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Early resective surgery causes favorable seizure outcome in malformations of cortical development

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ABSTRACT

Purpose: We analyzed consecutive cases of a large cohort of the spectrum of malformations of cortical development (MCDs) including focal cortical dysplasias (FCDs) who underwent presurgical evaluation through our epilepsy program from January 2000–December 2010. We analyzed factors predicting surgical candidacy, predictors of seizure outcome and reasons for deferring surgery.
Methods: 148 patients with MCD underwent detailed presurgical evaluation and 69 were operated. MCD was diagnosed based on characteristic findings in MRI and re-confirmation by histopathology in operated patients. Post-operative seizure outcome of non-operated and operated patients were assessed every 3 and 12 months and yearly intervals. Multivariate analysis and backward step-wise logistic regression analyzed factors predicting seizure outcome. Kaplan-Meier analysis predicted seizure-free survival rates.
Results: 66.67% patients were seizure-free and aura-free at last follow-up. On multivariate logistic regression, the predictors of seizure freedom in operated MCDs were completeness of resection (odds ratio 8.2; 95% CI 1.43–64.96, $p = 0.01$), shorter duration of epilepsy (odds ratio 1.19, 95% CI 1.02–1.39, $p = 0.02$), and absence of spikes in post-operative EEG at one year (odds ratio 4.2; 95% CI 2.52–16.6; $p < 0.002$). In FCD sub-group, shorter duration of epilepsy (11.1 versus 16.1 years, $p = 0.03$), absence of secondary generalized seizures ($p = 0.05$), absence of spikes in post-operative EEG on seventh day ($p = 0.009$) and one year ($p = 0.002$) were associated with favorable seizure outcome.
Conclusion: Majority of patients with MCD and refractory epilepsy when operated early remains seizure-free. Shorter duration of epilepsy is the single most important pre-operative variable and absence of spikes in post-operative EEG, predicts a long-term favorable seizure outcome.

1. Introduction

Malformations of cortical development (MCD) comprise a variety of developmental abnormalities of brain which are responsible for drug-resistant epilepsy in pediatric and adult patients. Focal cortical dysplasia (FCD), heterotopia, polymicrogyria, schizencephaly, lissencephaly, hemimegalencephaly and dysembryoplastic neuroepithelial tumor (DNET) are the different abnormalities which comprise the spectrum of MCD. The epileptogenic potential of these abnormalities vary widely, some of them like FCD, heterotopia, hemimegalencephaly and DNET are considered to be highly epileptogenic. Although they come under the common rubric of MCD, they remain quite heterogeneous in their clinical manifestations and propensity to cause seizures. Many classification schemes have been devised to elucidate their clinical, pathological and radiologic diversities (Palmini et al., 2004; Barkovich et al., 2005). The seizure outcome following surgery is variable with seizure-free rates in 30–90% of MCD/FCD in various series (Cohen-Gadol et al., 2004; Kral et al., 2003; Fauser and Schulze-Bonhage, 2006). Majority looked into FCDs alone since they comprise the vast majority of MCDs presenting as drug-resistant seizures and probably because the other MCDs are more diffuse and seldom undergo surgical evaluation.

We studied consecutive cases of a large cohort of the whole spectrum of MCDs who underwent presurgical evaluation through our comprehensive epilepsy care program for drug-resistant seizures from January 2000–December 2010. We sub-divided them into those who underwent surgery and those who were deferred surgical candidacy. We analyzed the various clinical characteristics,preoperative magnetic resonance imaging (MRI)

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findings,electrophysiological features,electrocorticographic findings (ECoG), pathological features, seizure outcome and predictors at last follow-up or at the end of two years whichever is later. By doing so, we attempted to compare and contrast the different subtypes of MCD and their seizure outcome, considering that they all have a common pathophysiological basis of origin. Also, we looked into the various factors which caused surgical deferral in these patients which is seldom analyzed critically.

2. Patients and methods

2.1. Patient selection

Between January 2000 and December 2010,148 patients underwent detailed presurgical evaluation for epilepsy caused by MCD. MCD was diagnosed depending on the characteristic findings in MRI and in those who were operated by a further confirmation by histopathology. Tuberous sclerosis was excluded since it is now considered a separate entity. The details of our pre-surgical evaluation protocol which includes clinical evaluation, optimum 1.5T magnetic resolution imaging (Signa, Milwaukee, USA), interictal scalp electroencephalography (EEG), video-EEG monitoring with scalp and/or sphenoidal or invasive electrodes, single photon emission computed tomography (SPECT) and positron emission tomography (PET) and neuropsychological assessment has been described previously (Chaudhry et al., 2010). An intracarotid amobarbital procedure and/or functional MRI (fMRI) was performed in selected patients to lateralize motor and language functions and/or to evaluate memory reserve. The Institutional Ethics Committee approved the study.

