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Surgical Treatment of Intractable Epilepsy Associated with Focal Cortical Dysplasia

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1. Introduction

Focal cortical dysplasias (FCDs), initially thought to be rare, are a common cause of drug-refractory epilepsy in both children and adults. Successful resection and subsequent characterization of FCDs was first described by Taylor et al. in 1971 from pathological specimens obtained in patients treated for intractable temporal lobe epilepsy (Tassi, et al.,2001; Becker, et al.,2002; Tassi, et al.,2002; Urbach, et al.,2002; Nobili, et al.,2009). The dysplasias include abnormalities of cellular proliferation, migration, and differentiation. From recent published reports, patients with cortical dysplasia constitute approximately 14% of all patients undergoing epilepsy neurosurgery. Cortical dysplasia is the most common etiology in younger surgical patients. Using the UCLA cohort as an example, cortical dysplasia was the histopathologic substrate identified in 75% of infants and children operated in the first 2 years of life. By comparison, cortical dysplasia was found in less than 10% in those having surgery who were older than age 21 years (Diaz, et al., 2008).
Surgical evaluation and treatment of FCDs requires an understanding of pathological, presurgical imaging, EEG findings and intraoperative mapping of epileptogenic zone and functional areas (Sisodiya,2011).

2. Histopathological characteristics of FCD

The establishment of a uniform terminology and classification of histopathological findings associated with FCDs has recently been proposed by a consensus panel of neuropathologists, neuroepileptologists, and neuroradiologists.
The Palmini classification has been adopted most widely to categorize these heterogeneous lesions. Palmini et al. determined that several distinct histopathological features of the cortex must be present for a lesion to be considered a true FCD. These include architectural abnormalities, either dyslamination or columnar disorganization with or without dysmorphic neurons, giant cells, or balloon cells. Palmini et al. described 2 major types and 4 subtypes of FCD: Type 1 dysplasia refers to the most subtle alterations in cortical lamination and ectopic neurons in the white matter or immediately adjacent to layer 1. 1a with isolated architectural abnormalities alone; Type 1b, including giant neurons; Whereas type 2 dysplasia refers to areas of more extensive dyslamination outside of layer 1 with the

absence (type 2a) or presence (type 2b) of cytomegalic or balloon cells (Crino,2009; Gumbinger, et al.,2009; Nobili, et al.,2009; Wong,2009; Kim, et al.,2010; Krsek, et al.,2010). (Table 1)

Type	Subtype	Pathology features
FCD type 1	1a	Architectural cortical abnormalities ±feature of mild MCD
	1b	Architectural abnormalities and giant or immature neurons
FCD type 1	2a	Architectural abnormalities with dysmorphic neurons but no balloon cells
	2b	Architectural abnormalities with dysmorphic neurons and balloon cells

Table 1. Pathological features of FCD subtypes as outlined in the system by Palmini et al.(2004)

Macroscopic abnormalities may be present in surgical resections from FCD cases. There may be apparent thickening of the cortical gray matter, blurring of the gray-white border and the tissue may appear firmer (Figure 1). The overall lesion size varies and can be up to several centimetres broad, involving both sulci and gyri. On histological examination, abnormalities of cortical laminar architecture (also called 'dyslamination') are common to all types of FCD with loss of distinction between cortical layers, more easily visualized with Nissl stain or NeuN immunohistochemistry(Crino,2009; Gumbinger, et al.,2009; Nobili, et al.,2009; Wong,2009; Krsek, et al.,2010; Wong,2010).

Patients with mild Palmini type 1 CD represent about 50% of the surgical cases, and these lesions tend to occur most often in the temporal lobe, often associated with hippocampal sclerosis. By comparison, patients with severe type 2 CD present at younger ages, often with multilobar extratemporal lesions, and more aggressive seizures(Morales, et al.,2009; Blumcke, et al.,2011; Palmini,2011).

Although strictly a pathological classification, an expected correlation with neuroimaging results was summarized within the classification system. Mild MCDs and Type 1a and 1b FCDs were not considered likely to have correlating characteristics on MR images, unlike Type II which would probably exhibit changes including increased cortical thickness, blurring of grey–white junction, and extension of cortical tissue toward the ventricle.

