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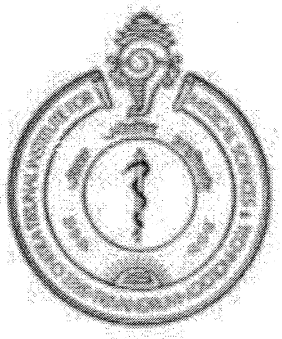

DISSERTATION

Dr. Atampreet Singh, M.D.

DM Neurology

October 2008

CERTIFICATE

I, Dr. Atampreet Singh, post graduate in Neurology hereby declare that I have carried out the project entitled **"Medically refractory epilepsy associated with focal cortical dysplasias: clinical, electrophysiologic, imaging and pathologic characteristics and seizure outcome."**

Place: Trivandrum

Signature

Date: 04.10.2008

Dr. Atampreet Singh, M.D.

CERTIFICATE

This is to certify that Dr Atampreet Singh, post graduate in Neurology has carried out the project entitled **"Medically refractory epilepsy associated with focal cortical dysplasias: clinical, electrophysiologic, imaging and pathologic characteristics and seizure outcome"**, reported as under.

Signature

Date: 04.10.2008

Dr. M. D. NAIR
Professor
Department of Neurology

PROJECT REPORT

"Medically refractory epilepsy associated with focal cortical dysplasias: clinical, electrophysiologic, imaging and pathologic characteristics and seizure outcome "

Name: Dr. Atampreet Singh

Guide: Dr. Ashalatha R

Program: DM Neurology

Month & year of submission: October 2008

ACKNOWLEDGEMENTS

First and foremost, I wish to express my sincere gratitude towards my teacher, Dr Ashalatha R, Consultant in Neurology, my thesis guide, who has shown a large and consistent interest in my project. She has carefully guided me through out the study with her continual counsel, without which I might not have been able to accomplish this goal.

Most of all, I'm deeply indebted to Dr. K.Radhakrishnan, Professor and Head of the Department of Neurology for his stimulating suggestions, interest and encouragement during the times.

I am very grateful to Dr. Muralidharan Nair, Professor, Department of Neurology for his constant guidance and enthusiasm.

I am also highly indebted to Dr V.V. Radhakrishnan, Professor and Head, Department of Pathology and Dr Keshavdas, Addl. Professor, Department of Radiology for their intellectual guidance. The project would haven been really impossible without their contributions.

I also thank Dr Sarma and Dr Savneet for their guidance in statistical evaluation.

I also thank medical record department, who have provided necessary help in data collection.

Most importantly, I thank all my patients in sincerely participating in the study, without co-operation of whom, this study would never have been possible.

Lastly, I owe my loving thanks to my wife who has helped me for preparation of this project and my little daughter for making me light during difficult times.

Most importantly, I wish to thank The Almighty for giving me the wisdom and strength to accomplish this great project.

Date: 04.10.2008

Place: Trivandrum

Dr. Atampreet Singh

CONTENTS

INTRODUCTION

Malformations caused by abnormalities of cortical development (MCD)[1] also known as disorders of cortical development[2], cortical dysplasias[3] cortical dysgenesis [4] or neuronal migration disorders (NMDs)[5] have been recognized increasingly in patients with drug-resistant epilepsy. Advances in basic and clinical neurosciences have opened exciting avenues for research on the mechanisms of epileptogenicity and cerebral dysfunction in patients with MCD.

The advent of various MRI techniques has facilitated the in vivo identification of a large group of cortical malformations in patients with epilepsy[6]. There has been progress in the understanding of various pathogenetic mechanisms, engineering and testing of various animal models of MCD; description of direct clinical-electrographic correlations, and the delineation of surgical strategies, for management of the various types of MCD associated with epilepsy. Despite these advances, it has become obvious that there was a lack of uniform, well-defined clinically sound histopathologic nomenclature for and classification of these disorders. Such classification may allow for further progress in

understanding these entities through improved communication at the clinical/electrographic, histopathologic, and basic scientific levels of research.

Thus far, the most comprehensive classification is that proposed by Barkovich et al.[1] who have included embryologic, histopathologic, imaging, and genetic aspects within their scheme. The major merit of this classification is its organization of the various types of MCD within an embryologic-pathophysiologic framework, recognizing that MCD could

be caused by abnormalities during specific stages of cortical development (neuroglial proliferation and differentiation, neuronal migration, and postmigratory cortical organization). This classification[1] did not emphasize a key issue in current epileptology, the existence of focal cortical dysplasias (FCDs), which are localized malformations increasingly associated with refractory seizures and currently operated on at most epilepsy centers.[7] There is increasing information on correlations between the histopathologic and electroclinical and MRI abnormalities of FCD.[2,8,9]

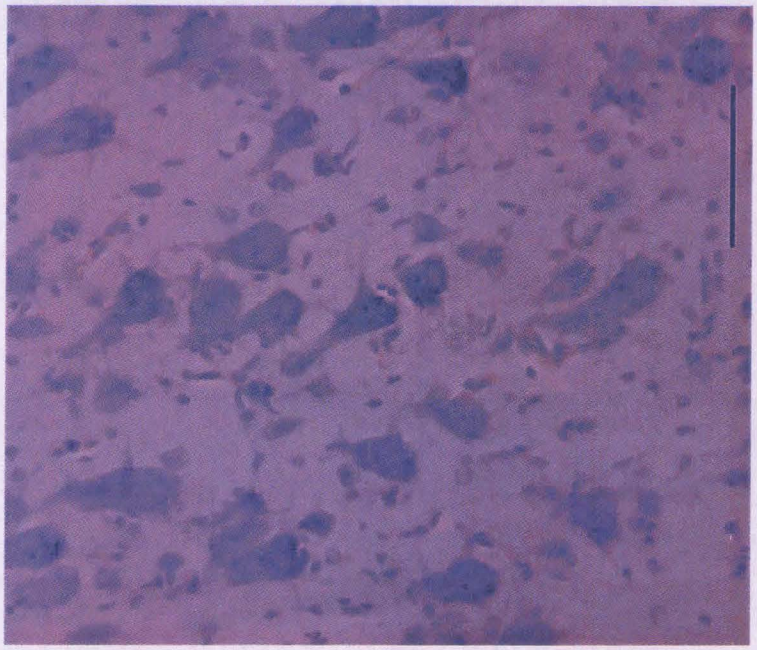

Figure 1: Cresylecht violet staining shows the dysmorphic neurons. Note the high Nissl stain density and the various directions of the neurons; scale bar, 50 μm.

Over the years, there has been some degree of heterogeneity in the clinical, surgical, and histopathologic literature, and terms like "focal cortical dysplasia," "mild cortical dysplasia," "Taylor-type focal cortical dysplasia," "balloon cell dysplasia," "non–balloon cell dysplasia," and "microdysgenesis" all have been applied to describe architectural and cellular abnormalities of the cortical mantle.[6,9,10] For example, some authors use the descriptor Taylor-type FCD only when balloon cells are present, [11] whereas others, including Taylor et al.[3] in their original report, include some patients whose lesions had dysmorphic neurons but lacked balloon cells.

Cellular abnormalities.

Dysmorphic neurons. These are misshapen cells with abnormal orientation, size, cytoskeletal structure, and atypical dendritic processes. Nissl substance can be seen in clumps, and the cells are rich in cytoplasmic neurofilaments (Figure 1).[12]

Balloon cells. These are abnormal cellular elements with a thin membrane; pale, glassy, and eosinophilic cytoplasm; and eccentric

nucleus (or nuclei, because some are multinucleated). Balloon cells usually are of increased size compared with gemistocytic astrocytes. Previous immunocytochemical studies have shown that these cells have neuronal or glial characteristics.[13] Most balloon cells are vimentin positive, but others are glial (e.g., glial fibrillary acidic protein) or neuron-specific enolase/MAP/NeuN-immunoreactive (Najm et al., personal communication). These data suggest some degree of heterogeneity among the cells with partial commitment toward glial or neuronal differentiation (Figure 2).

Giant neurons. These are neurons of increased size (compared with layer V pyramidal neurons) with central nuclei. However, they preserve a pyramidal morphology (i.e., are not dysmorphic) and do not overexpress cytoplasmic neurofilaments (Figure 3).

