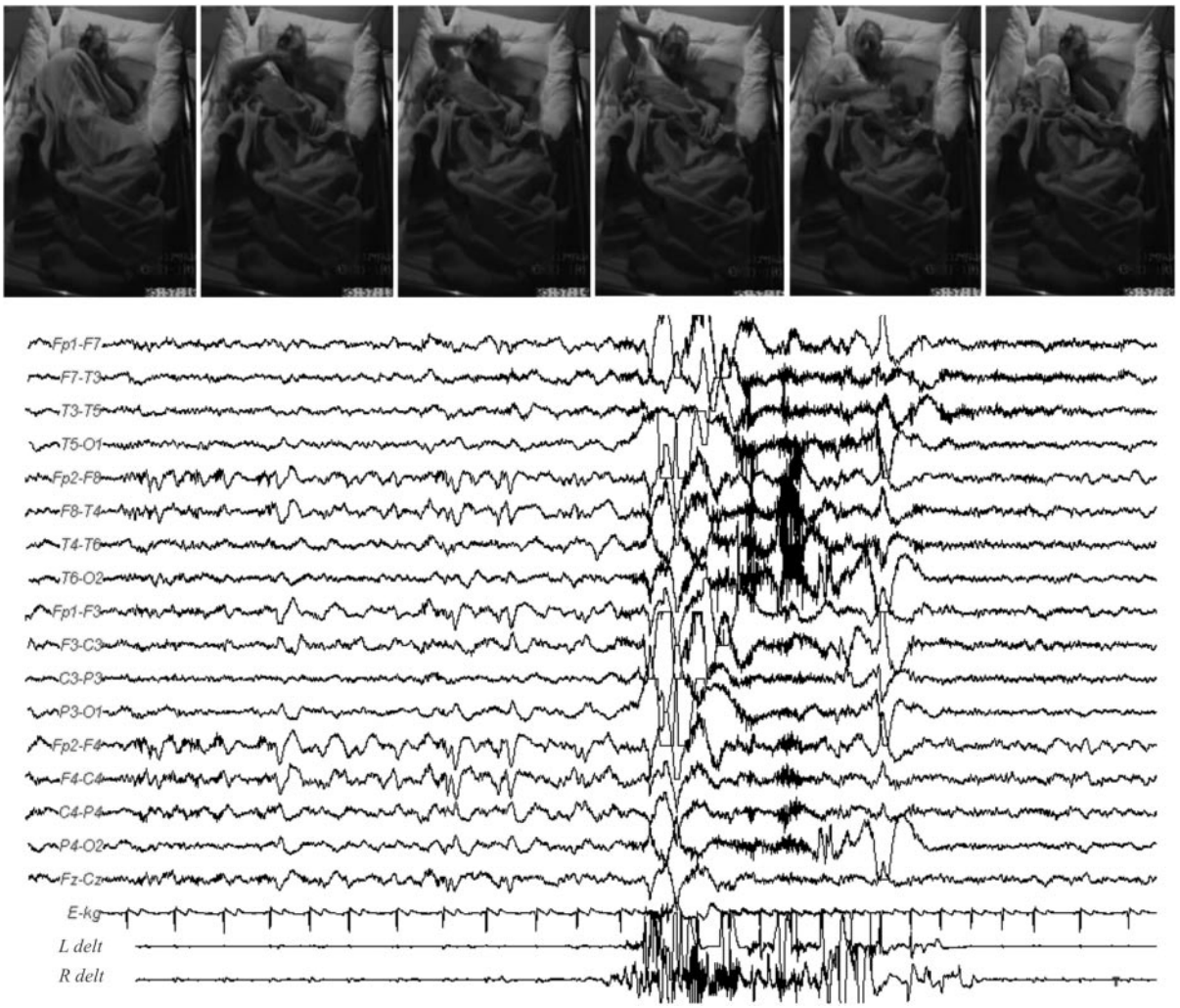

Fig. 1 Video-images (upper part) and scalp EEG recording (lower part) of a minor event (Case 3). The first electromyographic modification corresponds to the second snapshot from the left. L = left; R = right; delt = deltoid muscle.

and 60–300/month in 11. In two patients seizure frequency was >300/month and attacks were hardly countable. Five patients had a familiar history of epilepsy. The family history of one of these cases (Case 4) was positive for nocturnal paroxysmal episodes in his maternal grandfather, in his mother and in his sister, suggesting an autosomal dominant trait of inheritance. In six cases the personal history was positive for perinatal antecedents. Nine patients reported a non-restorative sleep and presented with EDS (score >10 on the Epworth Sleepiness Scale). The neurological examination was normal in all cases. All patients were referred for surgical consideration after several therapeutic attempts with different antiepileptic drugs in monotherapy or in association at maximal tolerated dosages, with poor results on their seizures.

Ictal clinical features

The main features of clinical manifestations reported by the patients and recorded during both scalp video-EEG and video-SEEG recordings in the 21 patients are reported in Table 2.

Subjective manifestations

All the patients reported some kind of isolated subjective manifestations. These occurred during wakefulness and they were not associated with major nocturnal attacks, except in Case 5. This patient was invariably awakened by a cephalic tingling and by a paraesthesic sensation in her right cheek, followed by her habitual ictal behaviour. The most frequently reported subjective manifestations were fear (eight cases) and different kinds of somatic, more or less localized, sensations (nine cases).

Objective manifestations

In 6 patients the clinically prevalent ictal manifestation was represented by an asymmetric posturing, whereas hyperkinetic automatisms were the prevailing signs in 10 cases. Four cases presented both hyperkinetic automatisms and motor tonic movements. One patient, after arousal provoked by aura, was dyspnoeic and presented mimetic automatisms.