The etiology of these lesions is poorly understood, and has been postulated to be due to possible in utero focal insults to cortex or to genetic mutations responsible for disordered cell proliferation or differentiation. Tuberous sclerosis complex (TSC) represents a more specific form of type 2b FCD, with the presence of areas of dysplasia containing giant cytomegalic cells as well as dysplastic neurons and astrocytes, termed "tubers." TSC1 and TSC2 are the genes that are found to be mutated in TSC, and encode for hamartin and tuberin, respectively(Lugnier, et al.,2009; Wong,2010). Hamartin and tuberin cooperatively inhibit excessive protein translation by acting to down-regulate the mammalian target of rapamycin (mTOR). The mTOR pathway has been shown to be upregulated in TSC, and some of its components are also overactive in non-TSC FCDs, suggesting that this pathway may be common to a wide range of cortical dysplasias(Crino,2009; Gumbinger, et al.,2009; Nobili, et al.,2009; Wong,2009; Krsek, et al.,2010; Wong,2010; Blumcke, et al.,2011; Palmini,2011).

The epileptogenicity of FCDs is hypothesized to be caused by abnormal synaptogenesis and dysregulated gaminobutyric acid-mediated inhibitory signalling. Enhanced neuronal

hyperexcitability may also play a role in the abnormal synchronization of neuronal populations, leading to prolonged trains of epileptic activity (Sisodiya, et al.,2009).

3. Preoperative evaluation

The presurgical evaluation for pharmacoresistant patients with cortical dysplasia is often challenging. There is no particular seizure semiology that characterizes patients with cortical dysplasia from other epilepsy surgery patients with lesions in different locations within the brain. Furthermore, there are no distinctive interictal or ictal scalp EEG "signatures" that are exclusively associated with cortical dysplasia in patients with refractory epilepsy. No one single test of the presurgical evaluation in CD patients is 100% accurate. Based on retrospective cohort studies, the accuracy of investigations are: interictal scalp EEG, 50%; ictal scalp EEG, 65%; MR), 66%; FDG-PET, 81%; and ictal SPECT, 57%. Combined evaluation of detailed history and physical examination, EEG, MRI and other functional Neuroimaging plays a vital role in presurgical planning in patients with intractable epilepsy (Duchowny,2009; Gumbinger, et al.,2009; Roper,2009; Sisodiya, et al.,2009).

3.1 Clinical findings

The preoperative evaluation in a patient with medically refractory seizure starts with a detailed history and physical examination. Seizure type may provide information about the location of the epileptogenic zone, and can contribute to the prognosis of seizure control after resection. Neurological deficits identified on physical examination may point to the area of cortex most affected and provide clues as to the focal, multifocal, or diffuse nature of the underlying pathological entity (Goldring,1987; Crino,2009; Nobili, et al.,2009; Sisodiya, et al.,2009; Tassi, et al.,2009; Kim, et al.,2010).

3.2 EEG

Patients with medically intractable seizures should undergo preoperative evaluation with video-assisted scalp EEG to correlate ictal EEG graphic events with the seizure semiology. The ictal onset zone is defined as the region showing focal rhythmic activity, bursts of high-frequency discharges, repetitive spiking, or electrodecremental patterns(Jiang, et al.,2010). The disadvantage of scalp EEG is that in patients with FCDs there is a high incidence of widespread interictal spiking, which may obscure identification of the epileptogenic zone. Interictal and ictal EEG findings often poorly localize to the MRI-identified lesion in patients with cortical dysplasia. Interictal findings localize on scalp EEG to the eventual area of resection in 48%, and ictal findings localize to one area in 68% of epilepsy surgery patients with cortical dysplasia (Francione, et al.,2003; Aubert, et al.,2009; LeVan, et al.,2010).

3.3 MRI

Identifying a focal lesion on MRI in patients with medically refractory epilepsy remains one of the most important factors in determining surgical outcomes. Therefore, there has been ongoing interest in utilizing new technologies to improve the rate of detection and thereby improve surgical outcomes. Although a number of lesions can result in epilepsy, FCDs remain the most difficult to detect. With new high-field and multichannel technology, the maximum gains in signal to noise are at the cortical surface, making patients with focal-onset refractory epilepsy the most likely to benefit from these technical advances (Bernasconi, et al.,2011; Kim, et al.,2011).