Immature neurons. These are round (or oval) cells, all homogeneous, with a large (immature) nucleus and a thin rim of cytoplasm. They are not dysmorphic or giant but sometimes are seen in association with giant or dysmorphic neurons. They are occasionally the most common cell types in macroscopically visible heterotopic nodules.[13]

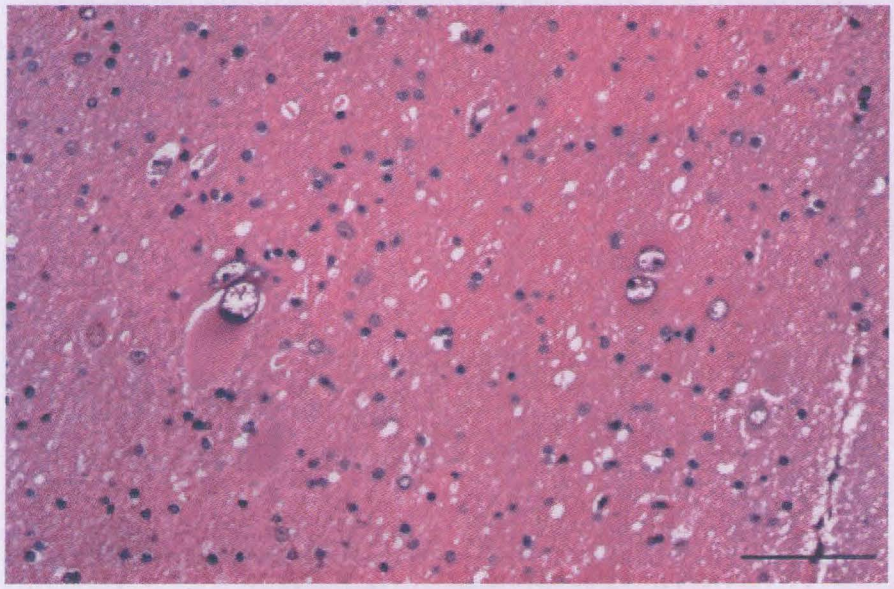

Figure 2: H-E staining shows a large balloon cell in the subcortical white matter. Note the large opalescent cytoplasm and the eccentric nucleus; scale bar, 100 μm.

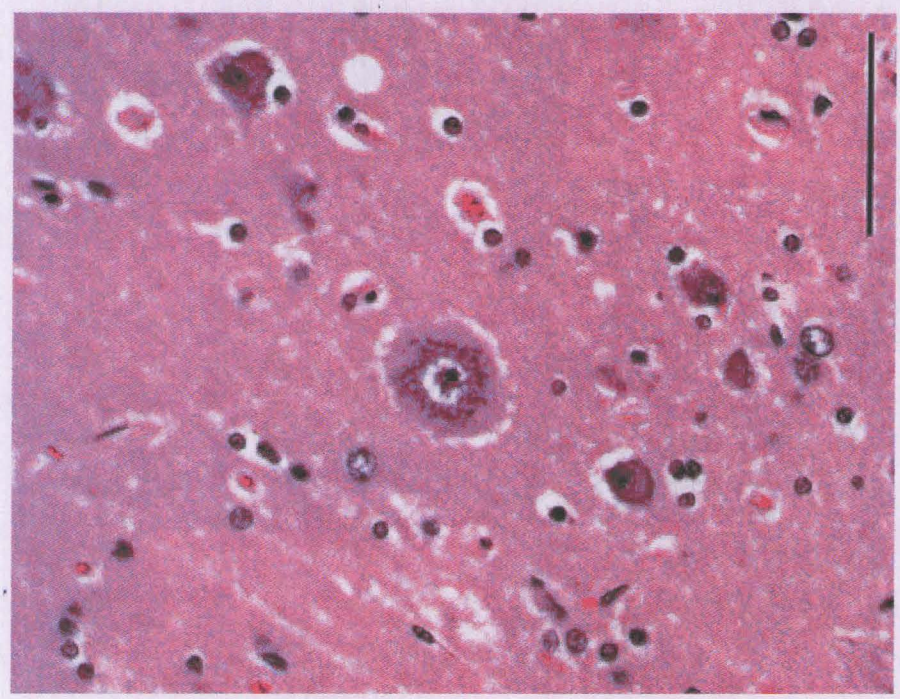

Figure 3: H-E staining shows a giant neuron with central nucleus. Note the presence of smaller dysmorphic neurons; scale bar, 100 μm.

The most frequent histopathologic pictures combining these elements are considered to be the following.

Isolated architectural abnormalities (dyslamina-tion). These are intracortical lesions that are characterized by dyslamination and columnar disorganization. These lesions represent the mildest end of the histopathologic spectrum of FCD and may most closely approximate the original description of microdysgenesis. In the medial temporal lobe, particularly in the hippocampus, abnormalities of the infolding of the dentate gyrus and focal dyslamination may occur.[14]

Architectural abnormalities associated with giant neurons. In these lesions, the defining abnormality is the presence of giant neurons. These lesions do not contain dysmorphic or balloon cells. Whether the presence of these cells has any clinical meaning and thus differentiates the lesions from those harboring only dyslamination is unclear.

Architectural abnormalities associated with dysmorphic neurons. Irrespective of the occasional co-occurrence of giant or immature neurons, the hallmark of these lesions is the presence of clearly dysmorphic neurons as defined previously.[12,13] Accumulation of neurofilaments within neuronal cytoplasm of these cells leads to distorted

morphology of the perikarya, proximal axons, and dendrites. It is theoretically conceivable that these reflect more severe abnormalities from a histopathologic standpoint. In the original publication of Taylor et al.,[3] 4 of 10 patients had this histopathologic picture.

Architectural abnormalities associated with dysmorphic neurons and balloon cells. These lesions are characterized mainly by the presence of balloon cells that are intermixed typically with dysmorphic neurons in patients with severe architectural disorganization. Six of the 10 original patients reported by Taylor et al.[3] had a similar histopathologic pattern. These lesions are considered to represent the most severe end of the spectrum of histopathologic abnormalities of FCD.[15]

There is preliminary evidence that the presence of dysmorphic neurons, with or without balloon cells, is associated with higher degrees of epileptogenicity.[2] Moreover, recent studies suggest that the main histopathologic subtypes that show MRI abnormalities are those that contain dysmorphic neurons with or without balloon cells.[16] These results suggest the separation of the histologic subtypes as delineated will allow much better electroclinical, imaging, and histopathologic correlations.

A classification scheme of FCD: Imaging and Histopathology

Mild MCD

Type I: with ectopically placed neurons in or adjacent to layer I

Type II: with microscopic neuronal heterotopia outside layer I

Structural imaging: both types probably are not detectable by current MRI techniques

FCDs

Type I: no dysmorphic neurons or balloon cells.

Type IA: isolated architectural abnormalities (dyslamination, accompanied or not by other abnormalities of mild MCD)

Type IB: architectural abnormalities, plus giant or immature, *but not dysmorphic* neurons

Structural imaging: it is unclear whether type I FCD as defined can be identified in vivo by current MRI techniques.

Histopathology: as described previously (Figure 4)

Type II: Taylor-type FCD (dysmorphic neurons without or with balloon cells)

Type IIA: architectural abnormalities with dys morphic neurons but without balloon cells

Type IIB: architectural abnormalities with dys morphic neurons and balloon cells

Structural imaging: these are the focal lesions most commonly identified on MRI. However, one should be aware that several different imaging possibilities might be observed in patients with Taylor-type FCD. MRI can be either normal,[17] despite the use of high-resolution techniques, or may demonstrate one or more of the following characteristics: 1) focal areas of increased cortical thickness [18]; 2) blurring of the cortex (gray)/white matter junction;[8,16] 3) increased signal on T2-weighted, proton density, or fluid-attenuated inversion recovery sequences (more likely to occur in balloon cell-containing lesions);[8,16] and 4) extension of cortical tissue with increased signal from the surface to the ventricle (transmantle dysplasia).[19]

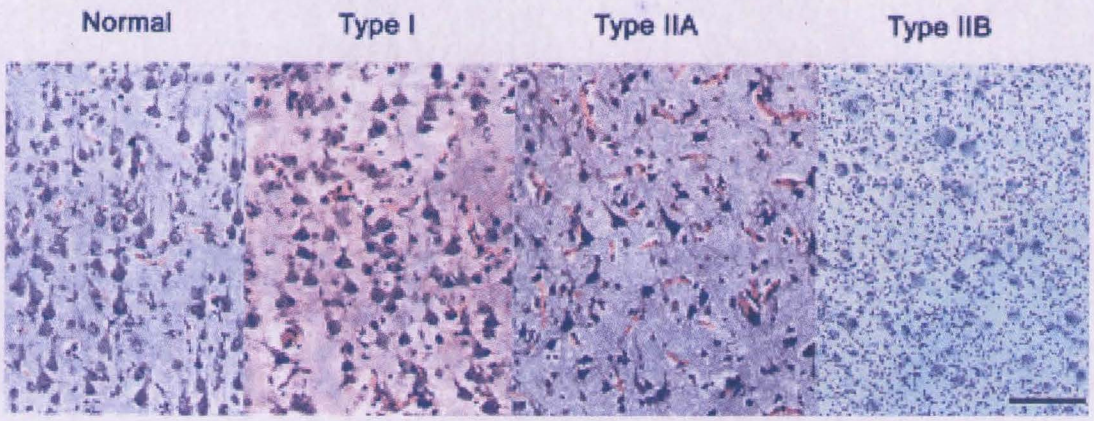

Figure 4: Cresylecht violet staining of sections representing normal neocortex and type I, type IIA, and type IIB malformations of cortical development; scale bar, 100 μm.

