Original article

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Electroclinical, MRI and surgical outcomes in 100 epileptic patients with type II FCD

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ABSTRACT – Focal cortical dysplasias (FCDs) are highly epileptogenic malformations associated with drug-resistant epilepsy, susceptible to surgical treatment. Among the different types of FCD, the type II includes two subgroups based on the absence (IIa) or presence (IIb) of balloon cells. The aim of this retrospective study was to investigate possible differences in electroclinical presentations and surgical outcomes between the two subgroups in 100 consecutive surgically treated patients with type II FCDs. All patients underwent a comprehensive presurgical assessment including stereo-EEG (SEEG) when necessary. No significant differences in gender, age at epilepsy onset, duration of epilepsy, age at surgery or seizure frequency were found between the two subgroups. Patients with type IIb FCD frequently showed sleep-related epilepsy. Their peculiar electrographic pattern was characterised by localised rhythmic or pseudo-rhythmic spikes or polyspikes ("brushes") enhanced during non-REM sleep and also associated with well-localised, brief, low-voltage fast activity. The incidence and frequency of short bursts of fast discharges, interrupted by activity suppression, increased during slow-wave sleep and often recurred pseudo-periodically. The occurrence of "brushes", present in 76% of the patients with type IIb FCD, was significantly associated ($p<0.001$) with the presence of balloon cells. We discuss the possible pathogenetic mechanisms underlying this activity. MRI diagnosis of type II FCD was made in 93% of the patients with balloon cells (BCs), suggesting that the presence of balloon cells might be, at least partially, responsible for the MRI features. Patients had very good postsurgical outcomes (83% in Engel class I) even after a long period of follow-up.

Key words: focal cortical dysplasia, epilepsy surgery, focal epilepsy, stereo-EEG, balloon cells

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The term focal cortical dysplasia (FCD), originally introduced by Taylor *et al*. (1971) to describe the particular aspects of focal malformations of the cortical mantle, is currently used for a wide range of cortical abnormalities characterised by variable histopathological patterns.

Recent classifications of FCD based on electroclinical, neuroimaging, and neuropathological data have given rise to two main forms of FCD: type I and type II. The latter is consistent with the description by Taylor *et al*. (1971) and is thus also referred to as Taylor-type FCD (Tassi *et al*., 2002; Palmini *et al*., 2004).

In most cases, type II FCD exhibits peculiar MRI findings that allow the lesions to be distinguished from low-grade tumours (Tassi *et al*., 2002; Bronen *et al*., 1997; Colombo *et al*., 2003; Colombo *et al*., 2009). The neuropathological characteristics are also different from type I FCD regarding the presence of dysmorphic neurons inside the dislaminated cortex and, in some cases, balloon cells (BCs). Furthermore, immunocytochemical (ICC) studies have revealed the peculiar aspect of the affected cortex suggesting that, in addition to the structural disarrangement, neurochemical organisation is also disrupted (Spreafico *et al*., 1998; Garbelli *et al*., 1999; Tassi *et al*., 2001). Recent electrophysiological studies performed on dissociated neurons and brain slices obtained from surgical specimens with proven type II FCD have also reported anomalous cellular behaviour (D'Antuono *et al*., 2004; Cepeda *et al*., 2007; Andre *et al*., 2008).

These abnormal cytoarchitectural, neurochemical, and electrophysiological characteristics suggest selective morphofunctional alterations in type II FCD that might explain the distinctive ictal and interictal EEG patterns (Tassi *et al*., 2002; Garbelli *et al*., 1999; Chassoux *et al*., 2000). This pathognomonic electrophysiological pattern, observed in both scalp EEG and particularly SEEG recordings, is characterised by disrupted focal background activity and the presence of pseudo-periodic spike and polyspike activity with different aspects during wakefulness and sleep (Tassi *et al*., 2002; Chassoux *et al*., 2000; Nobili *et al*., 2009). Furthermore, most patients with type II FCD experience numerous seizures and many of them present more than 75% of paroxysmal attacks during sleep, thus defined, according to the classification of the American Academy of Sleep Medicine (2005), as sleep-related epilepsy (SRE).

The recent ILAE classification (Blümcke *et al*., 2011) recognises three types of FCD based on electroclinical, neuropathological, and MRI data, but type II FCD is still divided into two subgroups based on the absence (type IIa) or presence (type IIb) of BCs. Whether this neuropathological distinction defines clinically homogeneous groups with different surgical outcome is still a matter of investigation.

