Epilepsia, 51(Suppl. 1):23–26, 2010
doi: 10.1111/j.1528-1167.2009.02437.x

Electrophysiology of the focal cortical dysplasias

Andre Palmini

Porto Alegre Epilepsy Surgery Program, Neurology Service, Hospital São Lucas, Pontificia Universidade Catolica do Rio Grande do Sul (PUCRS), Porto Alegre, Brazil

Partial epilepsies associated with focal cortical dysplasias (FCDs) can be singled out among the medically refractory epilepsies as an exceptionally severe type of neocortical epilepsy (Semah et al., 1998). The main reasons are that FCDs are intrinsically epileptogenic (Palmini et al., 1995; Dubeau et al., 1998) and the lesions display several clinical and electrophysiologic surrogates of hyperexcitability (Lerner et al., 2009). Adding to these, a somewhat novel concept proposes that dysplastic networks also display inhibitory properties that may be disrupted through a number of mechanisms, including partial resection and peripheral stimulation, resulting in severe, uncontrolled seizures. We review these peculiar aspects of the epileptogenicity of FCDs, with an emphasis on the role of electrophysiology as a generator of insights about the underlying mechanisms.

The Concept of Intrinsic Epileptogenicity of FCDs

The surgical treatment of neocortical partial epilepsies has received a considerable uplift with the advent of magnetic resonance imaging (MRI). Despite this, the major concept of an epileptogenic area surrounding cortical scars or tumors has remained until the mid-1990s. This was a time-honored idea formalized by Penfield and Jasper, who proposed that neurons surrounding neocortical lesions had disrupted morphology and function, and were prone to hypersynchronize and lead to seizures (Penfield, 1958). Inseparable from this conceptualization were electrocorticography (ECoG) recordings showing spikes in these perilesional regions (Penfield, 1958). The weight of this evidence was such that the concept that epileptogenicity in neocortical lesions depended on perilesional neuronal dysfunction has been a major tenet in epileptology (Palmini, 2006).

The identification of FCDs through MRI and the correlation between these lesions and acute ECoG or stereo-EEG (electroencephalography) recordings has led to modification of the concept of perilesional epileptogenicity. The finding that electrographic recordings *over* (Palmini et al., 1995) or *inside* (Chassoux et al., 2000) macroscopic and microscopic dysplastic lesions displayed highly epileptogenic potentials challenged the classical view: Epileptogenicity was not restricted to perilesional cortex but could indeed be generated within lesions—in this case, dysplastic lesions. Support for this concept of intrinsic epileptogenicity comes from the fact that epileptic discharges recorded from FCDs are extremely active, presenting virtually unique electrophysiologic manifestations (see subsequent text). Once this concept was established, interest in other aspects of the epileptogenicity of FCDs was increased, particularly concerning the hyperexcitability of these lesions.

Evidences for Hyperexcitability of Dysplastic Lesions

Refractoriness of seizures

FCDs represent the most prevalent etiology for medically refractory neocortical partial epilepsies (Lerner et al., 2009). With the increased identification of dysplastic lesions on MRI came the realization that patients with FCDs are usually refractory to antiepileptic drugs (Semah et al., 1998; Lerner et al., 2009). Such understanding, in turn, has led to a high degree of suspicion that an FCD *is* the etiology of medically refractory neocortical epilepsies when MRI is normal. The latter concept has been advanced in recent years, on account of (1) the fact that most other etiologies of neocortical epilepsies are identified on MRI, (2) FCDs can be microscopic (*or MRI-negative*), that is, may not be identified even through high-resolution MRI (Najm et al., 2007; Krsek et al., 2008), and (3) intracranial electrophysiologic recordings in patients with MRI-negative neocortical epilepsies often disclose focal regions of continuous spiking which prove, on histopathologic examination, to harbor a dysplastic lesion (Palmini et al., 1995; Chassoux et al., 2000).