PSG disclosed the presence of minor events in 14 patients. Five of these had both minor events and paroxysmal arousals

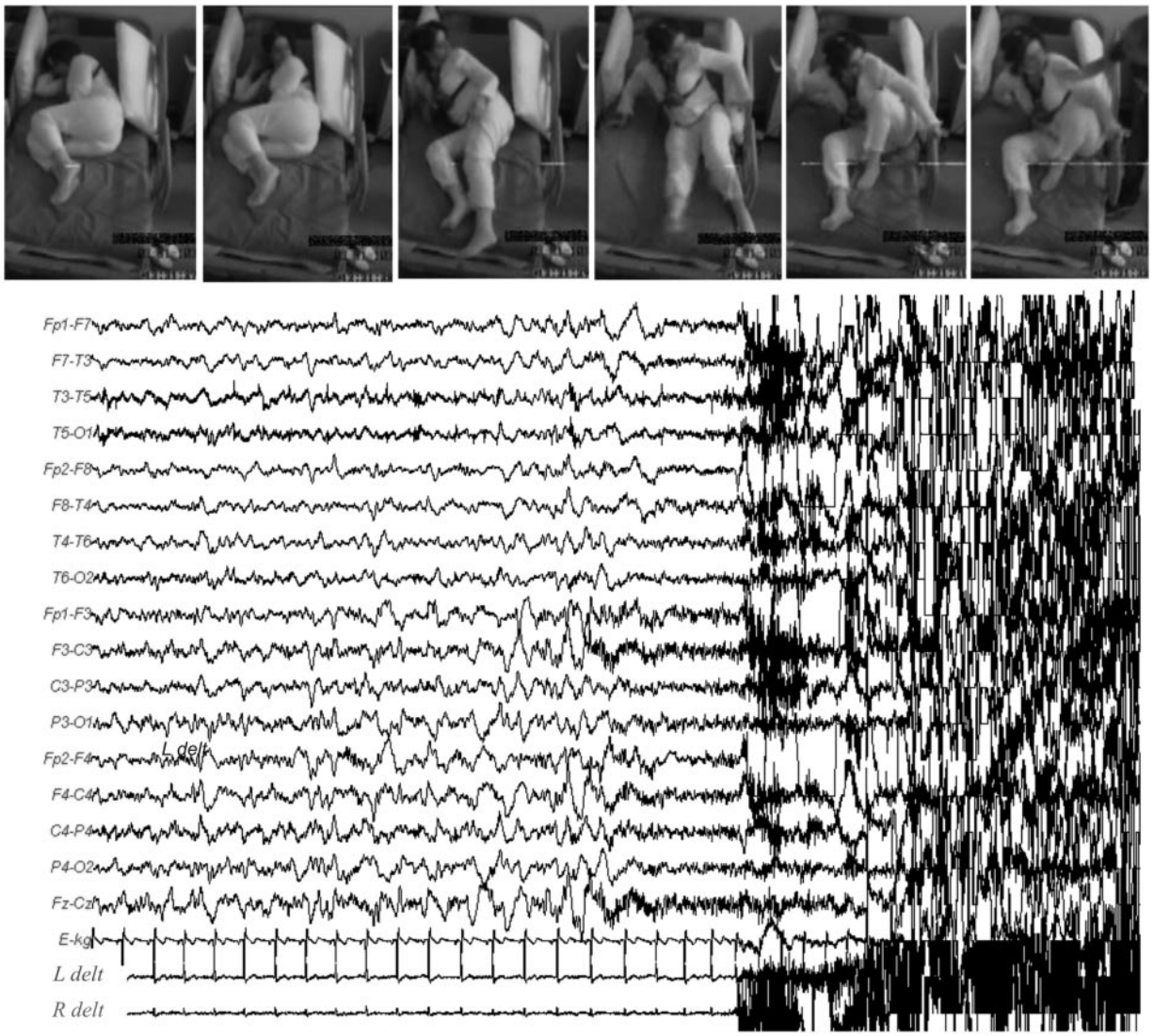

Fig. 2 Video-images (upper part) and scalp EEG recording (lower part) of a paroxysmal arousal (Case 8). The first electromyographic modification corresponds to the second snapshot from the left. L = left; R = right; delt = deltoid muscle.

and two patients presented minor events, paroxysmal arousals or ENWs. Paroxysmal arousals alone were recorded in four patients.

MRI

MRI (Table 3) did not show any relevant anatomical abnormality in 10 patients, including 2 patients who presented a surgical cavity resulting from previous frontal resections performed in other centres. In 11 patients a focal lesion of different size was disclosed in one frontal lobe (6 right side, 5 left side).

Electrophysiological investigations

Interictal and ictal EEG

The findings of interictal (during both wakefulness and sleep) and ictal scalp EEG are detailed in Table 4. Interictal EEG abnormalities were lateralizing and/or localizing in 17 subjects during wake and in 19 subjects during sleep recording. In two subjects (Cases 11 and 12) neither wake nor sleep recording provided lateralizing or localizing information.

Only in one subject (Case 17) no definite ictal discharge was detected during the seizures.

In three patients (Cases 8, 18 and 19) the available non-invasive anatomical (MRI), clinical and electrophysiological (video-EEG) findings were considered adequate to consistently localize the EZ, and to define a surgical strategy.

SEEG recordings

In 18 cases, a variable degree of inconsistency among anatomo-electro-clinical data, as to localization of the EZ, indicated the need for a SEEG investigation. The pertinent data concerning the SEEG explorations are shown in Table 5.