Dysplastic tumors: There are at least two types of tumor that may represent a more extreme end of the histopathologic spectrum of FCDs. Dysembryoplastic neuroepithelial tumors (DNETs) and gangliogliomas may be associated with surrounding cortical regions displaying abnormal cytoarchitecture (dyslamination) and large, at times dysmorphic, neurons and glial cells.[20] Subcortical heterotopic neurons also can be seen. *Structural imaging and histopathology:* Both lesions usually are restricted to the cortex and may present a combination of cystic and calcified areas. Perhaps the most striking imaging aspect is that the MRI signal often is irregular and poorly delineated, attesting to the presence of different histopathologic elements and the association of perilesional dysplastic and immediately subcortical heterotopic cells. There is no perilesional edema or mass effect. [21]

REVIEW OF LITERATURE

The expression "focal cortical dysplasia" is used to designate almost any localized cerebral developmental malformation. In 1971 Taylor et al.,[3] first described this distinctive pathology in 10 patients undergoing epilepsy surgery, with the characteristic feature of "masses of large aberrant neurons littered apparently in chaos through all but the first molecular layer." Since this description, there has been confusion over the classification of focal cortical dysplasia. Taylor et al.,[3] recognized the heterogeneity in this focal pathology in that only a proportion of the cases contained balloon cells.

The first large series was described by Palmini et al.,[10] in 1991. This series included 26 patients with focal neuronal migration disorders, 12 of whom had definitive FCD. Five of the 12 patients had lesions confined to one lobe or one area of the brain, and seven had multilobar involvement. Seven of the 12 patients had complete cessation or excellent control of seizures after surgery. Seizure control was highly correlated with successful resection of the entire lesion or at least the majority of the abnormal tissue. Complete resection did not necessarily predict cessation of seizures, however, as poor control of seizures remained in some

patients despite removal of all of the tissue associated with epileptiform discharges in EEG or electrocorticography findings.

In 1993, Hirabayashi et al.,[22] reviewed seventeen patients with cortical dysplasia who had surgical resection for medically intractable partial epilepsy were studied and compared with two groups of surgically treated patients with intractable epilepsy due to tumour (n = 20) and mesial temporal sclerosis (n = 40), patients with cortical dysplasia showed significantly more frequent extratemporal lesions, more frequent non-epileptiform EEG abnormalities and less favourable surgical outcome for seizure control. Patients with cortical dysplasia were younger at onset of seizures. Surgical outcome related to the extent of pathology but not to the histological abnormality. Lesions outside the temporal and frontal lobes were correlated with poor surgical outcome, as were generalised interictal EEG abnormalities, which may reflect extensive or multiple lesions. Ictal intracranial recordings were not useful for presurgical evaluation of cortical dysplasia.

In 1995, Palmini et al.,[7] further characterized his patients, as well as additional patients from two other institutions. In this series of 34

patients, outcome data were available for 27 patients. An important aspect of this study was the careful documentation of the EEG findings in patients with cortical dysplasia. Approximately two thirds of the patients demonstrated characteristic epileptic discharges, including repetitive electrographic seizure activity, repetitive bursting discharges, and continuous or quasicontinuous rhythmic spiking. In this expanded series with longer follow up, 75% of the patients who underwent complete resection of regions associated with abnormal electrical activities had a good outcome, and the patients in whom some of these areas remained had relatively poor seizure control. Thus, the concept of combined resection of areas showing radiological and electrophysiological abnormalities was emphasized.

In a series by Bronen et al., in 1997 [8] , described 8 patients with balloon cells focal cortical dysplasia and compared with 54 patients with low grade neoplasm over an 8-year period and concluded that the presence of gray matter thickening associated with a homogeneous hyperintense signal in the subcortical white matter that tapers as it extends to the lateral ventricle favors a dysplasia. A frontal lobe location favors

dysplasia, while a temporal lobe (especially medial temporal lobe) location is more suggestive of a neoplasm.

In one of the initial studies with ECoG by Chassoux et al.,[23] retrospectively analysed a series of 28 patients with FCD who had been investigated by stereoelectroencephalography (SEEG) between 1964 and 1995. Neurophysiological data were correlated with histological findings and surgical outcome. MRI was available for only seven patients. FCD was distributed equally between all lobes except for the temporal lobe, and was found predominantly on the mesial aspect of the cerebral hemispheres. SEEG findings provided evidence of dysplastic tissue epileptogenicity, as demonstrated by intralesional rhythmic spike discharges, the onset of ictal discharges and a low epileptogenic threshold. The epileptogenic zone corresponded to histologically defined FCD in 82% of the cases. Despite the lack of adequate neuroimaging in most cases, 64% of the patients became seizure-free after surgery. The main predictors of a favourable outcome were complete removal of the epileptogenic zone and complete removal of the dysplastic cortex. These results emphasized the usefulness of neurophysiological data in accurately assessing the extent of the FCD.

Colombo et al., [24] in 2003 reviewed the MR data of 49 patients treated surgically for intractable partial epilepsy, who received a histologic diagnosis of FCD and concluded that it was generally possible to distinguish Taylor's FCD from architectural or cytoarchitectural dysplasias (non-Taylor's FCD). Findings suggesting Taylor's FCD were focal cortical thickening, blurring of the gray-white matter junction, and hyperintensity (on T2-weighted images) of subcortical white matter often tapering toward the ventricle. Focal brain hypoplasia with shrinkage and moderate signal intensity alterations in the whitematter core were present in most patients with architectural dysplasia. The lesion was generally extratemporal in Taylor's FCD and temporal in architectural dysplasia. Ipsilateral hippocampal sclerosis was often present in architectural dysplasia (dual abnormality).

In a surgical series of 67 patients by Fauser et al., [25] in 2004 found that there was a tendency towards better postsurgical outcome related to the last follow-up visit in patients with more subtle abnormalities classified as mild malformations of cortical development (mMCD) (63% Engel Ia),

FCD type 1a (67% Engel Ia) and FCD type 1b (55% Engel Ia) compared with patients with FCD type 2a (43% Engel Ia) and FCD type 2b (Taylor type) (50% Engel Ia). Patients with dual pathology almost always had temporal lobe epilepsy; the outcome in this patient group was generally favourable (66% complete seizure freedom at the last follow-up visit). They concluded that patients with FCD type 1 and mMCD had a better outcome compared with those with more severe forms of cortical dysplasia. A higher incidence of FCD type 1 in temporal localization did not allow the effects of histological subtype and localization to be separated. A subanalysis of extratemporal FCDs, however, revealed a similar tendency for a better outcome with FCD type 1, suggesting that the histological subtype itself seems to be at least a relevant cofactor influencing postsurgical outcome.

In a study by Boonyapisit et al., [26] in 2003 of 15 pts with focal epilepsy due to pathologically confirmed MCD who underwent subdural electrode placement for extraoperative seizure localization and cortical mapping. Cortical areas with histopathologic subtype IIA showed significant higher numbers of slow repetitive spike pattern in comparison with type I and normal pathology. The ictal onset mainly came from

cortical areas type IIA. None of the seizures came from neocortical areas that showed balloon cell containing MCD type IIB and hence concluding that balloon cells are less epileptogenic than are closely located dysplastic regions.

In a study by Lawson et al., [27] in 2005 did a comparison between the pathological diagnosis of FCD and MRI abnormalities and found that the dysplasia-only subtype had higher rates of neonatal onset, hemiparesis, and severe mental retardation. The MRI features of focal cortical thickening with associated cortical T2 signal change showed excellent sensitivity (94%) and reasonable specificity (73%) for the diagnosis of the balloon cell subtype. The overall surgical outcome was 59% seizure freedom at 2 years suggesting that preoperative identification of these subtypes may impact surgical planning.

Widdess-Walsh et al., [28] retrospectively reviewed 145 patient data from epilepsy surgeries at the Cleveland Clinic Foundation and found that pathological subtypes 2A and 2B were predominantly frontal in location, and had a more severe epilepsy syndrome with lower intelligence quotient scores than subtypes 1A and 1B. Patients with subtype 1A FCD

had less severe, later onset epilepsy that was predominantly located in the temporal lobe. Risk factors for epilepsy included febrile seizures for type 1A, head trauma for types 1A and 1B, and perinatal adverse events for type 2B. Type 2B demonstrated significantly more FLAIR signal abnormalities than the other groups. Sixty-three percent of patients overall had an Engel I outcome at 6 months follow-up. The best outcomes were in the 2B subtype, and in those who did not require an invasive EEG evaluation

In a large series of 120 patients by Fauser et al., [29] in 2006 described the clinical characteristics of FCD patients. In the majority of patients, epilepsy began in the first 5 years of life. Age at epilepsy onset was not significantly different between temporal, extratemporal and multilobar localization of FCD. Patients without cytoarchitectural abnormalities (mild malformations of cortical development, FCD 1a) had significantly later epilepsy onset compared with patients with cytoarchitectural abnormalities (FCD 1b, 2a and 2b). In patients with additional hippocampal sclerosis (dual pathology) febrile seizures were significantly more frequently reported than in patients without dual pathology. First observed seizures were mainly tonic or generalized tonic–clonic. About

15.8% of the patients presented with status epilepticus during the course of disease. About 17% of the patients showed transient esponsiveness (>1 year seizure freedom) to antiepileptic drug therapy either after initial therapy (50%) or later in the course of epilepsy (50%). Different age at epilepsy onset and transient responsiveness to antiepileptic drugs in 17% of patients may reflect different dynamics in epileptogenicity of the underlying FCD. Dual pathology may be associated with different pathomechanisms in patients with and without febrile seizures.