Patients with medically intractable epilepsy should undergo MR imaging in 3 planes for best characterization of the potential underlying FCD. If a temporal lobe lesion is suspected, preoperative MR imaging should include T1-weighted sagittal studies, coronal MPRAGE, coronal FLAIR, and fast T2-weighted coronal sequences. Preoperative MR images obtained in patients with a suspected extratemporal lesion consists of axial fast FLAIR, fastT2-weighted axial, T1-weighted sagittal, and coronal MPRAGE MR imaging sequences.

Imaging findings of CDs include thickening of the cortex, blurring of the gray–white matter junction, abnormal cortical signal and increased T2/FLAIR (fluid-attenuated inversion recovery) and/or T1 hypointense signal extending from the ependymal surface to the cortical surface. Additional imaging features that have been described include focal hypoplasia, a deep sulcus with malformations at the depths of the sulci, broadening of the gyri, and white matter atrophy. Many of these features can be seen on both T1- and T2-weighted images, although the CD for a given patient maybe more apparent on any one of these imaging sequences. FLAIR, especially volumetric FLAIR at 3T, is very sensitive for identifying white matter involvement (Figure 1). There has been ongoing interest in utilizing new advanced MRI techniques to improve the ability to identify, diagnose, characterize, and delineate cortical dysplasias. Technologic gains such as multichannel coils(32 phased array and beyond) and higher field strengths (3T, 7T, and greater) coupled with newer imaging sequences such as arterial spin labeling (ASL), susceptibility weighted imaging(SWI) and diffusion tensor/spectrum imaging(DTI/DSI) are likely to increase yield(Diehl, et al.,2010).

To improve diagnostic accuracy, automated techniques are being developed that identify areas for closer scrutiny by an experienced neuroradiologist. One method for automated lesion detection is voxel-based morphometry. This technique employs the statistical parametric mapping techniques developed for functional MRI to allow voxel-based comparisons between patients and a cohort of control subjects with the goal of identifying areas of the brain that may be different in volume, signal intensity, texture, or sharpness of boundaries. However, in voxel-based morphometry it is difficult to interpret positive results, as differences in image intensity can occur due to differences in gyral folding, differences in relative cortical gray-to-white matter volume, incorrect segmentation, or other factors. Similarly, false-negative findings can be caused by the blurring of gray-white matter boundaries, which results when control groups are averaged (Chiang, et al.,2009; Rajan, et al.,2009).

3.4 MEG

In patients with seizures, MEG is usually most useful in patients with interictal activity, as ictal events are often associated with motion artifact. MEG and EEG appear to have similar sensitivity to record interictal events, with MEG and EEG often providing complementary data. In up to one-third of EEG-negative patients, MEG can be expected to detect interictal epileptiform activity and is particularly effective in neocortical epilepsy and FCDs (Andrade,2009; Beleza,2009; Fauser, et al.,2009) .

3.5 Other functional imaging

With patients presenting with nonlocalized scalp EEG and subtle or normal MRI scans, many centers incorporated additional functional and neuroimaging studies into the multimodality presurgical evaluation to increase the detection of patients with cortical dysplasia. Of these tools, FDG-PET has been shown to be one of the more sensitive