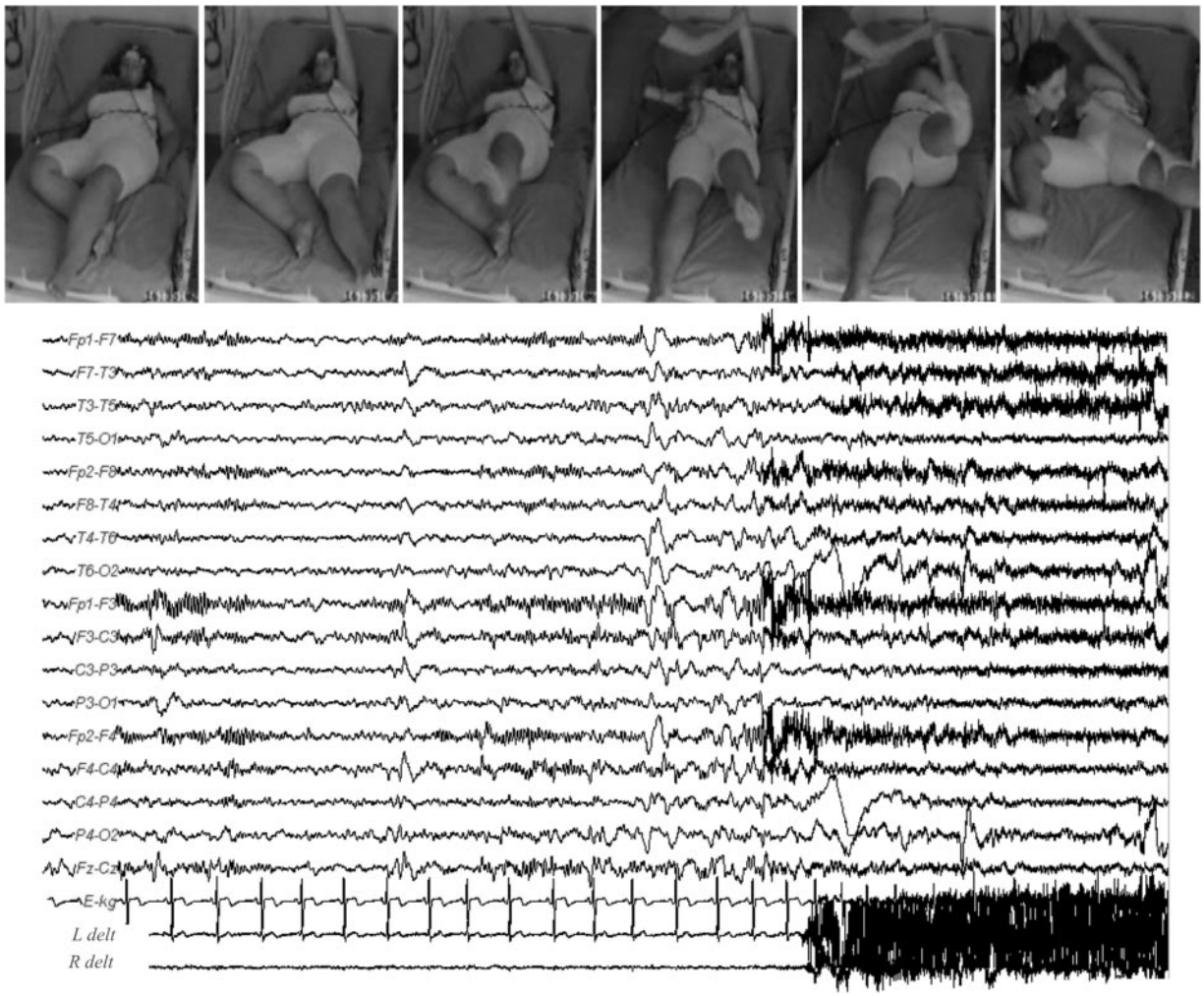

Fig. 3 Video-images (upper part) and scalp EEG recording (lower part) of a major seizure, consisting of a combined tonic–hyperkinetic motor behaviour (Case 1). The first electromyographic modification corresponds to the second snapshot from the left. L = left; R = right; delt = deltoid muscle.

The 10 patients with an unrevealing MRI received SEEG, as well as 8 patients with a focal frontal lobe lesion. Since one patient (Case 2) underwent two SEEGs, owing to recurrence of seizures after a first SEEG-based left frontal lobe resection, we performed a total of 19 SEEG procedures. Explorations were right-sided in nine procedures, left sided in seven and bilateral (but asymmetrical) in three. In all procedures a prevalent frontal lobe coverage was employed, with arrangement of electrodes customized to preferentially sample the regions of presumed onset of the ictal discharge, according to the pre-SEEG findings. Additional extrafrontal electrodes were also placed in the ipsilateral central (16 procedures), temporal (10 procedures), parietal (6 procedures), insular (6 procedures) and occipital (1 procedure) regions, to evaluate the modality and timing of spread, if any, of the ictal discharge. Moreover in three patients (Cases 10, 11 and 13) electrodes were placed contralaterally to the side of main coverage to assess the possible participation of contralateral structures to the ictal discharge.

For each SEEG an average of 13 electrodes were employed (range 9–17). Spontaneous seizures (from 1 to 18 per SEEG monitoring) were recorded in 17 patients. In Case 14 no spontaneous seizures occurred despite 9 days of intensive monitoring, and the definition of the EZ was based on the recording of two seizures induced by intracerebral electrical stimulations.

In both the spontaneous and induced recorded seizures, the ictal electrical activity (generally low-voltage fast activity) had a frontal lobe origin and preceded or was concomitant with the first ictal clinical symptom.

Surgery

The main features of surgery performed in the 21 patients are reported in Table 6. All the patients received a frontal lobe resection, which corresponded to the EZ according to the pre-surgical investigations (Fig. 5). In seven patients the surgical resection involved mainly the mesial cortex, in seven