Kral et al., [30] in 2007 retrospectively analysed the records of 49 patients and the resected tissue was classified as FCD type II b in 41 cases with an extratemporal and FCD type II a in 8 cases with a temporal localisation (100%). After a mean follow-up of 8.1 (4.5) years, 37 patients (76%) were seizure free, a subgroup of 23 patients (47%) had been completely seizure free since surgery and 4 patients (8%) had only auras. Over a 10 year follow-up, the proportion of satisfactory outcomes decreased, mainly within the first 3 years. During long term follow-up, 48% stopped antiepileptic drug treatment, 34% received a driver's license and 57% found a job or training and hence concluding that surgical treatment also has a satisfying long term outcome which remains constant

after 3 years of follow-up but is not associated with better employment status or improvement in daily living.

Widdess-Walsh et al [31] in 2007 retrospectively reviewed 48 consecutive surgeries guided by subdural electrode recordings between 1990 and 2004 in patients with a pathologic diagnosis of isolated FCD. 45% of patients were completely seizure-free. Most seizures recurred in the first 6 months or between years 2 and 3 after surgery. On univariate analysis, seizure recurrence was associated with bilateral EEG abnormalities, multiple semiologic seizure types, and incomplete resection of the ictal onset zone. The absence of an MRI lesion did not affect outcome, nor did proximity to eloquent cortex. Interictal paroxysmal fast and runs of repetitive spikes correlated with the ictal onset zone, whereas isolated spikes did not. The 6-month EEG predicted ultimate surgical failure in patients seizure-free at that stage. An ictal spread pattern from the edge of the subdural grids was an independent predictor of seizure recurrence on multivariate analysis.and concluded that successful surgical results can be obtained utilizing subdural EEG in carefully selected patients.

Krsek et al.,[32] in 2008 retrospectively reviewed clinical, electroencephalographic, magnetic resonance imaging,

neuropsychological, and surgical variables, and seizure outcome data in 200 children. Perinatal risk factors were more frequent in mMCD/FCD type I than FCD type II. Children with FCD type IIb had more localized ictal electroencephalographic patterns and magnetic resonance imaging changes. Increased cortical thickness,abnormal gyral/sulcal patterns, gray/white matter junction blurring, and gray matter signal abnormality in fluid-attenuated inversion recovery and T2-weighted sequences occurred more often in FCD type II, were infrequent in FCD type I, and rare in mMCD. Lobar hypoplasia/atrophy was common in FCD type I. Hippocampal sclerosis was most frequent in FCD type I.

Neuropsychological testing demonstrated no significant differences between the groups. There was a trend toward better surgical outcomes in FCD type II compared with FCD type I patients

Fauser et al., [33] in 2008 retrospectively analysed 120 patients with histologically proven focal cortical dysplasias (FCD) for prognostic factors for successful epilepsy surgery. Multivariate data analyses showed that older age at epilepsy surgery, occurrence of secondarily generalized seizures and a multilobar extent of the dysplasia were significant negative predictors. In univariate analyses,longer duration of

epilepsy, need for intracranial EEG recordings and incomplete resection of the FCD were factors which significantly reduced the chance of becoming seizure free. Histological subtype of the FCD and age at epilepsy onset had no significant predictive value. These findings strongly suggest early consideration of epilepsy surgery in FCD patients.

AIMS OF THE STUDY

The study was undertaken with the following objectives to assess:

1. Clinical, electrophysiologic, imaging and pathologic characteristics of patients diagnosed as focal cortical dysplasia who had undergone evaluation and surgery through our epilepsy program.

2. Postoperative seizure outcome and factors that influenced the outcome.

PATIENTS AND METHODS

Patient selection

Between January 2001 and December 2007, 33 patients underwent surgery for focal cortical dysplasia at the R.Madhavan Nayar Center for Comprehensive Epilepsy Care, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum, the capital city of the South Indian state of Kerala, India. The details of our presurgical protocol, which includes history, optimum 1.5T MRI (siemens), interictal scalp EEG, video-EEG monitoring with scalp /sphenoidal electrodes and neuropsychologic assessment has been described previously.

3 patients underwent invasive EEG monitoring, 3 had Wada test , one patient had PET scan and one underwent fMRI . For the purpose of the study, we selected patients whose surgical pathology revealed focal cortical dysplasia and who have completed $\geq$ 1 year of postoperative followup.

MRI data

All the preoperative MRI films to delineate the site, size and extent of the dysplasia as well as the contrast enhancement and FLAIR sequences for the same and associated hippocampal atrophy and sclerosis was reviewed by a neuroradiologist.

Interictal and ictal EEG data

Standard 10-20 system of extracranial electrode placement was used with additional anterior temporal (T1 and T2) electrodes .The distribution of interictal epileptiform discharges (IEDs) during prolonged video-EEG monitoring was assessed by visual analysis of interictal EEG samples of 15 secs every 15 mins.

Neuropsychological evaluation

All patients underwent comprehensive neuropsychology evaluation which encompassed domains pertaining to deficits to various lobe functions. We do not have validated battery for neuropsychology testing in children. Intellectual functions were assessed using Weschler Adult Intelligence Scale which included verbal and performance IQ., as well as full scale. The memory functions were assessed using Weschler Memory Scale subsets with immediate and 30 min recall. Visuospatial memory was tested using the Rey-Osterieth Complex figure attention was documented using trail-making tests and Rey Auditory verbal Learning assessed verbal learning and memory. Neuropyschology tests results

were classified into concordant, discordant or diffuse depending upon preoperative performance of the patient considering the side of surgery.

Surgical Procedure

All patients underwent lesionectomy, lobectomy/multilobar resection, hemispherectomy whenever indicated and standard anterior temporal lobectomy with amygdalohippocampectomy. All surgeries were performed under general anesthesia with assistance of ECoG.

Histology

Four-micrometer- thick histologic sections were generated from 10% formalin fixed, paraffin–embedded tissue and stained with hemotoxylin and eosin.

Histological dysplastic features were classified as suggested by Palmini[36]: dyslamination was the inclusion criterion for the diagnosis of FCD.

FCD 1a was defined as a blurred transition between different cortical layers and observed a relatively homogeneous population of neurons and a moderately increased cell density. Occasionally, dyslamination was characterized by a numerical reduction of pyramidal neurons and granule

cells and clusters of misplaced neurons (e.g. an increased number of pyramidal neurons in layers I or II with abundant ectopic neurons in the white matter).

FCD 1b was diagnosed if the laminar disorganization was more prominent and occurred together with cytoarchitectural abnormalities such as immature neurons (a population of neurons with a large nucleus and a thin rim of cytoplasma) and/or giant neurons.

Dysplastic tissue with the additional occurrence of dysmorphic neurons was classified as FCD 2a, and dysplastic tissue with additional balloon cells as FCD 2b.

Outcome assessment

Patients were regularly followed up at 3 and 12 months after surgery and at yearly interval thereafter. We determined the seizure outcome using the elaborate Engel seizure scoring system .[34] The postoperative seizure outcome at last followup was defined as seizure free with/without AED and non-seizure free outcome (seizure recurrence of any type following surgery). Neuropsychological assessment and EEG was performed during each follow-up visit until 3 years. Post operative MRI brain was taken only if there was seizure recurrence

Statistical Methods

Quantitative data is summarized as mean +/- standard deviation. Univariate regression analyses was used to assess the relationship between continuous variables such as duration of epilepsy, age at epilepsy surgery, age at epilepsy onset and postoperative seizure score. The relationship between categorical variables such as extent (unilobar vs multilobar) and localisation (temporal vs extratemporal) of FCD, histology (according to the Palmini classification, individual subtypes and group I vs II) and surgery outcome, seizure free with/without AED and non-seizure free outcome was assessed by two by two table analysis. Odds ratio was calculated at 95%CI and $p< 0.05$ was considered significant.

RESULTS

Patient characteristics and Neurological findings

A total of 33 patients were diagnosed pathologically as FCD, out of which 22 were males and 11 females. The demographic data and clinical features are provided in Table 1. The mean age of patients was 17.7 $\pm$ 10.14 years with a range of 1-44 years .The mean age of seizure onset was 5.57 $\pm$ 6.83 years. The mean age at surgery was 18.21 $\pm$ 10.35 years with range of 1-44 years. The mean duration of epilepsy was 12.65 $\pm$ 8.90 years with range of 9 months to 41 years.

Neurological history and findings included family history of epilepsy perinatal risk factors, febrile seizures, antecedent trauma, focal neurological deficits. No patient had family history of epilepsy. 2 patients had perinatal risk factors mainly birth asphyxia and both had IIA type of FCD. Febrile seizures was present in 6 cases of which 2 were IA, IB and IIB each. 2 patients of IIB with history of febrile seizures had multilobar dysplasias and also had focal neurological deficits in the form of hemiparesis . 8 patients had abnormal neurological findings mainly in the form of hemiparesis, of which 2 had type IIB FCD and 6 had type IIA FCD.