Generalized and partial status epilepticus/epilepsia partialis continua

Status epilepticus is a medical emergency, usually related to acute infectious, traumatic, or vascular brain

Address correspondence to Andre Palmini, Serviço de Neurologia, Hospital São Lucas da PUCRS, Avenida Ipiranga 6690, 90610-000, Porto Alegre, RS, Brazil. E-mail: apalmini@uol.com.br

insults or when the serum levels of antiepileptic drugs fall acutely (Duncan et al., 1995). This medical emergency is rare in the context of fixed cortical lesions. Interestingly, a number of patients with FCDs present episodes of generalized status epilepticus (Palmini et al., 1991) and an even higher proportion present with prolonged bouts of partial motor seizures, particularly focal myoclonus, characterizing epilepsia partialis continua (EPC) (Fusco et al., 1992). This tendency to present continuous myoclonus, usually refractory to antiepileptic drugs, is regarded as another evidence of the increased excitability of the dysplastic cortex. Among the FCDs, those harboring dysplastic neurons and/or balloon cells (type II FCD; Palmini et al., 2004) appear to be the ones with a higher incidence of EPC. These type II FCDs tend to cluster around perirolandic regions and display markedly abnormal distribution of excitatory amino acid receptors (see subsequent text) (Spreafico et al., 1998; Najm et al., 2007).

Dysplasia-associated reflex seizures

Reflex seizures are understood as hyperexcitable responses of sensorimotor cortical tissue to specific types of afferent volleys. Several epileptic syndromes present with reflex seizures, mostly related to genetic or destructive etiologies. FCD is a nongenetic, nondestructive etiology particularly related to the occurrence of reflex seizures (Palmini et al., 2005). Most likely, this reflects the increased excitability of these lesions.

Highly epileptogenic electrographic patterns

The same electrophysiologic findings that prompted the concept of intrinsic epileptogenicity of FCDs provide clear evidence for the extreme hyperexcitability of these lesions. Scalp EEG, acute and chronic ECoG, as well as depth electrode recordings all show highly epileptogenic patterns, which present as (1) continuous, rhythmic or semirhythmic spikes (Fig. 1A,B), (2) paroxysmal bursts of high frequency spikes, or even (3) recurrent electrographic seizures (Palmini et al., 1995; Gambardella et al., 1996; Chassoux et al., 2000). In particular, the continuous rhythmic spiking suggests that an intradysplastic pacemaker operates in a self-sustained, hyperexcitable, unstoppable fashion. Beyond suggesting a high degree of epileptogenicity, these three electrographic patterns are invaluable to delimit the epileptogenic zone and plan surgical resection. When restricting the analysis to type II FCDs, more than 80% of patients present one or more of these electrographic patterns, which can be conceived as the electrophysiologic surrogate of the underlying pathology (Palmini et al., 1995; Chassoux et al., 2000).

Basic science data

MRI advances and a higher degree of clinical suspicion have increased the incidence of discovered FCDs in epilepsy investigations. This has kindled the interest of basic researchers in unveiling the mechanisms of epileptogenicity in these lesions. Animal models of malformations of cortical development (MCD) and human dysplastic tissue resected at surgery have been used in basic science studies. Abnormal distribution and molecular composition of excitatory amino acid receptors probably lead to an increase in excitatory *N*-methyl-D-aspartate (NMDA)–mediated activity and bursts of evoked spikes in animal models of MCD (Calcagnotto & Baraban, 2005) and in FCD tissue (Spreafico et al., 1998; Najm et al., 2007). Furthermore, immunohistochemical studies of specific subregions of resected tissue show differential distribution of excitatory receptors in different parts of the lesion (Najm et al., 2007). The relevance of these findings for the understanding of the epileptogenicity of FCD and surgical planning is only beginning to be explored.

Puzzling Findings Suggesting Prominent Inhibition in Dysplastic Networks

The findings described earlier have led to the concept that FCDs are intrinsically and highly epileptogenic lesions. It is difficult to think otherwise given the high seizure frequency, frequent occurrence of EPC, high degree of refractoriness to antiepileptic drugs, and high incidence of continuous epileptogenic discharges from the cortical surface. However, a number of observations in the last years, coupled with basic science data, suggest that FCDs may harbor strong inhibitory components, which may be disrupted in specific circumstances, including peripheral stimulation and surgery.