2.2. MRI data

All the MRI films were reviewed independently by Neuroradiologists involved in the study (BT and CK) to delineate the site, size and extent of MCD, contrast enhancement if any and associated hippocampal atrophy and sclerosis (dual pathology). MRI abnormalities typical for cortical malformations were identified and analyzed blindly masking clinical features and histopathology data into: single or multiple; extent of abnormality (lobar, sublobar, multilobar, hemispheric and bilateral), blurring of the gray/white junction, *trans*-mantle sign, white and gray matter signal abnormalities in fluid attenuated inversion recovery sequences (FLAIR) and T2 weighted (T2WI) and proton density images, cortical thickening, abnormal sulcation, heterotopia, polymicrogyria and associated hippocampal changes. In all the cases done after 2008, we utilized diffusion tensor imaging tractography (DTIT) to map out the white matter tracts in close proximity to the MCD to avoid the risk of post-operative deficits and also a special MRI sequence called 3-D FLAIR to enhance the detection of occult lesions (Radhakrishnan et al., 2011; Saini et al., 2010).

In non-operated patients, we adopted the classification of MCD by Barkovich et al., where the neuroimaging features are relied to clinch the diagnosis (Barkovich et al., 2005). We divided the MCD into four groups as follows:

***Class I*:** MCD due to abnormal glial and neuronal proliferation-comprising FCD II and hemimegalencephaly. FCD II was diagnosed by T2 hyper intensity in sub cortical white matter, with extension to the superolateral wall of the lateral ventricle ("trans mantle sign"). Hemimegalencephaly is enlargement of part or all of the cerebral hemisphere with associated cortical thickening, abnormal sulcal pattern and abnormal signal intensity in the white matter between the cortex and the lateral ventricle.

***Class II*:** MCD due to abnormal neuronal migration-comprising gray matter heterotopia, where nodular masses of gray matter intensity on T1 and T2 weighted images occur between the lateral ventricle and the cerebral cortex without contrast enhancement or edema.

***Class III*:** MCD due to abnormal cortical organization-it includes FCDI, FCD III and polymicrogyria. FCD I is diagnosed if abnormal signal intensity is seen in the white matter resulting in a lack of contrast between the cortex and the white matter in FLAIR and T2 images.FCD III, if the former is associated with focal white matter atrophy and cortical thinning, hippocampal sclerosis, or a vascular malformation. Polymicrogyria, if multiple microgyri are present in the cortex or if the cortex appeared thickened (4–5 mm) with associated irregularity of the cortical-white matter interface.

***Class IV*:** MCD not otherwise classified.

2.3. Interictal and ictal EEG data

Standard 10–20 system of extra cranial 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 s every 15 min. Ictal and interictal EEG were analyzed by two trained epileptologists involved in the study (AR & RM). We classified IEDs as concordant, if 75% or more corresponded to the site of seizure origin (based on seizure semiology, MRI abnormality, and/or area resected) and discordant (contra lateral, bilateral independent, multifocal or generalized). The scalp recorded ictal EEG activity was categorized as localized to the presumed lobe of seizure origin, lateralized to the presumed hemisphere of seizure origin, and diffuse (uncertain hemispheric origin).

2.4. Treatment strategy

Invasive recordings with chronically implanted electrodes (depth, strip and grids) were used in selective cases when 1) inconclusive or discordant results were obtained after non-invasive EEG recording 2) high resolution MRI failed to clearly distinguish lesion margins from surrounding normal appearing brain tissue and 3) when the lesion to be resected and/or the presumed epileptogenic zone is at or close to the eloquent cortex (motor,sensory, language and visual cortex), thus requiring electrical stimulation and mapping.

Surgical strategies included lesionectomy, lobectomy, multilobar resection or hemispherotomy whenever indicated and/or standard anterior temporal lobectomy with amygdalohippocampectomy (in cases of dual pathology). All surgeries were performed under general anesthesia with the assistance of the electrocorticography (ECoG). We defined completeness of resection as complete removal of the ictal onset zone and/or the lesion utilizing a post-operative MRI.

Completeness of resection has been variably defined as resection of MRI visible lesion(s), area(s) of ictal onset, areas of persistent pathologic delta slowing, acute and chronic ECoG guided resection, tailoring of resection based on neuropathological examination revealing no dysplastic tissue at the resection borders, surgeon's impression after resection etc. (Cohen-Gadol et al., 2004; Francione et al., 2003; Kim et al., 2009; Alexandre et al., 2006). Each center follows their own protocol for defining completeness of resection and no firm guidelines have been established.