Table 1

Patient characteristics

Characteristics	**Study group (n= 33)**
Gender	
Male	22 (66)
Female	11 (33)
Age of patients with epilepsy(years)	17.7 ± 10.14 (1-44
Age at first unprovoked seizures (years)	5.57 ± 6.83 (0.15-33)
Age at Surgery (years)	18.21 ± 10.35 (1-44)
Presurgery duration of epilepsy (years)	12.65 ± 8.90 (0.75-41)
Preoperative seizure score	8.7 ± 1.25 (7-11)
Antecedents	
Febrile seizures	6(18)
Birth asphyxia	2(6)
Neurological signs	8(24)
Histopathological types	
Ia	2 (6)
Ib	5 (15)
IIA	15 (45)
IIB	11 (33)
FCD alone	27 (81)
FCD + HS	6 (18)
Postop outcome	
Seizure free	23 (69)
Unfavorable outcome	10 (30)

Data is represented as mean + SD (range) or n (%), n= no. of patients

Neuropsychology evaluation was done in 32 patients and showed concordant data in 24 patients, discordant in only one pt and diffuse involvement in 7 patients and all of them were having type II FCD as shown in Table 2.

Neuroimaging finding

The brain MRI findings were reviewed by a neuroradiologist. Six patients had lesion in temporal lobe, 13 had frontal lobe lesion, 2 had parietal lobe lesion and 12 had lesion involving more than one lobe i.e frontoparietal, temporooccipital and temporoparietal. MRI abnormalities typical for cortical malformations were identified like blurring of the gray/white matter junction, transmantle sign, white and gray matter signal abnormality in FLAIR, gray and white matter signal change in T2 W , any lobar hypoplasia, abnormal sulcation and associated hippocampal signal changes.

Table 2

Neuropsychology parameters in FCD patients classified according to pathology

Neuropsychology	IA	IB	IIA	IIB
Concordant	2	5	9	8
Discordant	0	0	1	0
Diffuse	0	0	4	3

Data is represented as no. of patients

Seizure characteristics and EEG data:

The predominant seizure type was complex partial seizure in 30 patients. Simple partial seizures were seen in 8 patients. 3 patients had epilepsia partialis continua of which 2 patients had type IIB and one was IIA FCD. History of status epilepticus was present in 3 patients and were mainly IIA and IIB FCD as shown in table 3. VEEG showed a good electroclinical correlate in all patients. Out of 33 patients, 22 had right hemisphere lesion and 11 had left hemispheric lesion.

Invasive monitoring and ECoG

Only 3 patients underwent invasive monitoring and one had invasive monitoring when he was admitted for reevualation for repeat surgery. 30 patients underwent ECoG out of total of 33 patients. Post operative only 3 patients had persisting spikes in ECoG (<90%) as shown in Table 5.

Surgical variables

20 patients underwent lesionectomy, 6 patients underwent lobectomy/multilobar , 2 had hemispherectomy and 6 patients underwent standard anterior temporal lobectomy with lesionectomy/lobectomy.

Table 3

Seizure characteristics in FCD patients classified according to pathology

Ind seizure type	**IA**	**IB**	**IIA**	**IIB**
Simple partial sz	0	0	5	3
Complex partial sz	2	5	15	11
Secondary GTCS	1	4	13	7
Epilepsia partialis continua	0	0	1	2
Status epileptcius	0	0	2	2

Data is represented as no. of patients

Table 4

Scalp-EEG finding in FCD patients classified according to pathology

EEG finding	IA	IB	IIA	IIB
Normal EEG	0	1	1	0
Slow BGA	1	0	1	1
Focal slowing	0	0	2	2
Regional interictal	2	5	13	9
Regional ictal pattern	2	5	13	8
Non localizing EEG	0	0	2	1

Data is represented as no. of patients

Table 5

ECoG findings in FCD patients classified according to pathology

ECoG finding	IA	IB	IIA	IIB
Spikes	2	3	14	11
Spikes				
a) Over the lesion	2	3	14	10
b) Adjoining the lesion	0	0	9	6
Type of spikes				
a) Rhythmic	1	0	6	5
b) Continuous	0	0	8	4
c) Electrographic seizures	0	0	0	0
d) Isolated spikes	1	3	4	4
Reduction of spikes				
a) < 90%	0	0	1	2
b) >90%	2	3	13	9

Data is represented as no. of patients

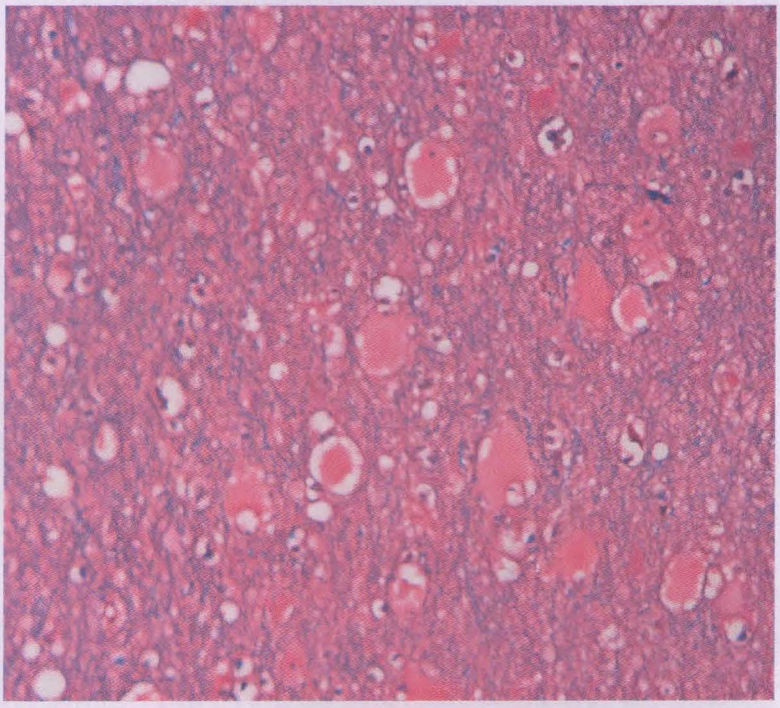

Figure 7 :H& E staining , High magnification (x250) showing the typical balloon cells

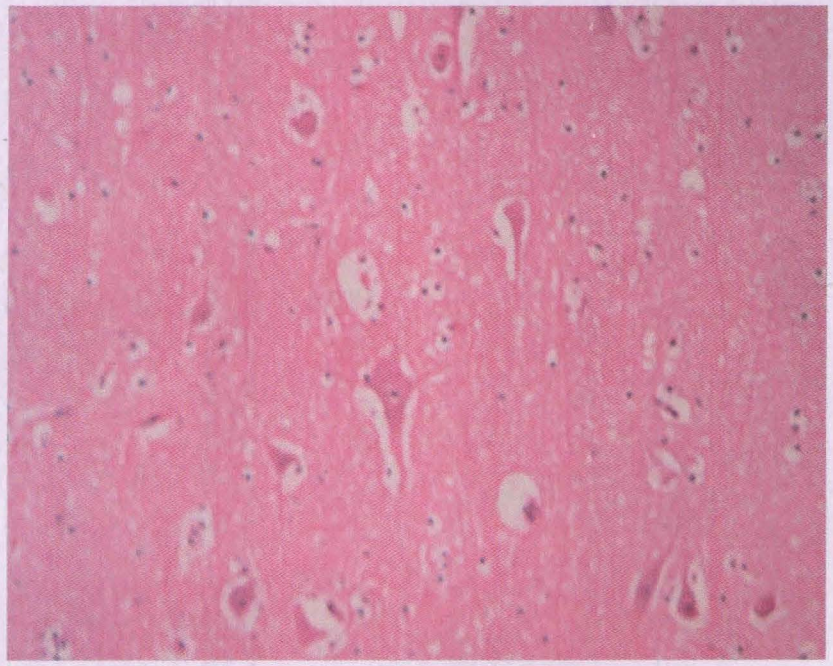

Figure 8 : H& E staining , high magnifcation (x250) showing the dysmorphic neurons and giant neurons

Pathology

Pathologically there were 12 patients of Type IIA and 11 of type IIB FCD diagnosed histopathologically. There were only 2 patients with type IA and 2 of type IB FCD.

6 patients had dual pathology mainly FCD with associated hippocampal sclerosis of which 3 patients had IB and 3 had IIA.

Seizure outcome

Seizure outcome was assessed using Engel's classification of seizure control. 23 patients became seizure free at the end of one year. The mean preoperative and postoperative seizure score was 8.7 $\pm$1.25 and 2.99 $\pm$1.91 respectively and mean duration of follow-up was 1.99$\pm$ 1.85.

One patient had readmission and evaluation as he had seizure recurrence and repeat MRI showed incomplete resection of the lesion.

Relationship between seizure score and continuous variables

We observed a significant negative correlation between the age of seizure onset and preoperative seizure score ($R= -0.33$, $p< 0.05$, Figure 5). However, there was a significant positive correlation between

postoperative seizure score and duration of epilepsy (R= 0.42, p< 0.01, Figure 6).

Predictors of outcome

10 patients had poor seizure outcome in comparison to 23 who were seizure free at the end of one year. Various parameters were assessed for non seizure-free or poor seizure outcome like location whether temporal or extratemporal, location of the lesion, histopathology, surgical strategy, ECoG pattern and postoperative scalp EEG (7^{th} day and 1 year). But none of the parameters were found to be statistically significant in our study (Table 6).