Spatiotemporal restriction of intensely epileptogenic phenomena

Undoubtedly, the occurrence of highly epileptogenic phenomena including the frequent presentation of EPC and of continuous spiking and other epileptiform ECoG patterns (Fig. 1B) point to hyperexcitability in FCDs. Interestingly, however, intense as they are, these abnormalities are restricted to focal seizures and localized, nonprogressive interictal phenomena. One could argue that EPC in the form of epileptic myoclonus occurring intermittently or continuously without progressing toward more intense partial motor seizures may indicate that inhibitory mechanisms within the rolandic cortex prevent progression of these seizures. In other words, there may be inhibitory mechanisms preventing the spread of epileptic activity to other neuronal pools within the rolandic region—which could lead to more intense motor seizures—and also the propagation of this activity outside the central strip, leading to variable degrees of generalization of the epileptic seizures. Furthermore, the protracted trains of rhythmic, virtually continuous spikes recorded

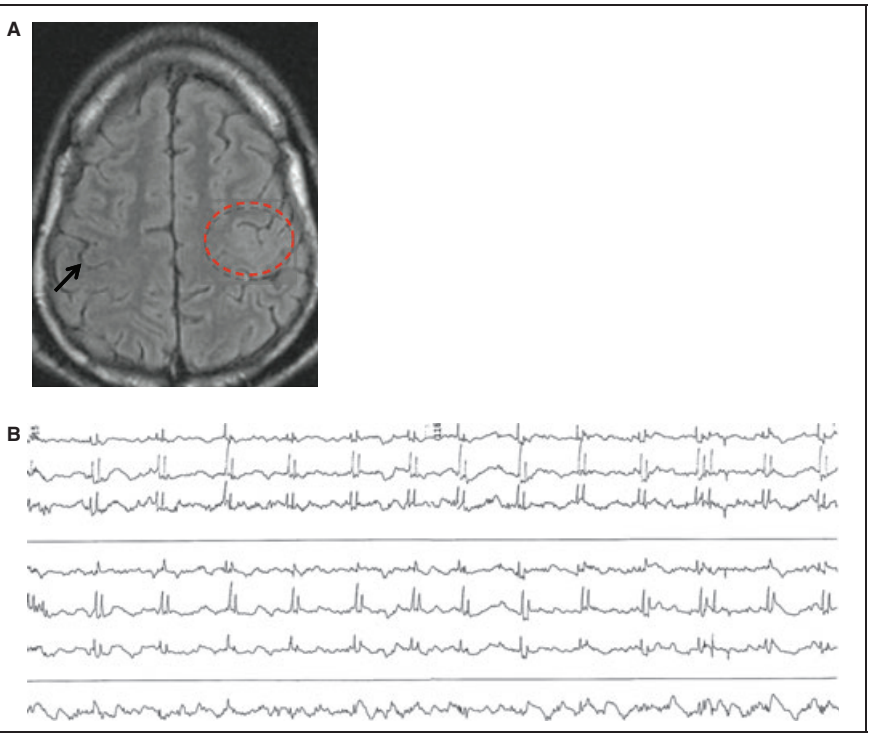

Figure 1.
(**A**) Axial fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI) of a 17-year-old boy with refractory partial motor seizures. Note that the "hand knob" in the dysplastic region (circled) is markedly different from the normal side (arrow). (**B**) Run of continuous semirhythmic electrocorticography (ECoG) spikes. This abnormality was unabated until resection of the tissue. Histopathology showed focal cortical dysplasia (FCD) type IIA.

from the dysplastic lesion, failing to progress to the full blown recruiting–derecruiting pattern of partial seizures could also be regarded as indicative of enhanced inhibition. In all likelihood, these intrinsic mechanisms interact with those operating to stop seizures in general (Lado & Moshé, 2008) to control the spread of epileptogenicity generated in the dysplastic cortex.

"De novo" epilepsia partialis continua following resection

We recently described three patients with medically refractory EPC who after months seizing were taken to surgery as a desperate measure (Palmini et al., submitted). Although continuous motor seizures were strictly unilateral for several months before operation, EPC reemerged in the *contralateral hemibody* 48 h after complete resection of the central cortex in one patient and 1 year later in the other two. Two of these patients, previously normal young females, were reported in an abstract in which we stated the total unexpectedness of such outcome, which led to the death of one patient and a severe encephalopathy in the other (Silva et al., 1995). All three patients had FCD type II on histopathology, despite the fact that 1.5T MRI was negative in two.