We retrospectively evaluated 100 consecutive patients, who received surgery for intractable epilepsy, with a neuropathological diagnosis of type II FCD, in order to investigate possible differences in the electroclinical presentation and surgical outcome between type IIa and type IIb.

Materials and methods

Patient selection

Between May 1996 and May 2006, 784 patients underwent surgery for drug-resistant partial epilepsy at the Claudio Munari Epilepsy Surgery Centre in Milan, Italy. Surgery was performed after obtaining informed consent from the patients or their parents, and after a comprehensive presurgical evaluation including detailed personal and family history, neurological examination, EEG, and Video-EEG (VEEG). In some patients, invasive stereo-EEG (SEEG) recording was mandatory for the precise identification of the epileptogenic zone (EZ).

The neuropathological data were retrospectively reviewed and 100 (13%) patients fulfilled the criteria for type II FCD. Patients with associated lesions of different aetiology (any kind of MCD, neoplasms, vascular malformations or scars) were excluded, as were those whose clinical, neuropathological, imaging, and genetic data suggested tuberous sclerosis.

MRI

MRI protocols were assessed according to those proposed by Colombo *et al*. (2003, 2009), including transverse double-echo spin-echo (SE) sequences of the entire brain during the early period of the study that were later replaced by T2-weighted transverse turbo spin-echo (TSE) and T2-weighted transverse TSE fluid-attenuated inversion-recovery (FLAIR) sequences; T2-weighted coronal and sagittal TSE FLAIR sequences, T2-weighted coronal turbo spin-echo (TSE) sequences, and T1-weighted coronal inversion recovery (IR) sequences.

Intravenous contrast was injected only in the rare cases of an uncertain diagnosis. The assessed features were focal thickening of the cortex, blurring of the grey/white matter junction, abnormal signal intensity in the cortex and subcortical white matter, transmantal sign, and sulcal-gyration anomalies.

Stereo-EEG procedure

SEEG recordings were considered mandatory in the patients for whom the ictal events, recorded by VEEG,

together with the MRI data and the clinical aspects of the seizures, were considered insufficiently reliable to identify the EZ. SEEG and final surgical strategy were planned after informed consent had been obtained from the patient or the parents of under-aged or intellectually impaired subjects.
SEEG was tailored to the patients' individual anatomical and electroclinical characteristics, as described by Cossu *et al*. (2005).

Surgery

The final surgical resection was performed for strictly therapeutic reasons in order to remove the cortical areas involved in seizure generation. In addition to corticectomy, the anatomical lesion was removed when identified, but in some patients only partial lesionectomy was performed. In each case, the extent of resection was carefully planned taking account of the severity of the epilepsy and other neurological symptoms, and the risk of further postsurgical neurological deficits.

Histopathology and classification

Inadequate surgical specimen was an exclusion criterion. The surgical specimens were fixed (10% neutral buffered formalin) and paraffin-embedded sections (4-10 μm) were coloured using haematoxylin and eosin, thionin, Kluver Barrera, and Bielschowsky stains. Routine immunocytochemical investigations were also performed using anti-glial fibrillary acid protein (GFAP, Roche Diagnostics, Mannheim, Germany) and anti-neurofilament (2F11 monoclonal, DAKO, Denmark). The diagnosis of FCD type IIa and IIb was based on the classification criteria proposed by Blümcke *et al*. (2011).

Statistical analysis

Mean age at epilepsy onset, the duration of epilepsy, age at surgery, and seizure frequency in the two histological groups (IIa and IIb) were compared using a t-test. A two-tailed Pearson χ^2 test or Fisher's exact test (when appropriate) were used for the bivariate binary analysis.
The associations between SRE, the presence of BCs, and surgical resection confined to the frontal lobe were evaluated using a multivariate logistic regression model. The same model was fitted in order to compare the outcomes of patients in Engel classes, other than class I, with multi-lobar surgery and the histological subtypes.
Kaplan-Meier survival curves were generated and compared using the log-rank test.
A p value of <0.05 was considered significant. The statistical analyses were made using SPSS software, v. 17.