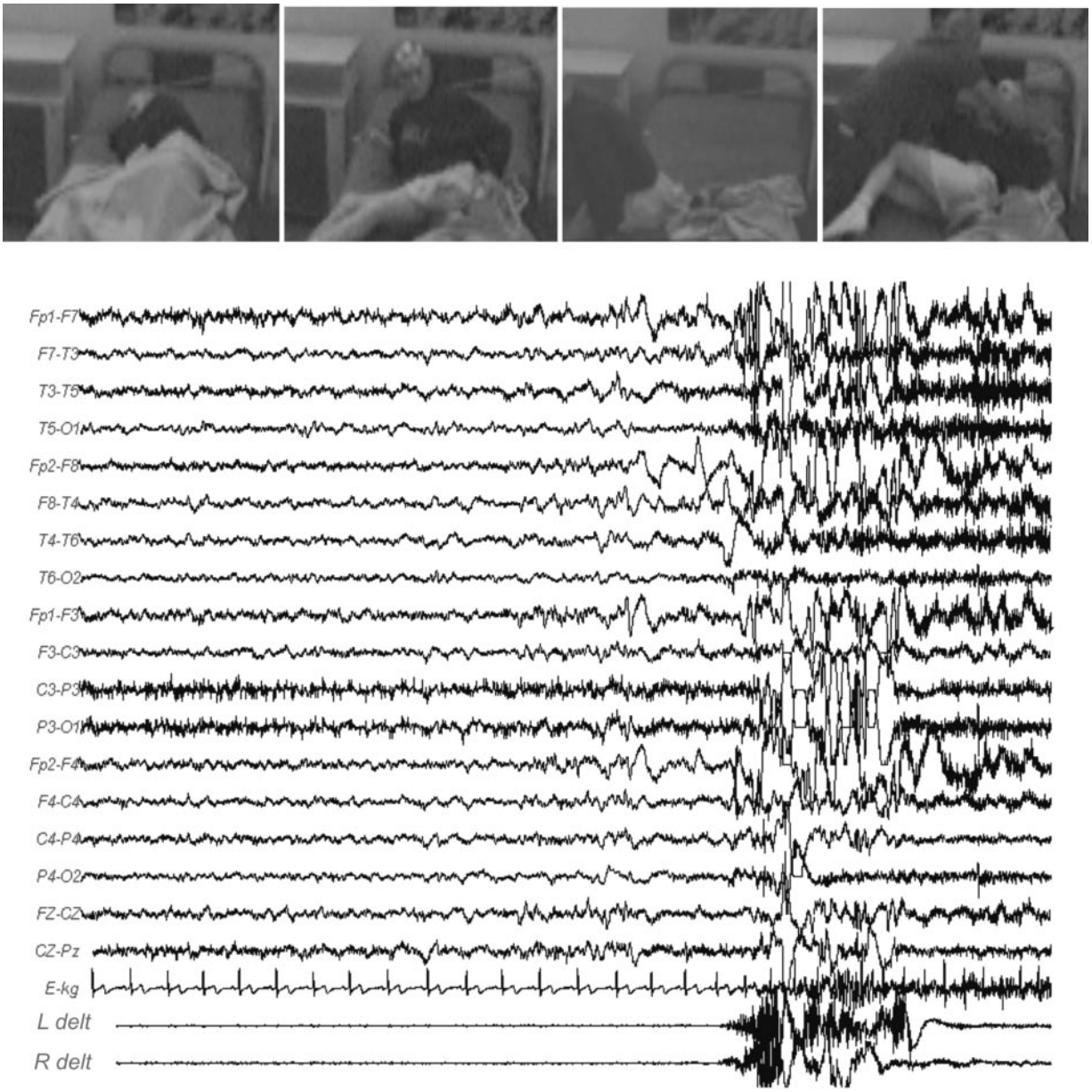

Fig. 4 Video-images (upper part) and scalp EEG recording (lower part) of an epileptic nocturnal wandering (Case 19), stopped by the EEG technician to prevent harmful behaviour. The first electromyographic modification corresponds to the second snapshot from the left. L = left; R = right; delt = deltoid muscle.

both the mesial and the dorso-lateral cortex, in five cases the orbito-polar region and in two cases the opercular region and the whole frontal lobe, respectively. The two patients (Cases 3 and 9) operated on before referral to our centre received additional resection in the same frontal lobe of previous surgery, as did the two patients (Cases 2 and 21) operated on twice by us. Surgery consisted of a frontal cortical resection in the 10 patients with an unrevealing MRI, in a lesionectomy associated with cortical resection in 9 cases and in a simple lesionectomy in 2 cases. The lesion was completely removed in 10 cases, as confirmed by post-operative MRI. In one patient (Case 6) a small portion of the lesion was intentionally left in place at surgery, because SEEG findings excluded its involvement in the ictal discharge.

Only transient postoperative morbidity was observed and it consisted in the vast majority of cases in motor deficits contralateral to the side of surgery, ascribable to resection of the supplementary motor area.

Histology

Histological examination of resected specimens (Table 6) disclosed in 16 patients a Taylor's FCD. No ballooned cells were observed in 2 cases, whereas they were present in 14 of

Table 1 Demographic and anamnestic data of the 21 patients

Case	Gender	Familiar history of epilepsy	Antecedents	Age at seizure onset (years)	Age at surgery (years)	Seizure frequency/month	EDS
1	F	No	No	4	17	60–300	No
2	M	No	No	5	15	60–300	No
3	M	Yes	Neonatal jaundice	0.5	29*	20–60	No
4	M	Yes	Neonatal cyanosis	3	22	>300	Yes
5	F	No	No	7	34	60–300	Yes
6	F	No	No	2	16	<20	No
7	M	No	No	7	24	60–300	No
8	F	Yes	Neonatal cyanosis	9	30	60–300	Yes
9	M	No	No	15	26*	60–300	Yes
10	M	Yes	Neonatal jaundice	3	11	60–300	No
11	F	No	No	8	35	20–60	Yes
12	M	No	No	3	34	20–60	Yes
13	M	No	No	17	23	20–60	No
14	F	No	No	4	23	60–300	Yes
15	F	No	Complicated delivery	9	13	20–60	No
16	M	No	No	16	28	>300	No
17	M	No	No	0.5	22	60–300	Yes
18	F	No	Complicated delivery	3	41	20–60	No
19	F	No	No	14	38	60–300	Yes
20	M	No	No	5	16	60–300	No
21	F	Yes	No	1	21	20–60	No

M = male; F = female; EDS = excessive daytime sleepiness.
*Patients 3 and 9 had previous resective surgery with no benefit in other centres.

Table 2 Main subjective and objective clinical ictal manifestations

Case	Aura	Type of major seizures (ILAE classification)*	MEs	PAs	ENWs
1	Tingling in upper limbs and left cheek	Contralateral motor tonic (1.1.1), hyperkinetic automatisms (1.2.5)	Yes	No	No
2	Ocular trembling	Vocal automatisms (1.2.11) and hyperkinetic automatisms (1.2.5)	Yes	No	No
3	Forced thinking	Hyperkinetic automatisms (1.2.5)	No	Yes	No
4	Fear	Motor tonic (1.1.1), hyperkinetic automatisms (1.2.5), vocal automatisms (1.2.11)	Yes	Yes	Yes
5	Cephalic tingling, paraesthesic sensation in right cheek	Awakened by aura, dyspnoea, mimetic automatisms (1.2.2)	Yes	Yes	No
6	Diffuse warming sensation	Oroalimentary automatisms (1.2.1), hyperkinetic automatisms (1.2.5)	No	Yes	No
7	Rising epigastric sensation	Omolateral versive (1.1.1.2.1), omolateral hyperkinetic automatisms (1.2.5)	Yes	No	No
8	Fear and epigastric discomfort	Omolateral versive (1.1.1.2.1), hyperkinetic automatisms (1.2.5)	No	Yes	No
9	Pressure in the eyes	Asymmetric tonic posturing (1.1.1.2)	No	Yes	No
10	Tingling in upper limbs	Asymmetric tonic posturing (1.1.1.2)	No	No	No
11	Fear, cephalic tingling	Asymmetric tonic posturing (1.1.1.2)	Yes	Yes	No
12	Cephalic indescribable sensation	Hyperkinetic automatisms (1.2.5)	Yes	Yes	No
13	Forced thinking	Motor tonic (1.1.1), hyperkinetic automatisms (1.2.5)	Yes	No	No
14	Palpitations, fear	Mimetic (1.2.2), vocal (1.2.11) and hyperkinetic (1.2.5) automatisms	Yes	Yes	No
15	Fear, thoracic pressure	Asymmetric tonic posturing (1.1.1.2)	Yes	No	No
16	Sensation of instability	Asymmetric dystonic posturing (1.1.1.2.2)	No	No	No
17	Sensation of estrangement	Asymmetric tonic posturing (1.1.1.2)	Yes	Yes	No
18	Fear	Mimetic (1.2.2) and hyperkinetic (1.2.5) automatisms	No	No	No
19	Fear	Mimetic (1.2.2) and hyperkinetic (1.2.5) automatisms	Yes	Yes	Yes
20	Diffuse chill	Hyperkinetic automatisms (1.2.5), asymmetric tonic posturing (1.1.1.2)	Yes	No	No
21	Fear	Hyperkinetic automatisms (1.2.5), vocal automatisms (1.2.11)	Yes	No	No

