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Long-term seizure outcome in pediatric patients with focal cortical dysplasia undergoing tailored and standard surgical resections

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ABSTRACT

Purpose: Focal cortical dysplasia (FCD) is the major cause of focal intractable epilepsy in childhood. Here we analyze the factors influencing the success of surgical treatment in a large cohort of children with histologically ascertained FCD.

Method: A retrospective study of the effects of FCD type, surgical intervention, and age at surgery in a pediatric cohort.

Results: A total of 113 patients (71 male; mean age at surgery 10.3 years; range 0–18) were analyzed; 45 had undergone lesionectomy, 42 lobectomy, 18 multi-lobectomy, and eight hemispherotomy. Complete seizure control (Engel Ia) was achieved in 56% after two years, 52% at five years, and 50% at last follow-up (18–204 months). Resections were more extensive in younger patients (40% of the surgeries affecting more than one lobe in patients aged nine years or younger vs. 22% in patients older than nine years). While resections were more limited in older children, their long-term outcome tended to be superior (42% seizure freedom in patients aged nine years or younger vs. 56% in patients older than nine years). The outcome in FCD I was not significantly inferior to that in FCD II.

Conclusions: Our data confirm the long-term efficacy of surgery in children with FCD and epilepsy. An earlier age at surgery within this cohort did not predict a better long-term outcome, but it involved less-tailored surgical approaches. The data suggest that in patients with an unclear extent of the dysplastic area, later resections may offer advantages in terms of the precision of surgical-resection planning.

1. Introduction

Focal cortical dysplasia (FCD) is a subgroup of cortical malformations characterized by abnormal regional neuronal migration and differentiation that result in aberrant cortical organization [1]. It is the most common anatomo-pathological feature in patients undergoing epilepsy surgery in childhood [2]. Prevalence figures have been rising over recent years due to improved MRI quality, but, even with the best methodology currently available, the sensitivity and specificity of imaging findings are limited and a diagnosis of FCD requires histological confirmation. Patients with FCD frequently present with a severe form of epilepsy characterized by pharmacoresistance to available antiepileptic drugs (AED) [3,4]. Surgery is considered to be of particular importance in children who—aside from seizures—may suffer from progressive developmental delay and behavioral disorders if their epilepsy is not controlled.

Several classification schemes have been proposed that rely on pathological characteristics. According to Palmini et al. [5], two main

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types of FCD can be histopathologically distinguished: Type I refers to architectural disturbances of cortical lamination (IA without, IB with giant or immature pyramidal neurons outside layer 5); Type II is characterized by dyslamination and the presence of abnormal cell elements (IIA when dysmorphic neurons are present and IIB when eosinophilic balloon cells are also identified). Particularly, giant and dysmorphic neurons are considered responsible for seizure generation in FCD Type II [6–9]. In 2011, the International League Against Epilepsy (ILAE) classified FCDs in a three-tiered system that additionally distinguished whether pathological findings of FCD are isolated or associated with other epileptogenic lesions [10].

Due to the therapeutic challenge that these patients represent, epilepsy surgery has been increasingly used in recent years, with several reports showing the benefits of the surgical treatment in patients with FCD [3,11–14]. The reported postsurgical outcome in FCD patients has, however, often been inferior to that in patients with other etiologies [15,16]. Still, progress in presurgical assessment has improved the outcome of the surgery at increasingly early ages [17,18]. Surgery has been found to be more effective in patients younger than 18 years compared to adults [19] and when performed in centers with extensive experience [20]. Even in patients younger than six months, surgery is considered a safe option [21].

We analyzed possible associations between age at surgery, type of resection, FCD type (classified according to Palmini et al. [5]), and long-term outcomes in one of the largest cohorts of patients with manifestation and surgery during childhood and with histologically confirmed FCD.

2. Methods

2.1. Patient selection

Patients with structural epilepsy due to FCD who were undergoing surgical treatment were identified from electronic charts. The inclusion criteria were: (1) age at surgery younger than 18 years; (2) epilepsy diagnosis confirmed by video-EEG monitoring; (3) surgical treatment at the University Hospital in Freiburg between 1999 and 2015; (4) histological confirmation of FCD based on resected specimens; and (5) clinical follow-up of at least 18 months.

Patients underwent presurgical evaluation, including long-term video-EEG recordings of habitual seizures, at the Epilepsy Centers of Kiel, Heidelberg, Kehl-Kork, and Freiburg and were later referred to the University Hospital of Freiburg for intracranial EEG recordings (if required) and surgical treatment. Individualized surgical approaches were selected depending on patient characteristics, with particular regard to the extension and localization of the lesion as judged by structural and functional investigations.