Results

General characteristics of the population as a whole

In the cohort of 100 patients (53 males and 47 females), the mean age at epilepsy onset was 6 years (SD 6; 0-30), the mean duration of epilepsy was 18 years (SD 11; 1-46), mean age at surgery was 24 years (SD 13; 1-53), and the mean monthly seizure frequency was 88 (SD 116; 1-600) (*table 1*).
Based on the neuropathological findings, BCs were detected in 66 patients (type IIb) and not in the remaining 34 (type IIa). In order to evaluate possible differences between the two neuropathologically identified subgroups, the results are presented separately.
No significant differences between the two subgroups were found in terms of gender, age at epilepsy onset, duration of epilepsy, age at surgery or seizure frequency.
Fifty-three patients had SRE, most of whom (67%) had BCs (*table 1*). The occurrence of SRE not only significantly correlated with the presence of BCs (p=0.001, OR 4.74; CI OR 95%: 1.85-12.16) but also with surgical resection confined to the frontal lobe (p=0.036, OR 2.54; CI OR 95%: 1.06-6.09).
The MRI diagnosis of type II FCD was based on the presence of the following signs: increased cortical thickness, blurring of the grey/white matter junction, an increased signal of the subcortical white matter on T2-weighted images and a decreased signal on T1-weighted IR, the "transmantal sign" (*figures 1A, 1B, 1F, and 1G*), and gyration anomalies (Colombo *et al*., 2009). The concurrent presence of various signs allowed the diagnosis of type II FCD in 84 patients; MRI was unrevealing in the remaining 16.
A correct diagnosis of type II FCD was made in 61/66 (93%) patients with neuropathologically verified FCD type IIb and in 23/34 (68%) patients with type IIa.

Electrophysiological data

The scalp-EEG recordings showed a peculiar electrographic pattern (never observed in patients with other neuropathologically defined lesions) characterised by rhythmic or pseudo-rhythmic spikes and polyspikes, intermingled with background activity (*figures 1C and 1H)*. This electrical activity increased during hyperpnoea (*figure 1D and 1I*) and drowsiness (*figure 1E and 1J*).
The SEEG recordings showed a peculiar intralesional pattern consisting of the absence of physiological

Table 1. General characteristics of the population.

Histology (No.)	Males/females (%)	Mean age at epilepsy onset (SD)	Mean age at surgery (SD)	Mean duration of epilepsy at surgery (SD)	Mean frequency of seizures at surgery (SD)	No. of pts with SRE (%)
With BCs (66)	32/34 (48-52)	6 (6)	25 (13)	18 (11)	87 (100)	44 (67)
Without BCs (34)	21/13 (62-38)	5 (5)	22 (15)	17 (12)	91 (145)	9 (27)
Total (100)	53/47	6 (6)	24 (13)	18 (11)	88 (116)	53

SD: standard deviation; BC: balloon cells.

background activity with sub-continuous rhythmic spikes and polyspikes and waves, usually at a frequency of between 1 and 3 Hz, alternating with short bursts of fast discharges ("brushes") and interrupted by suppression of electrical activity (*figures 2A and 2B*). This last pattern increased dramatically during non-REM sleep, with a tendency to recur pseudo-periodically about every four seconds (*figure 3A*), and during slow-wave sleep, frequently spreading over the surrounding non-lesional areas and progressing into a seizure (*figure 3C*). The electrical pattern during REM sleep was similar to that observed during wakefulness (*figure 3D*). The ictal pattern was represented by the intensification of the interictal abnormalities (particularly polyspikes) and the appearance of low-voltage fast activity (*figures 2C, 3C*).

All but four patients underwent surface/invasive recordings and 72 patients showed the typical "brushes" of type II FCD during either VEEG or SEEG monitoring, and 35 during both.

Fifty-five of the 72 patients showing the distinctive electrical activity (76%) had type IIb FCD and only 17 (24%) type IIa FCD (p=0.001), indicating a significant association between the occurrence of "brushes" and the presence of BCs. On the contrary, there was no association (p=0.36) between the presence of this electrographic activity and Engel class I surgical outcome.

Surgery and outcome

The surgical resection was confined to the frontal lobe in 49 patients, with a significant prevalence of patients with FCD type IIb (38 patients, 58%; p=0.016). On the contrary, type IIa FCD appeared to correlate, albeit without statistical significance, with a multi-lobar localisation (13 patients, 38%; p=0.007) (*table 2*).

The surgical outcome was very favourable, with 83 patients in class I (77 in classes Ia and Ic). The patients with FCD type IIb were more likely to become seizure-free, although the difference between the two subgroups was not statistically significant (χ^2 test; p=0.07; *table 3*). There were no significant correlations between outcomes and age at epilepsy onset or the duration of epilepsy. The patients undergoing multi-lobar resection were more likely to be in Engel classes other than class I (χ^2 test; $p<0.01$) and the logistic regression model showed that their poor outcome was related to the multi-lobar localisation of the dysplasia (OR 0.10, 95% CI: 0.03-0.33; $p<0.01$) and not to the absence of BCs (p=0.27).