MEs = minor events; PAs = paroxysmal arousals; ENWs = epileptic nocturnal wanderings. *When pertinent, numerical description of ictal symptoms, according to the ILAE classification (Blume *et al.*, 2001) has been added between brackets. Signs are reported in order of chronological occurrence.

Table 3 MRI findings in the 21 patients

Case	MRI abnormality	Side	Site
1	Focal lesion	Right	Frontal, dorso-lateral
2	No	—	—
3	No*	—	—
4	No	—	—
5	Focal lesion	Left	Frontal, dorso-lateral
6	Focal lesion	Right	Frontal, polar, mesial and cingulate gyrus
7	Focal lesion	Left	Frontal, polar
8	Focal lesion	Left	Frontal, mesial
9	No*	—	—
10	Focal lesion	Left	Frontal, dorso-lateral
11	No	—	—
12	No	—	—
13	No	—	—
14	Focal lesion	Left	Frontal, mesial
15	No	—	—
16	Focal lesion	Right	Frontal, mesial
17	Focal lesion	Right	Frontal, orbital
18	Focal lesion	Right	Frontal, dorso-lateral
19	Focal lesion	Right	Frontal, polar, mesial and cingulate gyrus
20	No	—	—
21	No	—	—

*MRI showed only the surgical cavities in cases previously operated on in other institutions.

these cases. An architectural FCD was diagnosed in four patients, and histology was unremarkable in one case.

Post-operative outcome

All the patients had a post-operative follow-up longer than 12 months (mean 42.5; SD 22.6; range 12–93). Sixteen patients (76%) were completely seizure-free since surgery (Engel's Class Ia), and five (24%) had significant improvement of seizure frequency and/or intensity (three in Class II and two in Class III). At 6 months following surgery, no patient had EDS on self-compilation of the Epworth Sleepiness Scale (Table 6). At last follow-up, anticonvulsive drugs had been withdrawn in 2 seizure-free patients, they had been tapered in 14 (13 seizure-free, 1 with recurrent seizures), and they were unchanged in 5 (1 seizure-free and 4 with recurrent seizures).

Discussion

NFLE is a rare entity, though no epidemiological data are available. Both a sporadic and a genetic form of NFLE have been described (Scheffer *et al.*, 1995; Oldani *et al.*, 1996, 1998; Provini *et al.*, 1999). The presented series of patients included sporadic NFLE cases, with the exception of Case 4, whose familial history suggested an autosomal dominant form of NFLE.

Although NFLE is generally considered a benign disorder, a significant proportion of drug-resistant cases has been reported (Hirsch *et al.*, 1994; Provini *et al.*, 1999). Moreover, even if seizures occurring during sleep are thought to have a lower disabling impact on the quality of life compared to wake-related fits, several patients may complain of non-restorative sleep, and of EDS (Foldvary-Schaefer, 2002; Alanis-Guevara *et al.*, 2005). This has been ascribed to the fragmentation of sleep structure due to recurrent motor seizures with different intensity and duration (Oldani *et al.*, 1998; Provini *et al.*, 1999; Zucconi *et al.*, 2000; Nobili *et al.*, 2006). Therefore, a surgical approach aimed at seizure control may be warranted in select cases with drug-resistant NFLE.

The clinical features of our population match those reported in other series of NFLE patients (Oldani *et al.*, 1996; Provini *et al.*, 1999); indeed, together with major seizures occurring during sleep, most of our patients presented a spectrum of motor events ranging from minor episodes to paroxysmal arousals and ENWs. Furthermore, as expected in this population, EDS was reported by several patients. Regarding major seizures, to better evaluate possible anatomo-electro-clinical correlations, we preferred to categorize the main ictal clinical features according to ILAE criteria (Blume *et al.*, 2001) instead of referring to the term 'nocturnal paroxysmal dystonia', which represents a synthetic definition of different complex ictal motor behaviours. Moreover, it has been reported that patients with nocturnal paroxysmal dystonia may present seizures of extrafrontal origin (Nobili *et al.*, 2004; Mai *et al.*, 2005; Ryvlin *et al.*, 2006).

The premise of a surgical treatment of drug-resistant focal epilepsy is the identification of the region to be resected, that is, the EZ [the cortical region of onset and of primary organization of the ictal discharge (Lüders *et al.*, 1993)]. The identification of the EZ in cases of FLE may be a challenging issue compared, for instance, to temporal lobe epilepsy. This is probably due to the large size of the frontal lobe, to the complexity of the functional network involved in the generation of frontal lobe seizures, to the related different clinical ictal patterns and to the frequent absence of definitely informative interictal and ictal EEG correlates (Munari *et al.*, 1995; Bartolomei and Chauvel, 2000; Williamson and Jobst, 2000). In addition, MRI is likely to be less informative in FLE than in temporal lobe epilepsy (Duncan, 1997).

For all these reasons, presurgical non-invasive investigations are often inadequate to define the EZ, and intracranial recordings are frequently required (Schramm *et al.*, 2002; Guye *et al.*, 2005). Only the judicious scrutiny of the anatomical and electroclinical findings may enable to restrict the surgical resection to a limited portion of the frontal lobe.