techniques in identifying areas of cortical dysplasia. Contemporary studies indicate that FDG-PET detects interictal hypometabolism that localized to areas of cortical dysplasia in approximately 81% of patients. By comparison, 57% of cortical dysplasia patients have localized ictal SPECT scans. For both FDG-PET and ictal SPECT, some patients with normal MRI show positive scans. Hence, adjunctive neuroimaging methods, such as FDG-PET, ictal SPECT, and MEG, have an important role in the presurgical evaluation of patients with cortical dysplasia (Fedi, et al.,2003; Chassoux, et al.,2010; Phi, et al.,2010).
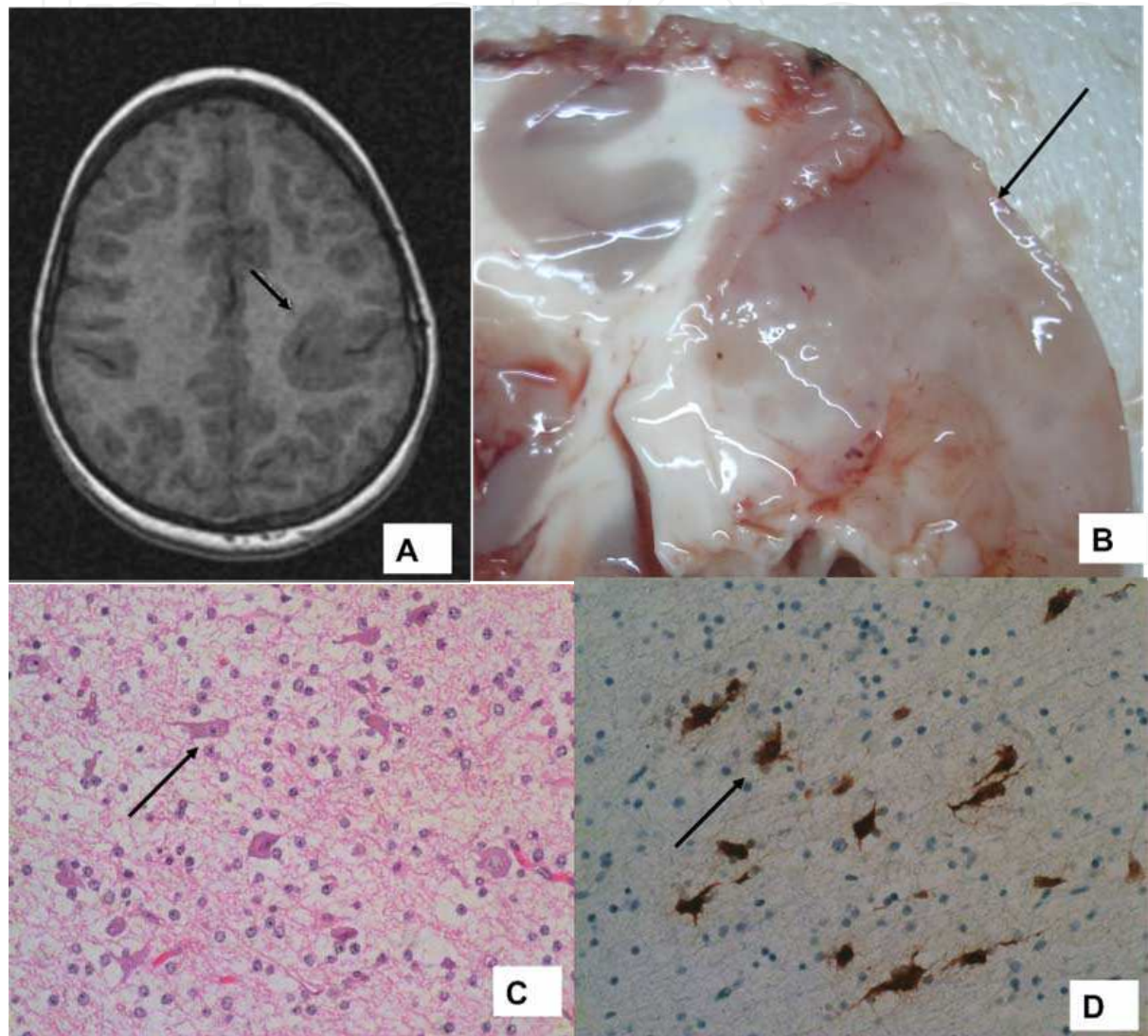
Fig. 1. The T1 weighted MRI(A), macroscopic findings(B) and microscopic findings with H & E stain (C) and in-situ immunohistochemistry with NeuN

4. Surgical considerations

The goal of clinical, EEG, and neuroimaging preoperative assessment is to identify the cortical area producing seizures and generating discharges and its anatomical and functional relationships. Concordance amongst the different modalities used to identify the lesion producing seizures is critical for surgical planning. Preoperative understanding of the epileptogenic zone, surrounding, or encompassing functional cortex, and the characteristic

vascularization of the area in individual patients provides a map for planning the surgical approach, the limits of excision, and determining the potential risk to function(Diaz, et al.,2008).