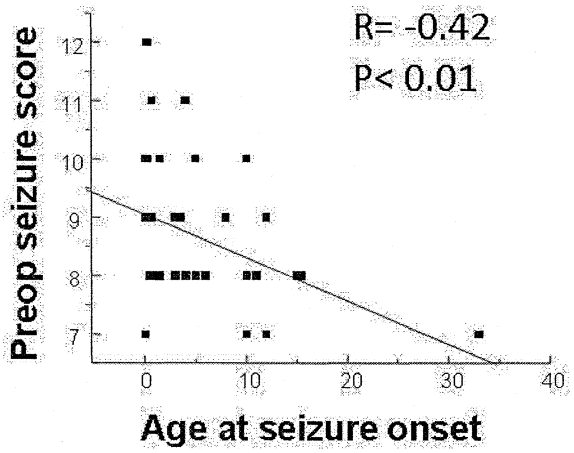

Figure 5: Linear regression analysis between preoperative seizure score and age at seizure onset shows a significant negative correlation.

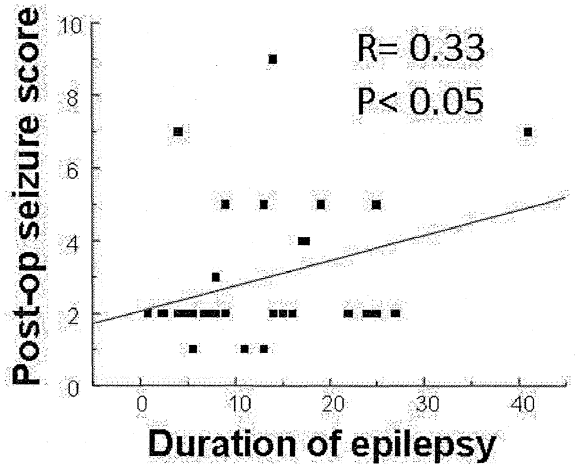

Figure 6: Linear regression analysis between postoperative seizure score and duration of epilepsy shows a significant positive correlation.

Table 6

Two by two table analysis between predictors and the outcome of FCD

Variable	Seizure-free	Non- seizure free	Significance p	OR (95% CI)
Location				
Temporal	6	1	0.29	3.17
Extratemporal	17	9		(0.3295<O.R.<30.6231)
EEG side				
Right	16	6	0.59	1.52
Left	7	4		(0.3248<O.R.<7.1495)
Histopathology				
Type I	6	1	0.29	3.17
Type II	17	9		(0.3295<O.R.<30.6231)
Type IIa	10	5	0.87	1.14
Type IIb	7	4		(0.2236<O.R.<5.8416)
Surgical strategy				
Lesionectomy	18	9		
Lobectomy/multilobar resection	5	1	0.42	2.5 (0.2528<O.R.<24.7202)
ECoG pattern				
Spike reduction				
>90%	21	8	0.83	1.31
<90%	2	1		0.104<O.R.<16.5568
Post op Scalp EEG (7^{th} day)				2.4
IEDs present	5	4	0.27	0.4812<O.R.<11.9706
IEDs absent	18	6		
Post op Scalp EEG (1 year)				1.87
IEDs present	8	5	0.41	0.4152<O.R.<8.4675
IEDs absent	15	5		

OR= Odds ratio (95% Confidence Interval)

DISCUSSION

We have reviewed the clinical, electrophysiological, radiological data and seizure outcome of 33 patients with focal cortical dysplasia who had undergone surgery in an epilepsy centre in a developing country.

Age of epilepsy onset

The vast majority of patients in our study had epilepsy onset in the first 16 years of life. Only one patient had epilepsy onset at 33 years of age. Our data on the age at epilepsy onset are comparable with data reported by Palmini et al [10] in a group of 30 patients with FCD. In their group, age at epilepsy onset ranged from 0 to 21 years (mean: 5.7 years, median: 4.5 years). In series by Fauser et al [29] the age at epilepsy onset ranged from <1 to 60 years (mean: 5.8 years, median: 3 years). In 61% of the patients epilepsy started before the age of 5 years, and in 92.5% of the patients before the age of 16 years.

The results of our study suggest that seizure onset at an earlier age is associated with a higher preoperative seizure score. Also, dysplastic tissue harbouring cytoarchitectural abnormalities (giant neurons, immature neurons, dysplastic neurons or balloon cells) are associated with an earlier age at seizure onset than dysplastic tissue showing only

architectural abnormalities. But a later epilepsy onset in patients with FCD type 1a compared with FCD 1b, 2a and 2b was observed by Widdess-Walsh et al [25] , in comparison to our study where in the mean age of onset was more in cases of IB as compared to IIA or IIB supporting the notion that dysmorphic neurons and giant neurons have a high epileptogenic potential [35] and may thus contribute to an earlier manifestation of clinically manifest seizures.

Febrile seizures and dual pathology

In patients with an associated hippocampal sclerosis (dual pathology) the FCD was always in the temporal lobe in 5 patients and one had temporo-occipital large lesion and all were on the same side of dysplasia.

This observation may be explained in different ways, namely owing to a common underlying cause for both the cortical dysplasia in the temporal lobe and the hippocampal sclerosis[37] or owing to repeated seizure propagation into the hippocampus inducing structural changes in the hippocampal architecture [38,39]. The second theory may be supported by the fact that seizure propagation from the dysplastic temporal neocortex into the hippocampus is very rapid (1–26 s in one study, 17.3 s in another study). [25,40]

In patients with febrile seizures, 2 patients had IA, 2 patients had IB and 2 patients had IIB type of focal cortical dysplasia on histopathology. In association with hipppocampal sclerosis and febrile seizures only one patient with IB had dual pathology i.e HS with dysplasia but none of the the other patients had dual pathology. This is in conjunction with the study by Widess-walsh et al [28] who had found febrile seizures to be a risk factors for type IA.

Perinatal risk factors and neurological abnormalities

8 patients with neurological signs mainly hemiparesis out of which 6 had IIA dysplasia and 2 had IIB FCD. Out of these 6 patients of type IIA, 2 had perinatal risk factors in the form of birth asphyxia and rest 4 did not have any prenatal or perinatal period risk factors.

In a series of 200 pediatric FCD patients by Krsek et al [32] reported 13 % prenatal and perinatal risk factors in their patients and more commonly in mCD and type I FCD. Widdess-Walsh et al [28] noted equal proportions of perinatal risks between FCD types however, little is known a about their role in the pathogenesis of FCD. A causative role for prenatal insults such as ischemia in the pathogenesis of cortical dysplasia has been

proposed based on experimental models [41] and observations in children with perinatally acquired encephalopathies .[42] Intrauterine insults could produce cytoarchitectural alterations of the developing neocortex that eventually cause the neuropathological findings compatible with "acquired" FCD. Our observations lend support to the belief that intrauterine factors operating during the late second or early third trimester of pregnancy could account for "severe" FCD (eg, type II), whereas events occurring closer to birth would explain "milder" forms of cortical malformation (eg, mMCD and FCD type I).[35]

MRI proof of FCD type I is often lacking as not easily diagnosed by routine MRI sequences, especially in cases with associated brain pathology. Hence, we hypothesize that MRI features of type II are easily recognized, well defined and described in literature whereas type I FCD are not well defined and easily overlooked in imaging and may be the reason for a low association with perinatal risk factors in type I.

Neuropsychology testing showed diffuse involvement in only 7 patients and all of them were of type II FCD. These findings are consistent with previous reported series by Widdess-Walsh et al [31] described that patients with below-average full-scale IQ were more frequently encountered in

both FCD type II groups (67% and 68%, respectively) than in FCD type Ia and Ib groups (38% and 57%, respectively). But in other recently reported series by Krsek et al prominent differences between children with FCD type I and FCD type II with significantly lower intelligence scores in FCD type I (eg, severe mental retardation with IQ less than 35 was encountered in 27% of FCD type II compared with 55% of FCD type I children; 33% of FCD type II but only 4% of FCD type I subjects had low/average intelligence .[32]

Seizure type and EEG variables

The main seizure semiology in our patients was complex partial seizure type and was seen in almost all types of FCD. In 8 patients of type II FCD , we observed simple motor seizures and none of the patients of type I had partial motor seizures. Another interesting observation in our study was the occurrence of epilepsia partialis continua and status epilepticus in 3(9%) and 4 (12%) patients respectively. In epilepsia partialis continua, 2 were of type IIB and one of type IIA of which one patient had parietal FCD and 2 had frontoparietal FCD. In status epilepticus, 2 patients had type IIB and one each of IIA and IB was

present. Location wise one patient had multilobar, one each had frontoparietal , temporooccipital and temporoparietal.

In the series by Fauser et al [29], status epilepticus occurred in 15.8% of patients. This number is much lower as compared with a series reported by Palmini et al [10] in which 30% of the patients had partial motor or generalized convulsive status epilepticus. The lower incidence in our series may be due to the location and extension of FCD. Partial motor status epilepticus was mainly reported in patients with parietal FCD, and generalized convulsive status epilepticus seemed to be associated with extensive structural abnormalities involving more than one lobe. In the series reported by Palmini at al [10], 90% of the patients presented with multilobar FCD and 40% with central involvement. Thus, not the aetiology of FCD per se but the localization and extension of the lesion seem to be risk factors for status epilepticus and epilepsia partialis continua.