On the other hand a detailed analysis of the ictal clinical symptoms may help to customize the arrangement of intracerebral electrodes: indeed, in patients with asymmetric tonic posturing seizures, we privileged the covering of the mesial frontal regions. In cases with prevailing hyperkinetic automatisms in whom an anatomoclinical correlation is more difficult, our SEEG investigations aimed to evaluate

Table 4 Interictal and ictal EEG at scalp video-EEG monitoring

Case	Interictal EEG (wakefulness)	Interictal EEG (sleep)	Ictal EEG
1	R fronto-central δ bursts; R > L frontal low-voltage fast activity bursts; L temporal δ waves	R frontal spikes	Bilateral frontal rhythmic fast activity R fronto-central rhythmic θ activity
2	L fronto-central sharp waves	L fronto-central spikes	L fronto-centro-parietal fast activity
3	R fronto-central δ waves; R frontal fast activity bursts; R temporal spikes	R fronto-centro-temporal δ waves and spikes	R fronto-centro-temporal fast activity
4	R fronto-temporal θ and δ waves	R fronto-temporal θ-δ and spikes	Bilateral fronto-centro-temporal fast activity (R > L)
5	L frontal δ activity and spikes	L frontal spikes	Left fronto-temporal low-voltage fast activity
6	R frontal δ and spikes	R frontal δ activity and spikes	Bilateral frontal low-voltage fast activity (R > L)
7	L fronto-temporal δ activity and spikes	L fronto-temporal spikes	L fronto-centro-temporal low-voltage fast activity
8	L fronto-central spikes	L fronto-central slow waves and spikes	L frontal fast activity
9	L frontal slow waves and fast activity bursts	L frontal slow waves and fast activity bursts	L parasagittal low-voltage fast activity (following first ictal sign)
10	L frontal δ waves; L fronto-central parasagittal spikes	L fronto-central spikes	L fronto-central low-voltage fast activity with early contralateral propagation
11	Uninformative	Uninformative	R fronto-central flattening
12	Bilateral fronto-temporal slow waves	L frontal and R temporal spikes	R temporo-frontal flattening
13	Bilateral frontal slow waves R > L	R fronto-central and parasagittal θ activity	R fronto-temporal flattening
14	L fronto-central sharp waves	L fronto-central sharp waves	L parasagittal and fronto-central flattening
15	R fronto-central slow waves	R fronto-centro-parietal spikes	R frontal and parasagittal fast activity
16	R fronto-centro-temporal θ activity	R centro-temporal θ activity	R fronto-central low-voltage fast activity
17	R fronto-temporal sharp waves	R fronto-temporal sharp waves	No definite ictal discharge
18	R fronto-temporal spikes	R fronto-temporal spikes	R fronto-central flattening
19	Bilateral frontal spikes and sharp waves	Bilateral frontal spikes and sharp waves	R frontal low-voltage fast activity
20	Normal	L fronto-central sharp waves	L centro-temporal and parasagittal rhythmic θ activity
21	R fronto-temporal θ activity	R fronto-centro-temporal θ activity	R fronto-central flattening

R = right; L = left.

the possible involvement of either the frontal dorso-lateral cortex, the orbital frontal cortex, the frontal and extrafrontal limbic structures, including the insula and the temporal lobe, according to the assumption that sleep-related complex motor seizures may have an extrafrontal origin (Nobili *et al.*, 2002, 2004; Mai *et al.*, 2005; Ryvlin *et al.*, 2006). Conversely, some cases with a high degree of coherence among clinical, eletrophysiological and morphological findings do not require invasive investigations, as in three of our patients.

Concerning the scalp EEG features, our population showed a high proportion of both interictal and ictal EEG abnormalities, with a substantial correlate as to lateralization and/or localization. In a previously reported study conducted in a large population of NFLE a quite lower proportion of positive interictal and ictal EEG was found (Provini *et al.*, 1999). This discrepancy may be ascribed to the fact that our cases represent a selected subgroup of drug-resistant patients scheduled for pre-surgical investigation. Moreover, it is possible that, at least for ictal EEG, our interpretation criteria may stress the significance of minimal electrical changes, such as EEG flattening concomitant with or preceding the ictal manifestations.

The valuable EEG contribution to localization is in part counterbalanced by the low incidence of positive findings at MRI, with ~50% of our patients presenting an unremarkable picture. An even more pronounced proportion of uninformative MRIs has been previously reported in NFLE (Provini *et al.*, 1999). Nevertheless, in 9 out of 10 of our patients with a negative MRI the histology demonstrated either an architectural or a Taylor's dysplasia, and a favourable surgical outcome was achieved in most of them. In our centre, MRI investigations are performed by last generation equipment according to a flexible protocol (Colombo *et al.*, 2003) which privileges the site(s) of presumed seizure onset, and neuroimages are accurately interpreted by highly trained, dedicated neuroradiologists. It is conceivable, however, that non-conventional MRI technologies, such as magnetic resonance spectroscopic imaging (Guye *et al.*, 2005) and texture analysis (Bernasconi *et al.*, 2001), may disclose subtle structural abnormalities in these more demanding cases.

Table 5 Main features of SEEG investigations

Case	SEEG	Side of SEEG	Sampled lobes	Number of electrodes	Number of recorded spontaneous seizures
1	Yes	Right	FCPI	11	4
2	Yes*	(1) Left (2) Left	(1) FCP (2) FCI	(1) 13 (2) 11	(1) 3 (2) 17
3	Yes	Right	FCPTI	16	3
4	Yes	Right	FTC	13	3
5	Yes	Left	FC	13	11
6	Yes	Right	FCT	14	1
7	Yes	Left	FCT	15	15
8	No	—	—	—	—
9	Yes	Left	FCP	13	18
10	Yes	Bilateral	FI (left) F (right)	11 (left) 2 (right)	6
11	Yes	Bilateral	FCTI (right) FT (left)	12 (right) 5 (left)	14
12	Yes	Right	FTCO	17	1
13	Yes	Bilateral	FCT (right) FC (left)	13 (right) 3 (left)	3
14	Yes	Left	FT	9	0**
15	Yes	Right	FC	12	10
16	Yes	Right	FCP	10	7
17	Yes	Right	FT	13	2
18	No	—	—	—	—
19	No	—	—	—	—
20	Yes	Left	FCPI	13	11
21	Yes	Right	FCT	11	4

F = frontal; C = central; T = temporal; P = parietal; O = occipital; I = insular. *Patient no. 2 received two SEEG evaluations; **No spontaneous seizures recorded; the identification of the epileptogenic zone was based on the two seizures induced by intracerebral electrical stimulations.