The fact that seizures emerged de novo from cortical tissue that had never produced seizures suggests that resection of dysplastic tissue in one rolandic area "disinhibited" a potential, secondary epileptogenic zone, in the homologous region of the contralateral hemisphere. Should this reasoning prove correct, it follows that inhibitory mechanisms were probably operative within a network involving both rolandic regions. Such a network was disrupted by resecting the primary abnormality that interfered with an inhibitory equilibrium and led to seizures from the other side. This was a most malignant outcome, because the original surgery involved complete resection of the motor cortex on one side (Palmini et al., Palmini A, Andermann F, Paglioli E, Dubeau F, Costa da Costa J, Olivier A, unpublished data).

"De novo" EPC following peripheral trauma

Another recent observation involved a 50-year-old man operated 10 years earlier for temporal lobe epilepsy associated with right hippocampal sclerosis and mild atrophy of the right hemisphere. He had a favorable outcome, with rare seizures, but reporting the persistence of the aura he had before operation, a feeling of paresthesias in the left hand. This aura was considered atypical for his temporal lobe epilepsy. Ten years after surgery, he sustained a small penetrating injury in the dorsum of the left hand and the following day developed continuous myoclonus in that hand. EPC could not be stopped by any combination of antiepileptic drugs or by local anesthetic block. General anesthesia, however, stopped the myoclonus and the patient was taken to epilepsy surgery under local anesthesia. ECoG displayed repetitive, continuous, semirhythmic spikes in the right sensorimotor cortex, in a pattern consistent with FCD (similar to that of Fig. 1B). Resection of the sensory strip and the posterior bank of the motor cortex in the depth of the central sulcus led to complete cessation of

the myoclonus and disappearance of the ECoG spikes. Histopathology showed a FCD type IB with cortical dyslamination and immature neurons. The patient had a paresis of the hand in the immediate postoperative period that resolved completely in the ensuing weeks.

The emergence of continuous epileptic myoclonus originating from the cortical sensory regions receiving afferent volleys from the injured left hand suggests disruption of an inhibitory equilibrium in a cortical dysplastic network. The abrupt onset of continuous seizures following the injury set this patient apart from others in whom epilepsy with occasional seizures began after different types of peripheral injury (Spiller et al., 2005). Although the mechanisms involved in the disinhibition of dysplastic networks by intense afferent stimuli are unknown, they are probably related to those operant in patients of malformations of cortical development who present reflex seizures (Palmini et al., 2005).

Basic science data

Despite the predominant focus of basic research on excitatory mechanisms in FCD, a number of studies have lent support to the notion that inhibition may (also) be increased in these lesions or at least in neuronal networks involving dysplastic tissue (Calcagnotto et al., 2005; Najm et al., 2007). For instance, a significant increase in the decay-time constant for evoked and spontaneous inhibitory postsynaptic current was found in human dysplastic tissue, likely reflecting a decrease in transporter-mediated γ-aminobutyric acid (GABA) reuptake function (Calcagnotto et al., 2005). Admittedly, these and other changes in inhibitory transmission are part of a more general picture of abnormal GABAergic function in dysplastic tissue. Nevertheless, the association of these findings related to inhibitory transmission with the excitatory amino acid receptor changes discussed earlier suggests that a mosaic of electrophysiologic abnormalities contributes to the apparently contradictory clinical findings suggestive of both enhanced excitation and enhanced inhibition in FCD.

Disclosure

The author has no conflicts of interest.

References

Calcagnotto ME, Baraban SC. (2005) Prolonged NMDA-mediated responses, altered ifenprodil sensitivity, and epileptiform-like events in the malformed hippocampus of methylazoxymethanol exposed rats. *J Neurophysiol* 94:153–162.

Calcagnotto ME, Paredes MF, Tihan T, Barbaro N, Baraban SC. (2005) Dysfunction of synaptic inhibition in epilepsy associated with focal cortical dysplasia. *J Neurosci* 42:9649–9657.

Chassoux F, Devaux B, Landre E, Turak B, Nataf F, Varlet P, Chodkiewicz JP, Daumas-Duport C. (2000) Stereoelectroencephalography in focal cortical dysplasia: a 3D approach to delineating the dysplastic cortex. *Brain* 123:1733–1751.

Dubeau F, Palmini A, Fish D, Avoli M, Gambardella A, Spreafico R, Andermann F. (1998) The significance of electrocorticographic findings in focal cortical dysplasia: a review of their clinical, electrophysiological and neurochemical characteristics. *Electroencephalogr Clin Neurophysiol* 48(suppl):77–96.