Predictors of outcome

We obtained 70% of seizure-free patients. This compares favorably with outcome of patients with hippocampal sclerosis[43] and low-grade neoplasms,[44] situations in which the surgical outcome has been viewed optimistically. Recent series suggest that 50—70% seizure-free outcome may be the best obtained result.[45,46]

We observed a significant negative correlation between the age of seizure onset and preoperative seizure score implying that younger the age, more is the seizure severity and seizure score. Another interesting observation was mean age of both type IIA and IIB was 3.5 and 4.5 respectively and more was seizure score 8.8 and 9 respectively but the number of patients in IA and IB was very small for this comparison. This is in comparison to study by Fauser et al [29] of 120 patients who had observed a mean age of 4.1 and 4.5 in IIA and IIB whereas in IA it was 8.6 and 4.4 in IB but this is in contradiction with recent study by Krsek et al [32] where histopathological subgroups did not differ in mean age at seizure onset, seizure type, seizure frequency, or incidence of status epilepticus. Hence our results support the previous observations that patients with FCD

type II have an earlier age of seizure onset and earlier age of surgical resection.[9]

We also found a significant positive correlation between postoperative seizure score and duration of epilepsy as a delay in surgery will have higher postoperative seizures and hence stressing the importance of early detection of FCD and surgery as that will cause less of mental retardation and neurological comorbidities because of AEDs and epilepsy per se.

There were no significant differences in seizure outcome between patient groups classified according to the parameters for location or topography of lesion, side of the lesion, histopathology of the lesions, and type of resection done for these patients. However, the greatest number of seizure-free patients (86%) belonged to type I FCD. Among the various histopathological types the lowest postoperative seizure frequency occurred in FCD type Ib as there was 100% seizure freedom. But in FCD II there was almost equal seizure freedom in the subtypes. In patients with poor seizure outcome, 90% occurred in FCD type II.

The seizure outcome results of this study are comparable with the outcomes by Fauser and colleagues[30] who found greater proportions of seizure-free patients in histopathologically "milder" forms of cortical malformations. These results may be part of bias as there were many with MTLE with hippocampal sclerosis. On the contrary seizure outcome results by Tassi et al and Widdess-Walsh et al [31] who reported slightly better results in FCD type II than in FCD type I.

The postsurgical outcome related to the histological subtype has only been investigated in few studies before.[23,46,47] Most of these studies agreed that FCD type 2b (with balloon cells) had a favourable outcome, although this subtype is supposed to be associated with clinically and electrocorticographically increased epileptogenicity compared with other subtypes.[48] It is possible that in patients with balloon cells the frequent electrographical spike activity as well as a better demarcation of the lesion in MRI contribute to a good delineation of the affected tissue. In an another study areas with histological characteristics of FCD type 2a were considered to be more epileptogenic than areas with histological characteristics of FCD type I .[26]

In our patients, the group with dual pathology of the temporal lobe had predominantly FCD types IB and IIA and 5 of the 6 patients had predominant temporal lobe lesion and only was one was temporooccipital lobe lesion and all of them had a particularly favourable outcome. Our results are in line with that even in the presence of severe neuronal ectopia in the temporal lobe, with or without associated hippocampal sclerosis, these patients may have a favourable clinical outcome following surgery.[49,50,51] But in a recent study, postsurgical outcome in dual pathology was found inferior to the outcome in other subgroups of focal cortical dysplasia [46]. The observed differences in outcome could be due to either a better outcome only because they are preferentially located in the temporal lobe or because of achieving complete surgical removal of the affected tissue.

Hence we hypothesize that patients with temporal lobe cortical dysplasias (with and without dual pathology) tend to have a better postsurgical outcome than patients with extratemporal cortical dysplasia and secondly also by the histological subtype FCD type 2a which may be histologically more widespread and the demarcation of FCD type 2a in MRI is less clear than in other subtypes or, even in the case of a similar

demarcation, incompleteness of the resection results in higher recurrence rates in FCD type 2a because of a higher epileptogenicity of small amounts of remaining tissue.

Considering the ECoG findings in our study which show that most of the type II FCD patients had rhythmic or continuous or both as compared to type I FCD. In type IIA FCD 70 % had rhythmic and continuous discharges as compared to 63% of type IIB FCD. This is in comparison with the study by Palmini et al [7] wherein approximately two thirds of the patients demonstrated characteristic epileptic discharges, including repetitive electrographic seizure activity, repetitive bursting discharges, and continuous or quasicontinuous rhythmic spiking, hence a conclusion can be made for the high epileptogenicity of type IIA and balloon cell dysplasia in our study but we could not conclude regarding the epileptogenicity of each subgroup separately may be because of small number of patients in each group especially in type I who had more of isolated spikes.

CONCLUSIONS

Although, our study comprised of a small sample group of 33 patients with FCD, however, it is the first comprehensive study on FCD from India. The major conclusions or highlights of the study are:

1) The vast majority of patients in our study had epilepsy onset in the first 16 years of life.

2) The results of our study suggest that seizure onset at an earlier age is associated with a higher preoperative seizure score.

3) There was no significant association with febrile seizures and dual pathology.

4) Patients with dual pathology almost always had temporal lobe epilepsy.

5) Neurological abnormalities mainly hemiparesis, epilepsia partialis continua and status epilepticus were more common in type II FCD than in type I .

6) 78% patients had type II FCD as compared to type I dysplasia of which 45% were had type IIA dysplasia.

7) Most of the type II FCD were localized to extratemporal location most commonly in frontal lobe and type I were commonly seen in temporal lobe.

8) 70% of patients were seizure free after a period of one year followup.

9) An early age of seizure onset or a longer duration of epilepsy or a delay in diagnosing FCD and surgical treatment is associated with a poor outcome of surgery.

10)90% of patients with a poor outcome belonged to type II FCD and suggesting the inherent epileptogenicity of type II FCD.

10) There were no significant differences in seizure outcome between patient groups classified according to the parameters for location or topography of lesion, side of the lesion, histopathology of the lesions,

type of resection and ECoG patterns. However, the results of statistical comparisons need to be validated in a larger sample size.

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	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
HP		5	F	0.75	5	4.25	9	2	2 1,5,3		2	F	1	1	2	F	1	sf	2	IIB	N	6
HK		25	M	0.3	25	25	10	2	2	1	2	TPO	2	1	1	large ML	0	nsf	5	IIB	N	1
RV		14	M	0.15	14	14	9	2	1 1,F,Rt		1	F	2	1	2	F	1	nsf	9	IIA	N	4
BN		30	M	6	30	24	8	2	1 1,F,3		1	F	2	1	2	F	1	sf	2	IIB	N	6
SG		7	M	1.5	7	5.5	8	2	2 1,1,2		2	F	1	1	2	F	0	sf	2	IIB	Y	2
TS		23	M	4	23	19	8	2,3	2 1,1,2		2	F	1	1	2	F	0	nsf	5	IIA	N	2
AM		9	M	1.5	9	7.5	10	2	1 1,1,2		1	FP	1	1	2	FP	1	sf	2	IIB	N	1
SK		20	F	8	21	13	9	2	1 1,1,1		1	F	1	1	2	F	0	nsf	5	IIB	N	4
ML		18	F	10	18	8	10	2	2 1,2,2		2	FP	2	1	2	CP	0	sf	2	IIA	N	4
SR		14	F	0.66	16	15	8	2,3	2 1,1,2		2	F	1	2	2	F	0	sf	2	IIB	Y	6
RG		21	M	12	21	9	9	1,2,3	2 1,1,2		2	F	1	1	2	F	1	nsf	5	IIA	N	3
NV		26	M	4	26	22	11	1,2	1 1,1,2		1	P	1	1	2	P	0	sf	2	IIB	N	3
PR		21	F	3.5	21	17.5	9	2,3	2 1,1,2		2	F	2	1	2	F	0	nsf	4	IIA	N	6
YA		15	M	0.1	15	15	7	2,3	1 1,1,1		1	F	2	1	2	C	0	sf	2	IIA	N	5
GS		16	M	10	14	4	7	2	1 1,1,2,3		1	PO	1	1	2	P	1	nsf	7	IIB	N	2
AB		3	M	0.75	3	2.25	11	2	1 1,1,1		1	FT	1	1	2	FT	1	sf	2	II A	N	1
RF		14	M	6	14	8	8	2	1 1,1		1	F	1	1	2	F	1	nsf	3	II B	N	1
SJ		7	F	3	7	4	8	1	1 1,1		1	F	np	2	2	F	0	sf	2	IIA	Y	0
AK		44	M	3	44	41	9	2	1 1,1,1		1	F	1	1	2	FL	0	nsf	7	II A	N	1
AKA		29	M	15	29	14	8	2	1 1,1,2,3		1	TO	1	1	2	TP	1	sf	2	IIA	Y	1
SVG		27	M	11	27	16	8	2	1 1,1,2,3		1	PO	1	1	1	large ML	1	sf	2	IIA	Y	2
SS		10	M	5	10	5	10	2	1 1,1,1		1	TO	1	1	2	TO	1	sf	2	IB	N	2
JB		17	M	15.5	18	2.5	8	2	1 1,1,T		1	T	1	1	AH	T	1	sf	2	IA	Y	2
FZ		18	M	1	18	17	8	2	1 1,1,T		1	T	0	1	ATL	T	1	nsf	4	IA	N	4
SUS		25	M	12	25	13	7	2	1 1,1,T		1	T	1	1	ATL	T	1	sf	1	IB	Y	1
AR		7	M	0.25	7	6.75	9	2	1 1,1,T		1	TP	1	1	1	T	0	sf	2	IIA	Y	5
RS		1	F	0.25	1	0.75	12	2	2 1,2,1		2	FPT	2	1	Hsctomy	large ML	1	sf	2	IIB	N	1
SB		5.5	F	0.5	6	5.5	8	2	2 2,1,2		2	T	1	1	ATL	T	0	sf	1	IB	Y	5
AT		40	M	33	40	7	7	2	1 1,1,T		1	T	1	1	2	T	1	sf	2	IB	Y	1
SY		21	F	10	21	11	8	2	2 2,1,T		2	T	1	2	ATL	T	1	sf	1	IB	Y	4
AN		17	M	0.1	27	27	10	1	1 1,1,FP		1	FP	1	1	Hsctmy	large ML	1	sf	2	IIa	N	2
NM		9	F	0.1	9	9	10	2	1 1,1,3		1	PO	1	1	2	largeML	0	sf	2	IIA	N	1
SDVR		27	F	5	30	25	8	2	1 1,1,1		1	F	1	1	2	F	0	sf	2	IIA	N	1