In all the patients with an asymmetric tonic posturing, SEEG evaluation showed a more or less early activation of the supplementary motor area, with a different degree of involvement of the intermediate mesial frontal cortex and of the frontal cingulate gyrus. In patients with a hyperkinetic ictal behaviour, SEEG revealed the involvement of either mesial-dorso-lateral, orbito-polar, opercular or larger lobar cortical regions. This is in good agreement with data obtained from studies more focused on the electroclinical features of frontal lobe epileptic syndromes (Morris *et al.*, 1988; Munari and Bancaud, 1992; Baumgartner *et al.*, 1996; Bartolomei and Chauvel, 2000; Kellinghaus and Lüders, 2004). The epileptic manifestations characterized by the association of fear and more organized motor behaviours (ENWs) seemed to correspond to the activation of anterior cingulate, orbito-polar and temporal regions. This may suggest, in agreement with other studies, that a network including frontal, and possibly extrafrontal, limbic structures is involved in the genesis of these complex epileptic manifestations (Biraben *et al.*, 2001; Bartolomei *et al.*, 2002; Nobili *et al.*, 2002). The activation of this circuitry seems to be independent from the aetiological factors: indeed, similar ictal sleep-related manifestations have been reported in a family in which a mutation markedly increasing the sensitivity to acetylcholine of the nicotinic receptor $\alpha 2$ subunit has been identified (Aridon *et al.*, 2006).

Surgical resections were tailored according to the convergent results of anatomical, electrophysiological and clinical findings. In particular, in cases submitted to SEEG evaluation, the resection margins resulted from the careful analysis of the spatial-temporal organization of the ictal discharge. Therefore, mesial frontal resections prevailed in patients with tonic posturing, whereas more anterior, wider dorso-lateral and lobar resections were performed in patients with more complex ictal behaviours.

Most of surgical complications were represented by transient motor deficits in the limbs contralateral to the resection. Eight out of the nine patients who developed this sign received resections of the postero-mesial portion of their superior frontal gyrus, which functionally corresponds to the supplementary motor area. The relationship between transient motor impairment and surgery in this region has been detailed in previous studies (Krainik *et al.*, 2001).

In this series surgery provided excellent results, with 76% of cases being completely seizure-free (Engel's Class Ia). Moreover, a significant improvement was achieved also in the remaining cases (Engel's Classes II or III). This figure compares favourably with the results obtained in other studies, which included cases with FLE irrespective of the presence of sleep-related seizures and which reported an Engel's Class I rate of 40–60% (Rougier *et al.*, 1992; Laskowitz *et al.*, 1995; So, 1998; Janszky *et al.*, 2000; Jobst *et al.*, 2000; Schramm *et al.*, 2002) and with the overall results obtained in frontal lobe resection in our centre (62% of cases in Engel's Class Ia, data not reported). This seems to indicate that surgical results are more favourable in patients with NFLE compared with FLE with seizures not exclusively related to sleep. The remarkable surgical results obtained in our NFLE patients could be explained by the high incidence of cases with a histological diagnosis of Taylor's FCD, all rendered seizure-free after surgery. Comparable findings, irrespective of the site of resection, have been reported in one study, which showed that, as far as FCDs are concerned, patients with Taylor's FCD had the higher rate of surgical success (Tassi *et al.*, 2002). Similar results can be extrapolated from the study conducted by Schramm, who reported a similar proportion of Class I outcome (72%) in a subpopulation of frontal lobe epilepsies with cortical malformations, even if the information about the sleep–wake distribution of seizures are lacking (Schramm *et al.*, 2002).

Less favourable results, as previously observed (Tassi *et al.*, 2002), have been obtained in five patients (24%) in whom the histopathological evaluation showed an architectural type of FCD (four cases) or it was unreavealing (one case). This may be explained by the more diffuse nature of architectural FCD as compared with Taylor's dysplasias. The focal onset of seizures, as documented by SEEG in patients with architectural FCD, is likely to represent only a part of a more diffuse epileptogenic propensity which probably involves a larger amount of abnormal cortex (Frater *et al.*,

Table 6 Main features of surgical resection, histology and postoperative follow-up

Case	Surgery				Histology	Follow up (months)	Outcome (Engel)	EDS
	Side	Site of surgery	Type	Postoperative transient morbidity				
1	R	Posterior F3, opercular portion of precentral gyrus	CR, Les	L facial palsy	Taylor FCD (bc)	18	Ia	No
2	(1) L	(1) Middle and posterior F2	(1) CR	(1) No	(1) Taylor FCD (bc)	16*	Ia*	No*
	(2) L	(2) F1 and anterior cingulate gyrus	(2) CR	(2) No	(2) Unrevealing			
3	R	Residual posterior F1 and F2, F3, anterior cingulate gyrus, subcallosal cortex and fronto-orbital cortex	CR	L motor deficit	Taylor FCD	36	Ia	No
4	R	F1, F2, posterior F3, anterior cingulate gyrus	CR	L motor deficit	Architectural FCD	34	IIc	No
5	L	Middle and anterior F1, F2, F3, anterior cingulate gyrus, lateral orbital cortex	CR, Les	Dysphasia	Taylor FCD (bc)	43	Ia	No
6	R	F1, posterior F2, frontal cingulate gyrus	CR. Les (st)	No	Taylor FCD (bc)	54	Ia	No
7	L	Fronto-orbital cortex, polar cortex, genu of cingulate gyrus, subcallosal cortex	CR, Les	No	Taylor FCD (bc)	18	Ia	No
8	L	Posterior F1, frontal cingulate gyrus	CR, Les	R motor deficit	Taylor FCD (bc)	46	Ia	No
9	L	Posterior F1, frontal cingulate gyrus	CR	R motor deficit, dysphasia	Taylor FCD (bc)	76	Ia	No
10	L	F1, F2, anterior cingulate gyrus	CR, Les	No	Taylor FCD	23	Ia	No
11	R	Posterior F1, frontal cingulate gyrus	CR	L motor deficit	Taylor FCD (bc)	93	Ia	No
12	R	F1, anterior cingulate gyrus, subcallosal cortex, rectus gyrus	CR	No	Architectural FCD	48	IIIa	No
13	R	Middle and posterior F1, anterior cingulate gyrus	CR	No	Taylor FCD (bc)	70	Ia	No
14	L	Middle F1, anterior and frontal cingulate gyrus	CR, Les	No	Taylor FCD (bc)	32	Ia	No
15	R	Posterior F1 and F2, frontal cingulate gyrus	CR	L motor deficit	Architectural FCD	40	IIc	No
16	R	Posterior F1	Les	L motor deficit	Taylor FCD (bc)	47	Ia	No
17	R	Middle and anterior F1 and F2, anterior F3, frontal cingulate gyrus, subcallosal cortex, fronto-orbital cortex	CR, Les	L motor deficit	Taylor FCD (bc)	48	Ia	No
18	R	Middle and anterior F1 and F2, frontal cingulate gyrus	Les	No	Taylor FCD (bc)	46	Ia	No
19	R	Anterior F1, genu of cingulate gyrus, rectus gyrus, subcallosal cortex	CR, Les	No	Taylor FCD (bc)	12	Ia	No
20	L	Middle and posterior F1 and F2, frontal cingulate gyrus	CR	R motor deficit, aphasia	Architectural FCD	14	IIa	No
21	(1) R	(1) Anterior F1, rectus gyrus	(1) CR	(1) No	(1) Unrevealing	78*	IIIa*	No*
	(2) R	(2) Middle F1, frontal cingulate gyrus, subcallosal cortex, mesial fronto-orbital cortex	(2) CR	(2) No	(2) Unrevealing			