The Kaplan-Meier curve (*figure 4*) shows that the surgical results lasted over time. The difference between the two subgroups was not statistically significant (log rank test=0.77). Forty-six patients completely stopped antiepileptic treatment after surgery and for 30, therapy is being reduced.

Discussion

FCDs are currently acknowledged to be among the most important causes of epilepsy. Because of the severity and refractoriness to drug therapy, surgical treatment of epilepsies associated with FCD is a valid therapeutic option, and surgical specimens allow a precise neuropathological diagnosis and identification of histopathological variants.

The possible differentiation between type IIa and IIb FCD based on biomolecular features goes beyond the scope of this study, of which the aim was to investigate possible differences in the electroclinical presentation, MRI findings, and surgical outcomes of a large cohort of patients with histopathologically proven type IIa or IIb FCD who received surgery for intractable epilepsy, in order to verify the possibility of a differential clinical diagnosis between the two subgroups.

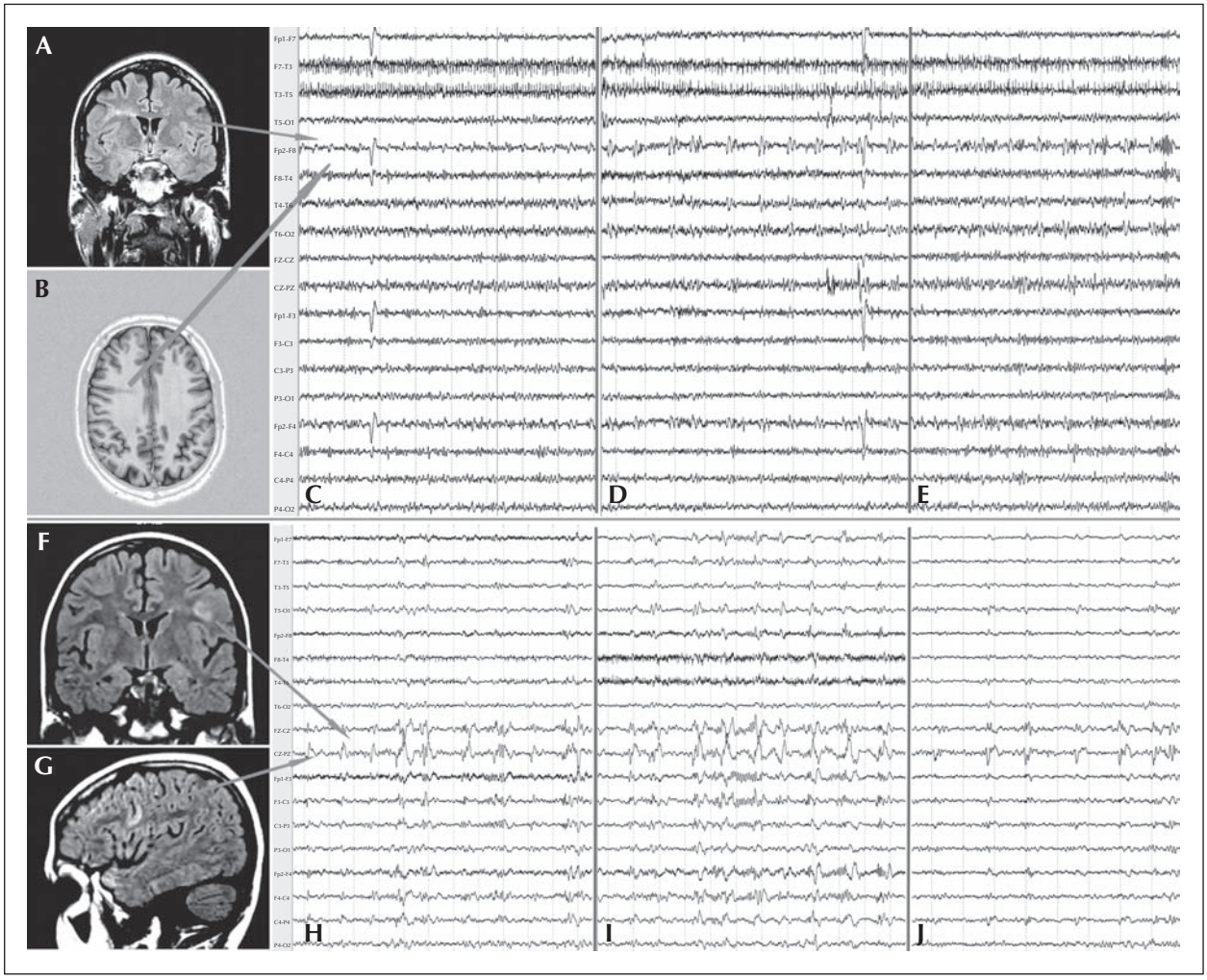

Figure 1. Scalp EEG activity in two different patients with type IIb FCD. In the first, an MRI coronal FLAIR image (A) showed the lesion located in the third frontal convolution on the right side and tapering towards the ventricle, which was confirmed by the axial IR slice (B). Interictal EEG during wakefulness (C) showed the presence of pseudo-periodic sharp waves located in the right frontotemporal region, increasing during hyperpnoea (D) and becoming faster during drowsiness (E).