Key to Appendix I

1:Initials
2: age(yrs)
3: sex
4: Age of sz onset(yrs)
5: age at surgery(yrs)
6: duration of epilepsy(yrs)
7: Seizure score preoperative
8: seizure type
9: EEG side
10: pre op EEG
11: MRI data side
12: MRI data location
13:Neuropsychology
14: ECoG
15: Surgery
16: Site
17:post op outcome
18: mapping IO/EO
19: post operative seizure score
20: pathology
21:AEDs stopped
22: FUP(yrs)

PROFORMA

I.MEDICALLY REFRACTORY EPILEPSY ASSOCIATED WITH FOCAL CORTICAL DYSPLASIA: CLINICAL, ELECTROPHYSIOLOGIC, IMAGING AND PATHOLOGIC CHARACTERISTICS AND POST-OPERATIVE OUTCOME

R.MADHAVAN NAYAR CENTER FOR COMPREHENSIVE EPILEPSY CARE

SREE CHITRA TIRUNAL FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM.

Hosp No: ..... Category :.....

Name : .....

Address : .....

.....

.....

.....

Tele#: .....

Date first seen in the Epilepsy clinic: .....

Date of epilepsy surgery: .....

Seizure Characteristics

Age at onset: .....
(YY/MM)

Seizure type(s) ever had:

1. SPS .....
2. CPS .....
3. Sec GTCS .....
4. Pri GTCS .....
5. Myoclonic .....
6. Absence .....

Predominant seizure type: .....
(number as above)

Siezure frequency during one year
prior to surgery:
Per day .....
Per month .....
Per week .....
Per day .....

Present ENGEL score .....

Date of last seizure: .....
(MM/DD/YY)

H/o Status epilepticus: (1=yes, 0=no):.....

Seizure score in the one year: .....
prior to surgery:

Seizure freedom>1 year: .....
anytime from onset to surgery
(1=yes, 0=no)

Antecedents (1=yes, 0=no)

Birth asphyxia .....
Febrile seizures .....
Head injury .....
Encephalitis .....
Meningitis .....

Status epilepticus .....
(preceding epilepsy onset)

Any others (specify) .....

Neurologic localizing signs (1=yes, 0= no)

Present (1), absent (0) .....
Mono/hemiplegia .....
Hemianesthesia .....
Hemiatrophy .....
Hemianopia .....
Others .....
.....

Preoperative EEG data

Scalp EEG

IEDs:	Localized	……..
(1=yes, 0= no)	Generalized	……..
	None	……..
Delta:	Localized	……..
(1=yes, 0= no)	Generalized	……..
	None	……..

Localization:……..
(1= Frontal, 2= Parietal, 3= Occipital, 4= SSMA, 5= no localization)

Right (1), left (2), bilat:ind: (3) ……

Temp. IEDs ……..
(1=present, 0= absent)

Right (1), left (2), bitemporal (3) ……..

Ictal Scalp EEG-video data: ……..

Seizure onset localized ……..
(1=yes, 0= no)

Localization: ……..

(1= Frontal, 2= Parietal, 3= Occipital, 4= SSMA)

MRI data

Focal lesion ……
(1=present, 0= absent)

Localization ……..
(number as above)
Right (1), left (2)

Lobar localization (Frontal(F),Parietal(P),Temporal(T),Occipital(O) ……..

Additional lesion (s) .....
(1=present, 0= absent)

MRI diagnosis: (in detail) .....
.....
.....

Neuropsychologic evaluation

Performed (1), not (0) .....
Localization (1), no (0) .....
Concordant (1), discordant (0).....
FSIQ.....

Wada test

Done (1), not done (0).....

Language localization

Right .....
Left .....
Bilateral .....
Ipsilateral .....
Side to surgery

Memory localization

Ipsilateral .....
Side to surgery
Contralateral .....

SPECT data

SPECT done .....
(1=yes, 0= no)
Ictal SPECT only .....
(1=yes, 0= no)
Ictal SPECT .....
(Lo-localising,La-lateralising only,Flo-false localizing,Fla-false lateralizing,
N-non-contributory)
Interictal SPECT .....
(classification as above)

SISCOM .....
(1=yes, 0= no)

Localization .....
(1=present, 0= absent, 2= uncertain)

Site of localization .....
(1= Frontal, 2= Parietal, 3= Occipital, 4= SSMA)
Right (1)/Left (2)

Additional temporal localization.....
(1= present, 0= absent)

Functional MRI .....
(1=done, 0=not done)

fMRI.....(details)

Extraoperative mapping .....
(1= done, 0= not done)
Electrode used (1= yes, 0= no)

Subd. Strip .....
Subd. Grid .....
Depth .....

Result .....
.....
.....

Intracranial EEG-video data

Performed (1), not performed (2) .....

Type (s) of electrode used
Subd. Strip .....
Subd. Grid .....
Depth .....

Ictal Onset .....
(1= localized, 0= not localized)

Localization .....
(Number as above)

Right (1), left (2).....

EcoG performed .....
(1= yes, 0= no)

Acute ECoG .....
(IEDs (1=present, 0=absent)
(3=localizing,4=non-localizing)

Postresection .....
(IEDs (1= present, 0= absent)

Other investigations
(1=done, 0=no)

MRS.....
PET.....
Others.....
.....
.....

Surgery
Date:...../...../.....
(MM/DD/YY)

Type .....
(1= lobar resection, 2= lesionectomy, 3= stereotaxic lesionectomy)

Side .....
(1= right, 2= left)

Site (s) of surgery (1= yes, 0= no)

Frontal lobectomy .....
Anterior frontal .....
Convexity frontal .....
Parasagittal frontal .....
Frontal plus any others .....
Central (sensori-motor) region.....
Parietal .....
Occipital .....
Large Multilobar .....

Describe anatomical area resected .....

.....
.....
.....

MST (1=yes, 0=no)

Performed .....
MST only .....
Resection + MST .....

Postoperative complications
(1= yes, 0=no)

Mono/hemiparesis .....
Hemihypothesia .....
Infection .....
Hematoma .....
Cranial nerve palsy .....
Visual deficit .....

Intraoperative mapping (1= done, 0= not done)

Electrode used (1=yes, 0= no)
Subd. Strip .....
Subd. Grid .....
Depth .....

Details .....
.....
.....

Seizure Outcome

Seizure< 24 P.O .....
(1= yes, 0= no)
Number .....

Seizure 24 h-7th day .....
(1= yes, 0= no)
Number .....

7 days- 3 months .....
(1= yes, 0= no)

Number .....

3 mon-1 year .....
(1= yes, 0= no)
Number

Seizure score

First P.O year .....
Second year .....
Third year .....
Fourth year .....
Fifth year .....
Last year .....

Date of first P.O seizure ...../...../.....
(MM/DD/YY)

Date of second P.O seizure ...../...../.....
(MM/DD/YY)

Predominant type of P.O seizure

Habitual (1=yes,0=no).....
Aura only .....
SPS .....
CPS .....
Sec. generalized .....

Disabling .....
(1= yes, 0= no)

Patient perceived improvement
(1= yes, 0= no) in seizures .....

Occupational outcome .....

1= preop umemployed, postop employed
2= employment status same pre & postop
3= underemployed postop
4= better employment after surgery
5= pre & post unemployed
6= preop employed, postop unemployed

Pathology

Specify (type of dysplasia) .....
Associated lesions .....
Other details .....

Postoperative MRI .....
(1= done, 2= not done)

Residual lesion .....
(1= present, 2= none)

Repeat surgery .....
(1= yes, 0= no)

Date for first surgery .....
(MM/DD/YY)

Date of second surgery.....
(MM/DD/YY)

Postoperative EEGs: .....
(1= IED present, 0= absent, 2= not done)

7-10th day .....
3rd month .....
1 year .....

Date of death ...../...../.....
(MM/DD/YY)

Cause of death (1= yes, 0= no)

Surgery .....
Seizure .....
Unknown .....
Unrelated .....
Specify..... .....

Cost incurred for

VEEG+MRI.....
Surgery.....
Invasive monitoring.....
Others:SPECT.....
fMRI.....
Any others:.....

QOLIE outcome (QOLIE 31 score) .....