The purpose of surgical intervention in the management intractable epilepsy with underlying histological evidence of cortical dysplasia is to improve seizure control and maximize the potential for normal neuropsychological development. The surgical approach to FCD is dependent on the presence of a lesion visible on MR imaging, its location to eloquent cortex, and the concordance of presurgical EEG and functional neuroimaging with identifiable lesions. If a well-defined lesion is visible on MR imaging that correlates with EEG localization of the epileptogenic focus, resection may be performed in a single-stage procedure with intraoperative electrocorticography as a guide. If no lesion is visible on MR images or if it is localized within eloquent cortex based on the results of noninvasive preoperative studies, a 2-stage procedure with invasive EEG monitoring should be considered for the purpose of locaizing the primary and secondary ictal epileptogenic zones, irritative zones, and cortical mapping of eloquent cortex to guide the focal cortical resection. Once the epileptogenic zone is identified, different surgical strategies can be used: lesionectomy, focal cortical resections, or regional or hemispheric surgical disconnection. En-bloc resection between cortical vessels, sparing as many vessels as possible to avoid local arterial or venous infarction is essential. An important reason for incomplete resection is the intentional avoidance of the eloquent cortex. Intraoperative corticography or invasive EEG monitoring prior to extension of resection may be considered if the lesion is not well defined on preoperative neuroimaging or noninvasive EEG studies. The extent of further surgery after a first procedure is often limited by the proximity of the remnant epileptogenic zone to the functional cortex. Subsequently, there is a greater risk of neurological impairments such as paresis or visual field deficits after repeated surgery, depending on the location of the surgical target. Mapping studies of epilepsy surgical patients reveals a close association between dysplastic tissue, the epileptogenic zone, and eloquent cortical function. Seizure onset commonly occurs within or near cortical areas for language, motor function, or vision. Structural and functional overlap is frequent in FCD(Goldring,1987; Diaz, et al.,2008; Crino,2009; Duchowny,2009; Roper,2009; Kim, et al.,2010).

Invasive video-EEG monitoring with subdural grids or depth electrodes may be indicated to aid in localization of the epileptogenic zone particularly in patients with cryptogenic lesions on MR imaging, lesions located in or near eloquent cortex, or evidence of bilateral or multifocal seizure onset as determined by scalp video-EEG. Subdural electrodes allow extraoperative mapping of the eloquent cortex including critical somatosensory, motor, and language areas. These techniques can be used on any patient, but may be more important in children in whom intraoperative cortical mapping is impossible. This technique provides important information about the function and spatial relationship of the epileptogenic zone to functional cortex (Goldring,1987; Crino,2009; Duchowny,2009; Roper,2009; Kim, et al.,2010).

5. Seizure outcome after surgery

Contemporary series report that 62% of patients with CD are seizure free after resective neurosurgery, with higher rates for complete (77%) compared with incomplete (20%) removal of the lesion. Temporal location of FCDs lesions is associated with an 87% rate of freedom from seizures. Negative prognostic factors include long duration of epilepsy before

surgery, older age at surgery, multiple seizure types, the occurrence of secondary generalized seizures after surgery, the need for invasive EEG recording, and incomplete resection of the epileptogenic area. In a series of patients who underwent frontal lobectomy for frontal lobe epilepsy, independent predictors of seizure recurrence were no MCD/FCD found on MRI, extrafrontal MR imaging abnormalities, generalized ictal EEG patterns, acute postoperative seizures, and incomplete resection. When no lesion was visible on pre-operative MR images, only 37% of adults and children were seizure-free 1 year postoperatively. Positive prognostic factors for good seizure control include the presence of local epileptogenic discharges, a well-defined lesion on preoperative MR images, and coincidence of ictal SPECT findings with the resection site. The completeness of resection appears to have the most predictive power for long-term seizure-free outcome.Surgical failure, defined as the presence of persistent or recurrent seizure activity, is highly dependent on the completeness of resection of the epileptogenic cortex. Intra-operative challenges to complete resection include poorly defined epileptogenic zone margins on neuroimaging or EEG, the presence of important vascular structures in the epileptogenic zone, proximity of the epileptogenic zone to eloquent cortex, or an epileptogenic zone that has important cortical function. It is important to understand that epileptic foci and underlying cortical dysplasia may occur outside of the clearly delineated areas of abnormality demonstrated on MR imaging (Diaz, et al.,2008).

Morbidity (<3%) and mortality (0.2%) are low for patients with CD undergoing epilepsy neurosurgery. The rate of transient postoperative complications after cortical resection, lobectomy, or hemispherectomy for cortical dysplasia has been reported as 10.9%. Significant permanent neurological deficits are rare, but initial neurological deterioration (for example hemiparesis, dysphasia, dysnomia, and/or memory disturbance) is very common in a high proportion of cases(Krsek, et al.,2010; Phi, et al.,2010; Tassi, et al.,2010).