In the second, coronal (F) and sagittal (G) FLAIR images showed that the lesion was in the left precentral third frontal convolution. Scalp EEG during wakefulness (H) revealed sharp waves and spikes and waves in the left frontoprecentral region spreading to the vertex and to the left temporal areas; the activity increased during hyperpnoea (I) and became periodic during drowsiness (J).

Electroclinical data

There are no significant differences between the two subgroups in terms of gender, age at epilepsy onset, the duration of epilepsy, age at surgery, and seizure frequency. One aspect emerging from our data is the high incidence of SRE in patients with type IIb FCD. Many studies have shown that frontal lobe seizures occur more frequently during sleep, but recent studies have shown that the presence of type II FCD, regardless of its frontal or extra-frontal localisation, increases the risk of SRE 14 fold (Nobili *et al*., 2009, 2007). Our data not only confirm these reports but also indicate that SRE is significantly related to type IIb FCD.

It has been suggested that interictal scalp EEG does not reveal any specific electrographic characteristic which allows to differentiate between patients with type I, type II FCD or other patients with refractory epilepsies undergoing presurgical evaluation (Krsek *et al*., 2008, 2009; Noachtar *et al*., 2008). However, in line with previous reports (Palmini *et al*., 1995; Gambardella *et al*., 1996), careful analysis of the EEG recordings of our patients revealed a peculiar electrographic pattern never observed in patients with other types of lesions. This distinctive pattern was observed in 72 patients, recorded during both VEEG and SEEG in half of the patients, and detected in 76% of the patients with type

