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Comparison of clinical features and surgical outcome in focal cortical dysplasia type 1 and type 2

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ABSTRACT

Introduction: Recent ILAE classification defined focal cortical dysplasia (FCD) patients with accompanying epileptic lesions as a separate group. We investigated data of patients with sole FCD lesions regarding long-term seizure outcome and different characteristics of FCD type 1 and type 2 patients.
Methods: Eighty children and adult patients underwent surgery for FCD were included to the analysis of factors differentiating FCD type 1 and type 2 groups and their effect on long-term outcome.
Results: FCD type 2 patients had earlier epilepsy onset (8.1 vs. 6.1 years. p = 0.019) and underwent surgery younger than type 1 (18.2 vs. 23.7 years. p = 0.034). FCD type 2 patients were more prominently MR positive (77.8% vs. 53.8%. p = 0.029), which increased within FCD type 2 group as patients become younger (p = 0.028). FCD Type 1 lesions showed mostly multilobar extension and FCD type 2 mostly located in frontal lobe. Seizure freedom was achieved in 65.4% of FCD type 1 patients and 70.4% of FCD type 2 patients. Seven patients had permanent de novo neurological deficits. Mean follow-up time was 5.5 years (Range: 1–11 years).
Conclusion: Surgical intervention in carefully selected patients may facilitate favorable seizure outcome leading to better quality of life. FCD type 1 and type 2 groups present with evident differences, which may promote medical and surgical management of these pathologies.

1. Introduction

Focal cortical dysplasia (FCD), first described by Taylor et al. in 1971, was initially considered as a rare variant of malformations of cortical development. (Taylor et al., 1971) However, with the emergence of modern imaging and histopathological examination techniques, rate of FCD in epileptic population was found to be higher than first expected. (Becker et al., 2006; Harvey et al., 2008) In addition to that, patient series confirmed that FCD, rather than being a uniform disease, consists of a wide spectrum of patients with clinical and radiological presentations ranging from mild epileptic seizures starting at adulthood with suspected signs of a lesion on magnetic resonance imaging (MRI) to a more severe epileptic seizures presenting in childhood with evident MRI signs. (Krsek et al., 2009b; Lerner et al., 2009) Moreover, FCD may be accompanied with other epileptogenic pathologies such as hippocampal sclerosis and glial or glioneuronal tumors.

Several classification systems based on radiological and histopathological characteristics of FCD have been proposed. (Barkovich et al., 2005; Blumcke et al., 2011; Palmini et al., 2004) Most recent classification system proposed by ILAE task force stated that patients with an isolated FCD lesions will be categorized under ILAE Type 1 or Type 2 regarding their histopathological features, and patients with accompanying epileptic lesions will be grouped as ILAE Type 3, whether histopathological FCD features of that individual is concordant with Type 1 or Type 2. (Blumcke et al., 2011)

Evaluation of postsurgical seizure outcome and other features of FCD population according to previously introduced classification systems have been widely discussed in the literature. (Fauser et al., 2004; Kim et al., 2011; Kral et al., 2007; Krsek et al., 2009a; Mathern, 2009; Phi et al., 2010; Rowland et al., 2012; Sarkis et al., 2010; Sisodiya et al., 2009; Urbach et al., 2002; Widdess-Walsh et al., 2007; Widdess-Walsh et al., 2005) However only a few studies that focused on the use of ILAE classification has been published in the current literature. (Cossu et al., 2013; Fauser et al., 2013; Leach et al., 2014; Martinoni et al., 2015; Muhlebner et al., 2012; Wu et al., 2014)

In this study, seizure freedom rates of surgically treated 80 patients

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diagnosed with isolated FCD lesions (FCD Type 1 and Type 2) were examined. Different aspects of the patient cohort for each FCD type were analyzed and compared to each other to determine prognostic factors for postoperative epilepsy outcome.

2. Patients and method

2.1. Patient population

Patient cohort retrospectively studied in this study consists of both pediatric and adult patients with histopathologically proven FCD only, who underwent surgical treatment for the drug-resistant epilepsy at Istanbul University Cerrahpasa Faculty of Medicine, Turkey. Patients with tuberous sclerosis complex, polymicrogyria, lisencephaly, hemimegalencephaly and other malformations of cortical development were excluded from the present study. In addition to that, patients with concomitant epileptic lesions such as hippocampal sclerosis and glial or glioneuronal tumors, namely FCD Type 3, were also excluded, allowing our analysis to be limited only with FCD Type 1 and 2 patients.

Eighty consecutive patients operated and followed up between 2006 and 2017 with a minimum follow-up time of 1 year were included. There were 43 adults and 37 (< 18) children. Twenty-six patients were histopathologically diagnosed as ILAE Type 1 FCD and 54 patients as ILAE Type 2 FCD. Number of patients in FCD subgroups were as follows: 5 patients with Type 1 a, 20 patients with Type 1 b, 1 patient with Type 1 c, 24 patients with Type 2 a, and 30 patients with Type 2 b.