6. Challenges and future directions

Future challenges include the noninvasive identification of patients with CD with 100% accuracy, evaluation of long-term out comes in surgical patients, and devising new treatments based on a better understanding of the neurobiology leading to seizures in CD tissue.

6.1 Identify refractory epilepsy patients with cortical dysplasia with 100% accuracy

A substantial proportion of epilepsy surgery patients with cortical dysplasia have non localizing foci using scalp EEG and ''normal'' MRI scans. Many of these are patients have mild cortical dysplasia. Thus how many patients with cortical dysplasia are we missing using current presurgical protocols that rely on structural MRI scans? We need more precise presurgical protocols and technologies that can screen patients with refractory epilepsy noninvasively for the presence of subtle cortical dysplasia (Bernasconi, et al., 2011; Kim, et al., 2011).

6.2 Determine the long-term outcomes for epilepsy surgery patients with mild and severe cortical dysplasia

At present, there appear to be minimal differences for patients with type 1 and type 2 cortical dysplasia in the percentage of patient's seizure free 1–2 years after surgery, if the lesion is completely removed. However, it is unclear if patients remain seizure free many years after surgery. In addition, we do not know if patients have long-term improvements in

assessments of quality of life and psychosocial outcomes. Hence, long-term outcome studies are needed to determine if there are differences in the percentage of patients who are seizure free along with developmental and psychosocial results, for patients with mild and severe cortical dysplasia (Diaz, et al.,2008).

6.3 Devise new and improved treatments for drug-refractory epilepsy patients with cortical dysplasia

A proportion of medically refractory patients with cortical dysplasia are poor surgical candidates because the lesion cannot be completely removed if it involves areas of important functional cortex. A future challenge will be to develop new therapies that control seizures so that more patients with cortical dysplasia can be treated successfully without increasing the risk of new neurologic deficits. This may involve remedies based on mechanisms learned from the basic science laboratory involving abnormal cells and circuits in cortical dysplasia tissue. These therapies will also need to include emerging knowledge of the genetic abnormalities that may be different in patients with mild and severe cortical dysplasia. Hence, there is a need for more research to understand mechanisms of epileptogenesis and pathogenesis along with genetics in patients with cortical dysplasia, and whether these mechanisms are different in those with mild and severe disease. The use of human tissue may be an important research opportunity for patients with cortical dysplasia, as it offers the opportunity to try new pharmacologic treatments on this disease. In the future, we hope to understand more about the clinical characteristics and mechanisms of epileptogenesis in patients with mild and severe cortical dysplasia that can be translated into novel therapies(Beleza,2009; Crino,2009; Duchowny,2009; Roper,2009).

7. Acknowledgements

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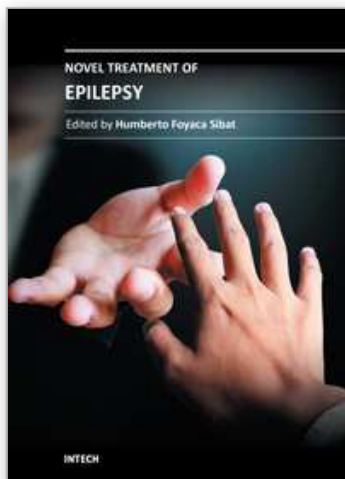
Novel Treatment of Epilepsy

Edited by Prof. Humberto Foyaca-Sibat

Epilepsy continues to be a major health problem throughout the planet, affecting millions of people, mainly in developing countries where parasitic zoonoses are more common and cysticercosis, as a leading cause, is endemic. There is epidemiological evidence for an increasing prevalence of epilepsy throughout the world, and evidence of increasing morbidity and mortality in many countries as a consequence of higher incidence of infectious diseases, head injury and stroke. We decided to edit this book because we identified another way to approach this problem, covering aspects of the treatment of epilepsy based on the most recent technological results â€œin vitroâ€ from developed countries, and the basic treatment of epilepsy at the primary care level in rural areas of South Africa. Therefore, apart from the classic issues that cannot be missing in any book about epilepsy, we introduced novel aspects related with epilepsy and neurocysticercosis, as a leading cause of epilepsy in developing countries. Many experts from the field of epilepsy worked hard on this publication to provide valuable updated information about the treatment of epilepsy and other related problems.

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