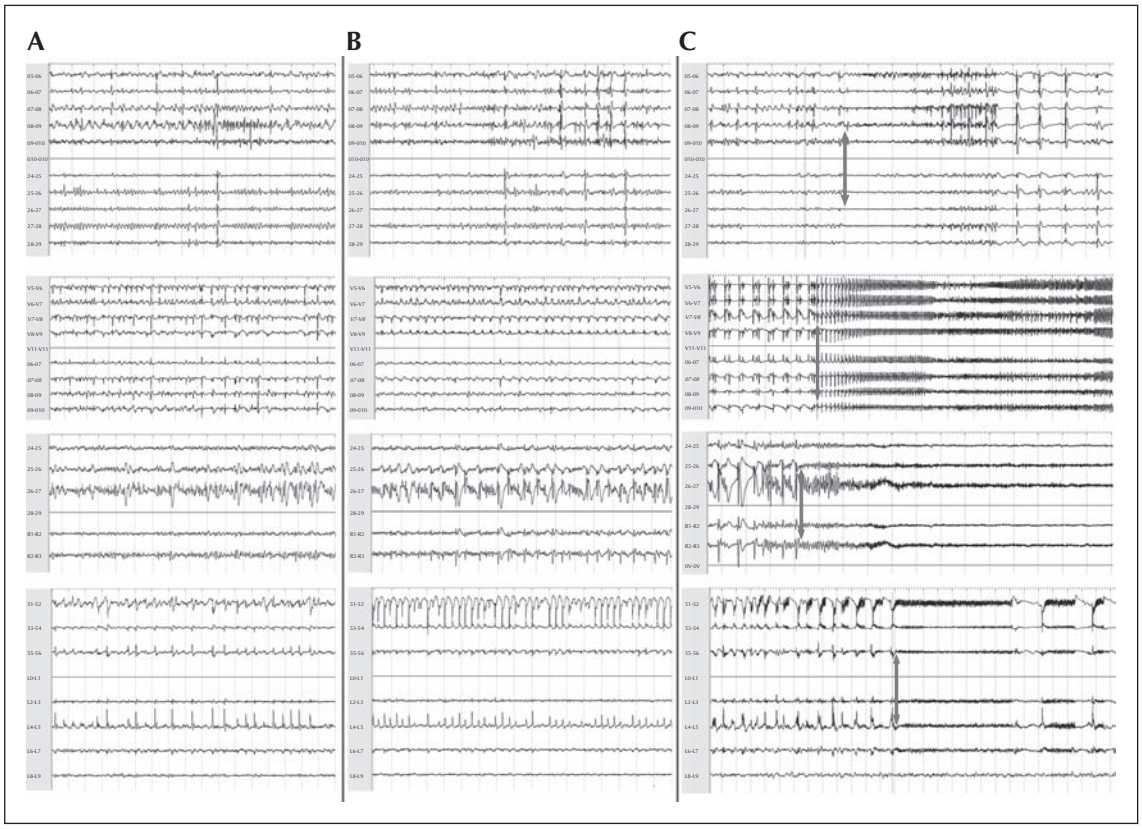

Figure 2. SEEG recordings in four patients; all but one had negative MRI findings.
Only two electrodes were included, positioned in different parts of the anatomical dysplastic lesion. Patient 1 had left frontal epilepsy, Patient 2 (with positive MRI in the occipital lobe) had right occipito-temporal epilepsy, Patient 3 had right pre-central epilepsy, and Patient 4 had right insulo-opercular epilepsy.
Two epochs of wakefulness are shown for each patient (A and B), and one spontaneous seizure (C, arrows).

IIb FCD, indicating a significant association with the presence of BCs. The reason for this association is still unknown.

Neuropathological studies have shown that BCs are not contacted by synaptic terminals (Garbelli *et al*., 1999; Alonso-Nanclares *et al*., 2005). *In vitro* electrophysiological studies demonstrated that while dysmorphic neurons, showing abnormal electrophysiological properties, may play a pivotal role in the generation of epileptic activity, BCs do not have any active voltage- or ligand-gated currents, and do not seem to receive synaptic inputs (Cepeda *et al*., 2007). However, recent data suggest the involvement of electrical synapses (gap junctions) in epilepsy and it has been reported that the expression of connexin (Cx) 43 protein is increased in patients with epilepsy associated with brain tumours, as well as in hippocampal sclerosis (Aronica *et al*., 2001; Fonseca *et al*., 2002). These studies related the increase in astrocytic Cx43 protein levels to the up-regulated junctional communication induced by intense electrochemical activity under epileptic conditions. We have recently found selective increased Cx43 expression in a subset of reactive astrocytes and BCs in specimens from patients with type IIb FCD (Garbelli *et al*., 2011), suggesting that these cells may play a role in the homeostatic mechanisms facilitating the spatial buffering of extracellular ions and neurotransmitters. Thus, although not directly involved in the genesis of paroxysmal discharges, the pattern of Cx43 distribution may be implicated in the development of the (hyper)synchronisation of neuronal discharges, providing a "short circuit" between electrically involved neurons acting as "bridges" between different areas of clustered neuronal hyperexcitability, thus enabling rapid propagation of electrical activity (Fonseca *et al*., 2002).

The selective occurrence of clustered gap junctions in a subset of BCs not only confirms data showing differences in the neuronal and glial antigens expressed by individual BCs in different patients with type IIb FCD (Englund *et al*., 2005), but may also explain the appearance of the peculiar electrical pattern observed in some (but not all) of our patients with type IIb FCD. Whatever the mechanism(s), our data suggest that type IIb FCD neurons are particularly sensitive to the