The data analyzed were: documented age at epilepsy onset, invasive EEG recordings prior to surgery, age at surgical treatment, seizure types and frequencies, disease duration, FCD location, completeness of resection in MR-positive cases (based on the postoperative MRI), postsurgical follow-up, and pharmacological treatment prior to surgery, after surgery, and at last follow-up. Patients gave informed consent to use their data for scientific purposes.

The severity of epilepsy prior to surgery was classified as severe if one of the following factors was present: daily seizures; cognitive stagnation/regression; or presence of bilateral epileptic discharges in more than 50% of the awake recordings or in more than 80% of the sleep recordings. For some statistical analysis, patients were divided into two age groups depending on their age at surgery (either at most 9 years [the middle of the age range] or above) or on their age at epilepsy onset (either younger than two years or above). Additionally, descriptive data are provided by year for interventions and outcomes depending on the age at intervention.

Magnetic-resonance imaging (MRI) was performed with 1.0, 1.5, or 3 T scanners (Siemens Magnetom Vision, Trio or Prisma, Erlangen, Germany). T1-weighted sequences with and without gadolinium-diethylenetriaminepentaacetic acid (DTPA), T2-weighted images, fluid-attenuated inversion recovery (FLAIR) sequences, and MPRAGE (magnetization-prepared rapid gradient echo) sequences were performed. To analyze mesio-temporal structures, axial images with a modified angulation parallel to the long axis of the temporal lobe were acquired. Criteria used for MRI-based FCD detection were gyration anomalies, focal thickenings of the cortex, blurring of the gray-/white-matter junction, and abnormal cortical and subcortical signal intensity.

The surgical resections were classified as follows: tailored resections based not on the anatomical border of lobes but on imaging (lesionectomy) or electrophysiological findings (topectomy); unilobar resection (when the resected area followed one lobe's anatomical border); multilobar resections (when it followed several lobes' anatomical borders); and hemispherotomy (when functional disconnection was employed).

2.2. Histology

The cortical specimens of patients with FCD were classified by the Institute of Neuropathology of the University Hospital of Freiburg according to the Palmini classification [5]. Additionally, information about the presence of other epileptogenic lesions in MRI or histological specimens, i.e., hippocampal sclerosis (dual pathology), was included [11,22,23].

2.3. Postoperative outcome

The postoperative seizure outcome was classified according to Engel: Ia. free of seizures; Ib. auras or seizures with drug withdrawal; II. occasional seizures (< 2 seizures/year or > 90% seizure reduction); III. 90–75% reduction of seizure frequency; IV. < 75% reduction in seizure frequency [24]; and according to Wieser: 1. free of seizures and auras; 2. isolated auras; 3. 1–3 days with seizures per year; 4. at least four days with seizures per year or ≥50% seizure reduction; 5. < 50% seizure reduction; 6. > 100% seizure increase in comparison to preoperative frequencies [25], as assessed at follow-up times evaluated twice yearly during the first two years and annually thereafter. For those patients who underwent surgery twice, only the last surgery was considered for outcome analysis.

2.4. Statistical analysis

Statistical analysis was done with IBM SPSS Statistics 23, MS Excel 2010, and R version 3.2.5. P-values were calculated by the chi-square test, Fisher's exact test, and Kruskal–Wallis test. All tests were two tailed, with the threshold for significance set at $p < 0.05$. Correlations were quantified using Pearson correlation coefficients (r) and their 95% confidence intervals (95% CI).

3. Results

A total of 113 patients (71 male, 42 female; mean age 10.3 years) met the inclusion criteria and were analyzed. The demographic and clinical data of the patients are summarized in Table 1. The mean age at epilepsy onset was three years (range 0–15; median 1.5).

The duration of the disease prior to first surgery was on average 7.2 years (range 0–18; median 6.2). Fifty-five patients (49%) had a severe manifestation of epilepsy, and 58 patients (51%) had a relatively mild form; severe epilepsy was similar in children with onset of epilepsy during the first two years (30/57 severe) as compared to those with later onset (25/56 severe; differences n.s.). Forty-nine patients (43%) were investigated with invasive EEG. The mean age at surgery was 10.3 years (median 10.7; range: 0–18 years), and 16 patients (14%) underwent re-operation. The age distribution of patients with FCD undergoing resective surgery is shown in Supplementary Fig. 1.