R = right; L = left; F1 = superior frontal gyrus; F2 = middle frontal gyrus; F3 = inferior frontal gyrus; CR = cortical resection; Les = lesionectomy; st = subtotal; FCD = focal cortical dysplasia; bc = presence of ballooned cells in Taylor FCD; EDS = excessive daytime sleepiness 6 months after surgery. *Follow-up, outcome and EDS relate to the second operation for patients with repeated surgery.

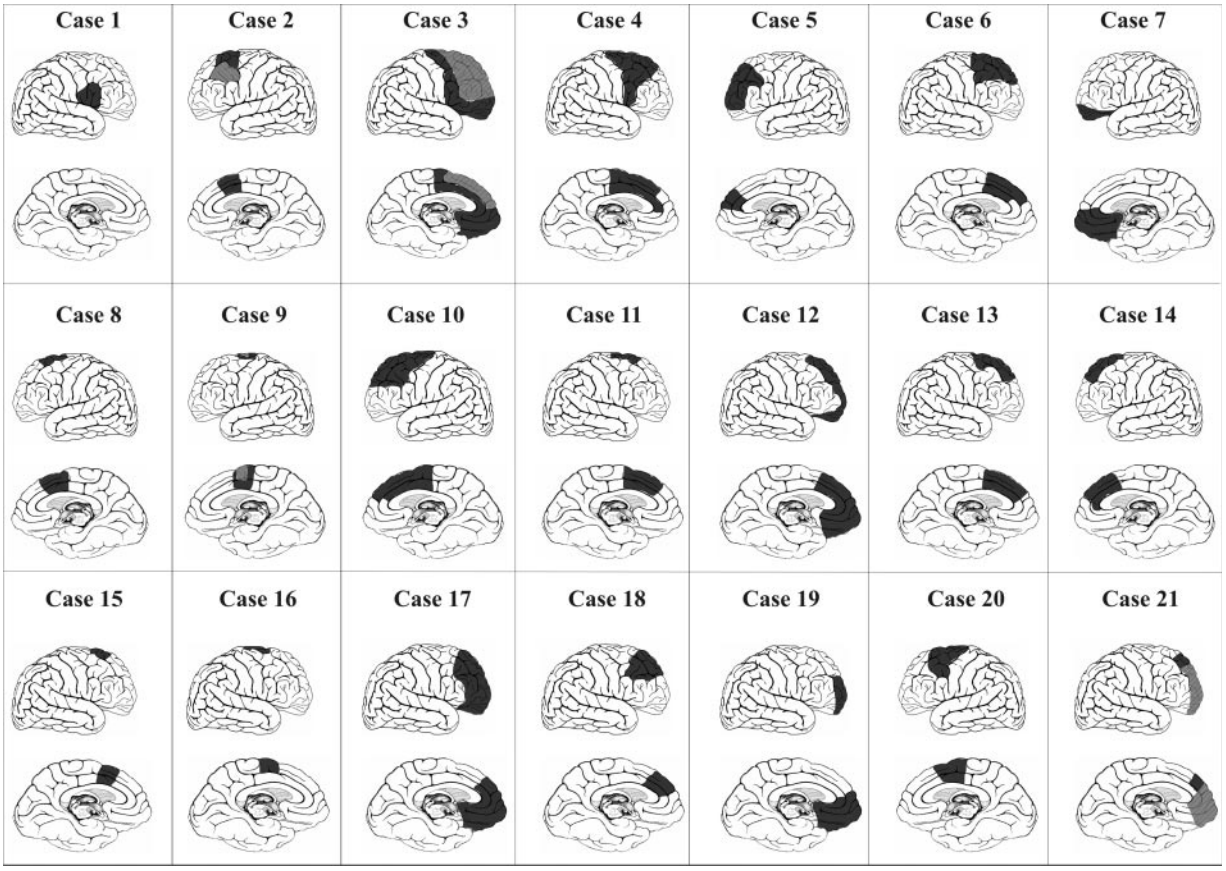

Fig. 5 Schematic drawings of frontal resections (black-shadowed areas) performed in the 21 patients. Grey shadowed areas indicate either previous resections in other institutions (Cases 3 and 9) or first resections performed in our centre (Cases 2 and 21).

2000). Interestingly, one patient with architectural FCD (Case 4) had a familial pedigree suggestive of autosomal dominant NFLE. Data concerning the possible presence of structural brain abnormalities in patients with autosomal dominant NFLE are lacking. Further studies are required to investigate the possible relationships among genetic abnormalities, sleep-related epilepsy and cortical dysplasias.

Nevertheless, irrespective of a possible genetic aetiology, our data suggest a strong, still unexplained association between FCD and sleep-related seizures. In our patients this association seems to be independent of the location of FCDs which were found in multiple frontal regions. Moreover, previous studies have revealed a high rate of FCDs, particularly the Taylor-type, also in patients with sleep-related seizures of extrafrontal origin (Nobili *et al.*, 2004, Mai *et al.*, 2005).

Sleep disturbances and EDS may be relevant factors in determining the impaired quality of life in epileptic patients (Alanis-Guevara *et al.*, 2005), especially those with sleep-related seizures. In our series, the finding that both seizure-free and improved patients, who preoperatively suffered from EDS, reported disappearance of this symptom despite maintenance of the preoperative antiepileptic drug regimen, further strengthens the efficacy of the surgical approach to these cases.

In conclusion, patients with drug-resistant, disabling sleep-related seizures of frontal lobe origin should be considered for resective surgery. Several of these patients may present with an unrevealing MRI, but rarely this reflects the absence of a pathological substrate. Excellent results may be obtained by an accurate presurgical evaluation, which often requires invasive recording.

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