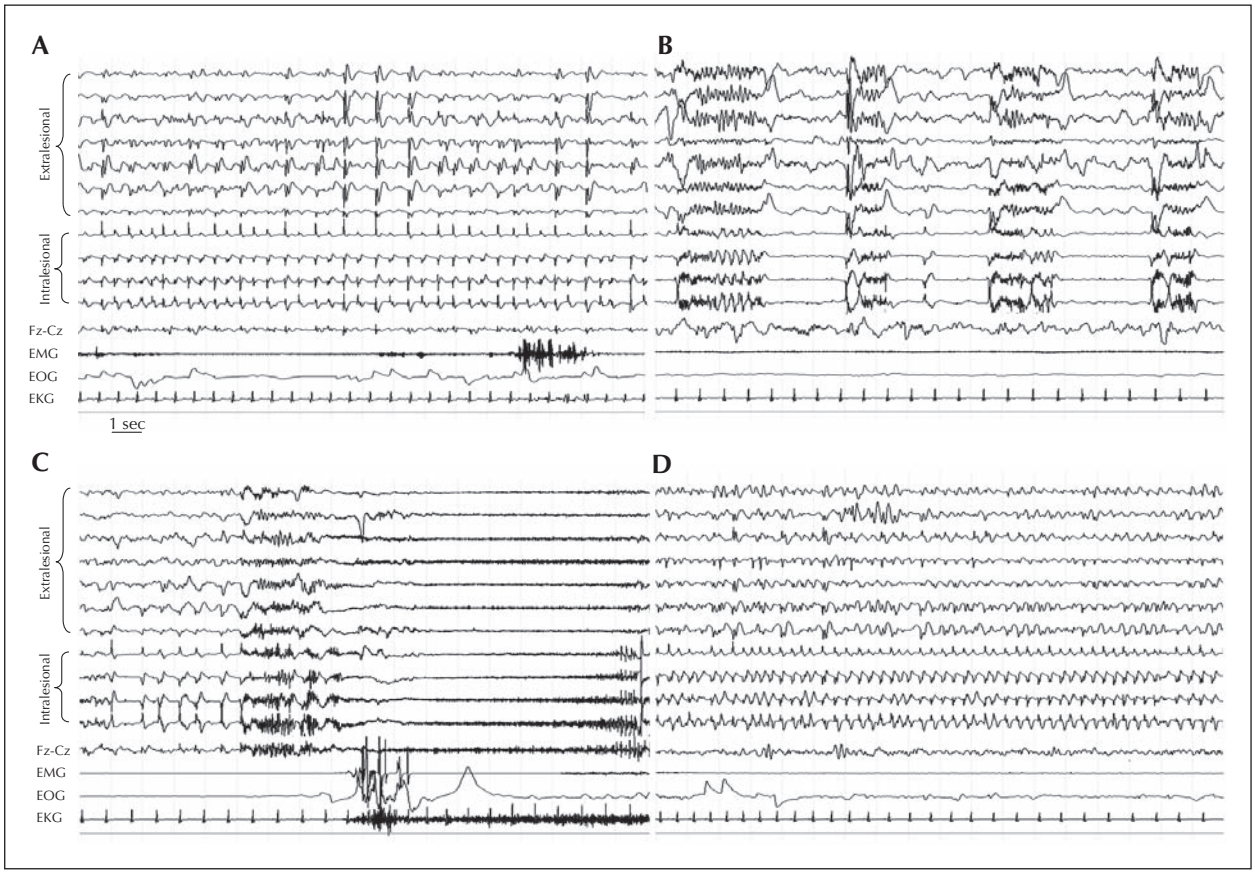

Figure 3. SEEG recordings during wakefulness and sleep. In the lower part, the intracerebral contacts are within the type IIb FCD (intralesional) and, in the upper part, outside (extralesional). (A) Pathognomonic activity during wakefulness, with repetitive "brushes" inside the anatomical lesion. (B) During non-REM sleep, FCD activity was pseudo-periodic (about four seconds) and the interictal activity spread to the non-lesional areas. (C) The onset of a seizure during stage II non-REM sleep. (D) REM sleep.
Fz-Cz: scalp activity on the anterior vertex; EMG: electromyography (chin); EOG: electro-oculogram; EKG: electrocardiogram.

synchronising effects of the oscillatory mechanisms operating during non-REM sleep. It is interesting to note that the electrophysiological behaviour of type II FCD appears to be similar to that of neurons in the thalamic reticular nucleus (Rt), the pacemakers of sleep spindles. In the transition from wakefulness to non-REM sleep, Rt neurons switch from a tonic to a bursting mode, characterised by the periodic occurrence of fast discharges in the spindle frequency. These bursts are strongly synchronised within the Rt nucleus by mutual GABAergic inhibition and mediated by gap junctions (Fuentealba *et al*., 2005). The distinctive intrinsic organisation of type IIb FCD, characterised by its particular GABAergic circuit (Garbelli *et al*., 1999; Alonso-Nanclares *et al*., 2005) and the rearranged gap junctions (Garbelli *et al*., 2011), supports

Table 2. Histological data *versus* anatomical localization.