All patients reported in present article have focal onset seizures (with or without impaired awareness and motor or nonmotor onset) according to recent ILAE Classification of Seizure Types. (Fisher et al., 2017)

Parameters studied were age at surgery, duration of epilepsy, MRI and positron emission tomography (PET) findings, location of the lesion, type of surgery, types of FCD, presence of invasive monitoring, emergence of postoperative new neurological deficit, postoperative outcome according to Engel's score, and follow-up duration. These data were collected by examining databases of departments, patient hospital charts, at outpatient visits, or through phone calls.

2.2. Presurgical evaluation

All patients underwent interictal and ictal video-EEG monitoring. Concomitantly, a high-resolution 1.5 T MRI scan (years 2006–2009) or a 3 T MRI scan (years 2010-present) was obtained for each patient with following sequences: 3D T1 weighted sagittal images of 1 mm slice thickness; T1W coronal, 1 mm slice thickness; T2W axial and coronal, 2 mm slice thickness; fluid-attenuated inversion recovery (FLAIR) axial and coronal, 2 mm slice thickness. MRI scans were evaluated by the members of the epilepsy surgery team as well as with an experienced neuroradiologist to detect signal changes in gray and/or white matter, abnormalities in gyral/sulcal pattern, gray-white matter junction blurring, increased cortical thickness, reduction of white matter volume, transmantle sign, and hippocampal atrophy. Patients with no proof of these signs were further examined with a 3T MRI before registered as "MR negative". In this instance, we registered 56 "MR positive (+)" patients and 24 "MR negative (−)" patients. Additionally, 43 patients were tested with interictal 18FDG-PET to localize the lesion and strengthen the hypothesis for the epileptic network. MR negative patients are the subject of another paper under preparation.

Before resective surgery, 41 patients underwent invasive monitoring with subdural electrodes, depth electrodes, or stereo EEG.

All patients underwent neuropsychological evaluation and some had psychiatric interview when needed.

2.3. Neuropathological analysis

All paraffin embedded specimens were examined by two experienced neuropathologists. Brain tissue was fixed overnight in 10% buffered formalin, orientated and cut perpendicular to the cortical surface at 5-mm-thick sections. Following routine paraffin embedding (Leica EG1150, Leica Microsystems, Nussloch, Germany), 4-µm-thin sections were stained with Hematoxylin-eosin (H & E). In addition to the review of H & E-stained material, representative formalin-fixed, paraffin-embedded tissue blocs were selected for immunohistochemical procedures. Immunohistochemical reactions were performed using an automated staining apparatus and the streptavidin-biotin method (Ventana, Strasbourg, France) and 3,3-diaminobenzidine as chromogen as well as Hematoxylin counterstaining. Antibodies used in this study were directed either against Neu-N (monoclonal antibody, clone A60, diluted 1:500,) or anti-neurofilament antibody (SMI-211 ab24575) (diluted 1:1500; ABCAM). ILAE classification for FCD was used for evaluation (Blumcke et al., 2011). Pathological specimens evaluated before 2011 are re-evaluated according to current classification. FCD Type 1 refers to isolated forms of FCD, characterized by an abnormal cortical layering. FCD Type 1 a is characterized by abnormal radial migration, as well as neuronal maturation with immature small diameter neurons organized in microcolumns. FCD Type 1 b is characterized by abnormal cortical layering affecting the 6-layered tangential organization of the neocortex and including a large spectrum of histopathological features ranging from alterations of the entire neocortical architecture to a more subtle abnormal layering involving specific layers, such as layer 2 or 4 or both. FCD Type 1 c refers to isolated lesions characterized by abnormal cortical layering affecting both radial and tangential cortical organization. FCD Type II refers to an isolated malformation characterized by disrupted cortical lamination and cytological abnormalities and includes two subtypes, FCD Type 2 a (with dysmorphic neurons, but without balloon cells) and FCD Type 2 b (with dysmorphic neurons and balloon cells).

2.4. Postoperative follow-up

Patients were evaluated initially at 3 months postoperatively and then every 6 months at the epilepsy outpatient clinic. Postoperative epilepsy outcome was assessed according to Engel's classification. (Engel and Rasmussen, 1993)

2.5. Statistical analysis

Two patient groups consisting of FCD type 1 and type 2 patients were formed. Data regarding age, gender, age at epilepsy onset, duration of epilepsy, age at operation, being treated in pediatric or adult age, presence of lesion in MRI and PET, concordance of MRI and PET number of operations, resection site, type of resection, invasive monitoring, postoperative new neurological deficit, Engel score at last visit were compared between these two groups.

Categorical analysis was performed using chi-square test for qualitative data with Bonferroni corrections. Other quantitative comparisons were done using Wilcoxon test for dependent variables, and Mann-Whitney *U* test if two independent variables are present and Kruskal-Wallis test if more than two independent variables are present.

Prognosis according to Engel classification was assessed as "Engel 1 vs Engel 2–3-4" or "Engel 1–2 (favorable outcome) vs Engel 3–4 (unfavorable outcome)". Influence of histopathological subtypes of FCD and age at operation (children vs. adult), on seizure outcome were analyzed by logistic regression test.

Data analyses were performed using the IBM SPSS 22 software statistical package (SPSS Inc., Chicago, IL, USA). The significance level was set at 5% ($p < 0.05$).