Duncan JS, Shorvon SD, Fish DR. (1995) *Clinical epilepsy*. Churchill Livingstone, London.

Fusco L, Bertini E, Vigevano F. (1992) Epilepsia partialis continua and neuronal migration anomalies. *Brain Dev* 14:323–328.

Gambardella A, Palmini A, Dubeau F, Andermann F, Da Costa JC. (1996) Usefulness of focal rhythmic discharges on scalp EEG of patients with focal cortical dysplasia and intractable epilepsy. *Electroencephalogr Clin Neurophysiol* 98:243–249.

Krsek P, Maton B, Korman B, Pacheco-Jacome E, Jayakar P, Dunoyer C, Rey G, Morrison G, Ragheb J, Vinters HV, Resnick T, Duchowny M. (2008) Different features of histopathological subtypes of pediatric focal cortical dysplasia. *Ann Neurol* 63:758–769.

Lado FA, Moshé SL. (2008) How do seizures stop? *Epilepsia* 49:1651–1664.

Lerner JT, Salamon N, Hauptman JS, Velasco TR, Hemb M, Wu JY, Sankar R, Donald Shields W, Engel J Jr, Fried I, Cepeda C, Andre VM, Levine MS, Miyata H, Yong WH, Vinters HV, Mathern GW. (2009) Asessment and surgical outcomes for mild type I and severe type II cortical dysplasias. A critical review and the UCLA experience. *Epilepsia* 50:1310–1335.

Najm IM, Tilelli CQ, Oghlakian R. (2007) Pathophysiological mechanisms of focal cortical dysplasia: a critical review of human tissue studies and animal models. *Epilepsia* 48:21–32.

Palmini A, Andemann F, Olivier A, Tampieri D, Robitaille Y, Andermann E, Wright G. (1991) Focal neuronal migration disorders and intractable partial epilepsy: a study of 30 patients. *Ann Neurol* 30:741–749.

Palmini A, Gambardella A, Andermann F, Dubeau F, da Costa JC, Olivier A, Tampieri D, Gloor P, Quesney F, Andermann E. (1995) Intrinsic epileptogenicity of human dysplastic cortex as sugested by corticography and surgical results. *Ann Neurol* 37:476–86.

Palmini A, Najm I, Avanzini G, Babb T, Guerrini R, Foldvary-Schaefer N, Jackson G, Lüders HO, Prayson R, Spreafico R, Vinters HV. (2004) Terminology and classification of the cortical dysplasias. *Neurology* 62(suppl 3):S2–S8.

Palmini A, Halasz P, Scheffer IE, Takahashi Y, Jimenez AP, Dubeau F, Andermann F, Paglioli-Neto E, da Costa JC, Rosenow F, Fritsch B. (2005) Reflex seizures in patients with malformations of cortical development and refractory epilepsy. *Epilepsia* 46:1224–1234.

Palmini A. (2006) The concept of the epileptogenic zone: a modern look at Penfield and Jasper's views on the role of interictal spikes. *Epileptic Disord* 8(suppl 2):S10–S15.

Penfield W. (1958) Pitfalls and successes in the surgical treatment of focal epilepsies. *BMJ* 45:669–672.

Semah F, Picot MC, Adam C, Broglin D, Arzimanoglou A, Bazin B, Cavalcanti D, Baulac M. (1998) Is the underlying cause of epilepsy a major prognostic factor for recurrence? *Neurology* 51:1856–1862.

Silva LF, Palmini A, Da Costa JC, Andermann F, Paglioli-Neto E. (1995) MRI-invisible rolandic cortical dysplasia presenting with intractable epilepsia partialis continua: the ominous question of unsuspected bilateral symmetrical lesions. *Epilepsia* 36(suppl 4):15.

Spiller AE, Guberman A, Bartolomei F, Zifkin B, Andermann F. (2005) Epileptogenesis due to peripheral injury as a cause of focal epilepsy. *Epilepsia* 46:1252–1255.

Spreafico R, Battaglia G, Arcelli P, Andermann F, Dubeau F, Palmini A, Olivier A, Villemure JG, Tampieri D, Avanzini G, Avoli M. (1998) Cortical dysplasia: an immunocytochemical study of three patients. *Neurology* 50:27–36.