Histology (%)	Temporal lobe	Frontal lobe	Occipital lobe	Parietal lobe	Central lobe	Multilobar
With BCs	8 12	38 58	0	4 6	2 3	14 23
Without BCs	9 27	11 32	1 3	0	0	13 38
Total	17	49	1	4	2	27

BC: balloon cells.

Table 3. Surgical outcomes related to balloon cells.

Engel class (%)	I				II	III	IV	Total
	Ia + Ic	Ib	Id	Total class I				
With BCs	54 82	3 5	1 2	58 88	0	2 3	6 9	66
Without BCs	23 68	2 6	0	25 74	3 9	0	6 18	34
Total	77	5	1	83	3	2	12	100

BC: balloon cells.

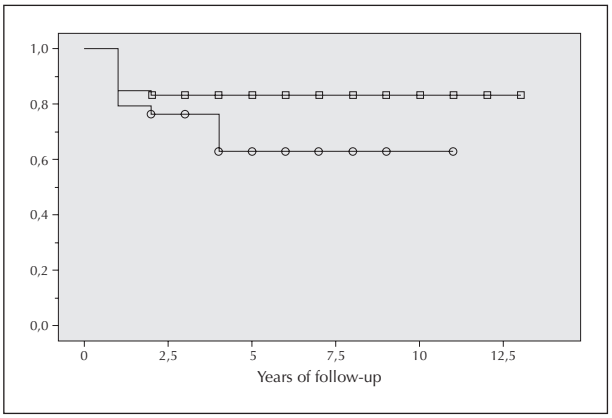

Figure 4. Kaplan-Meier curve after a mean follow-up of 81 months.
Squares: FCD II with BCs; circles: FCD II without BCs.

the hypothesis that the lesion may behave intrinsically like Rt circuitry, thus superimposing activity on the physiological rhythmic slow oscillations that occur during non-REM sleep. Our data appear to suggest that these oscillations, together with fluctuations in arousal (Terzaghi *et al.*, 2008), trigger the appearance and spread of periodic epileptic discharges in type IIb FCD neurons and promote the occurrence of sleep-related seizures. This hypothesis might also explain why the peculiar activity, observed in patients with type IIb FCD, is independent of lobar location (Nobili *et al.*, 2007).

MRI findings

A few published studies have attempted to identify the differential characteristics of the various subtypes of FCDs (Tassi *et al.*, 2002; Colombo *et al.*, 2003, 2009; Krsek *et al.*, 2009; Ruggieri *et al.*, 2004; Lawson *et al.*, 2005). The data suggest that MRI features of type II FCDs are, in general, different from those observed in type I. However, it is generally considered that type IIa and type IIb are indistinguishable by MRI. The detailed analysis of the differential MRI aspects of the two subgroups is the matter of a parallel study. Regarding the present paper, a correct diagnosis of type II FCD was made in 93% of patients with type IIb and in 68% with type IIa. More refined neuropathological information is needed to clarify whether it is the presence of BCs or some other structural alterations in the white matter that positively influences the diagnosis.

Surgical outcome

One of the problems of evaluating surgical outcomes in patients with epilepsy is that authors in the literature refer to different criteria for the classification of FCD or include patients in a single "cortical dysplasia" group. Furthermore, most of the published cohorts include patients with dual pathologies, thus introducing another bias.
The careful neuropathological examination of surgical specimens is essential in order to classify the variants of FCD and is important for making correlations with presurgical electroclinical data and postsurgical outcomes (Blümcke *et al.*, 2011). Our cohort only included patients with neuropathologically defined type II FCD alone and was divided into type IIa and IIb subgroups. Eighty-three percent of the patients are currently in Engel class I and, although the difference is not statistically significant, the outcomes of those with type IIb FCD (88%) are better than those with type IIa (74%). These results indicate that type II FCD has a very good prognosis regardless of the site of surgery (mainly extratemporal). The worst outcomes are generally associated with multi-lobar resections and in patients with incomplete resection due to the presence of the lesion in eloquent areas.
Unlike patients who received surgery for TLE, the long-term (mean follow-up of 81 months) Kaplan-Meier analysis of our patients with type II FCD shows that seizure recurrences are very rare, thus demonstrating that surgical outcomes are related to the completeness of the resection. These data are further corroborated

by the fact that the patients have remained seizure-free after stopping (46 patients) or reducing pharmacological therapy (30 patients). □

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Disclosures.
The authors have no conflicts of interest to declare. Ethics approval was provided by the local ethics committees. Presurgical and surgical procedures were performed after obtaining the informed consent of the patients or their parents

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