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Single stage epilepsy surgery in children and adolescents with focal cortical dysplasia type II – Prognostic value of the intraoperative electrocorticogram

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HIGHLIGHTS

- Prospective study evaluating the significance of epileptic activity in ECoGs in children.
- Relationship between fast activity recorded in the ECoGs and unfavourable seizure outcomes.
- Fast activity recorded with a relatively simple ECoG-equipment might be an alternative to high-frequency oscillations.

ABSTRACT

Objective: To evaluate prospectively the informative/prognostic value of epileptic discharges in the post-resection ECoGs of children with drug-resistant epilepsies and Focal Cortical Dysplasia type II (FCD-II).
Methods: Included were consecutive patients with focal epilepsies and suspected FCD-II who were planned for single-stage epilepsy surgery based on non-invasive presurgical evaluation results. Intraoperative ECoGs were recorded using a 32-channel system with strip- and/or grid-electrodes. Spikes were defined as transients with a mainly negative component and duration of 20–70 ms. Fast activity was defined as rhythmic bursts of polyspikes >13 Hz. All ECoGs were analysed visually. The significance of both spikes and fast activity in the post-resection ECoG for seizure outcomes 24 months after surgery was evaluated.
Results: Data from 18 patients (five girls) were analysed. 10/18 patients (55.6%) showed spikes in their post-resection ECoGs, five of them showed additional fast activity. 24 months after surgery, 12/18 patients (66.7%) were seizure-free. There was a significant correlation between unfavorable seizure outcomes and fast activity in the post-resection ECoGs ($p = 0.009$), whereas spikes alone were not predictive ($p = 0.502$).
Conclusion: Even when recorded with non-sophisticated techniques, presence of fast activity in post-resection ECoGs might be a valid negative outcome-predictor after surgery in paediatric patients with FCD-II associated drug-resistant epilepsies.
Significance: Fast activity recorded with a relatively simple ECoG equipment seems also to have prognostic significance and by this might be an alternative to HFOs recorded with highly sophisticated and expensive technologies.

1. Introduction

With up to 80% of well-selected patients becoming seizure-free, epilepsy surgery has proved to be a successful therapeutic option

Abbreviations: ECoG, electrocorticography; FCD, focal cortical dysplasia.

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for children and adolescents with drug-resistant epilepsies (Bittar et al., 2002; Dorfer et al., 2013; Gröppel et al., 2015; Jenny et al., 2016). However, seizure freedom after surgery depends on the complete resection/disconnection of the epileptogenic zone (Muthaffar et al., 2017; Rosenow and Luders, 2001). Currently, none of the available diagnostic tests applied during pre-surgical evaluation permit direct measurement of the epileptogenic zone. Therefore, a variety of techniques have to be used to define the symptomatic-, irritative-, ictal onset-, and functional deficit zones as well as the epileptic lesion each of which is a more or less precise indicator/surrogate marker of the location and extent of the epileptogenic zone (Rosenow and Luders, 2001). Despite tremendous recent technical innovations there are still significant limitations when evaluating paediatric epilepsy patients: MRI which has become the method of choice in detecting and defining epileptogenic lesions is often unable to delineate their exact boarders and results remain subtle or diffuse (Widdess-Walsh et al., 2006). This holds especially for infants and very young children in whom myelination is still in progress. Further, the epileptic zone does not always overlap with the epileptogenic lesion or is at least larger than expected from the lesion visible on MRI (Rosenow and Luders, 2001). Sophisticated non-invasive techniques that usually help to define the epileptogenic zone in adults (e.g. fMRI, MEG,...) are hampered by the inability of young and/or retarded children to cooperate adequately and the impossibility to perform these investigations under general anaesthesia. Scalp EEG and seizure semiology (defining the irritative, seizure onset and symptomatogenic zones) are often not localizing or even lateralizing, but bilateral or even generalized (Rosenow and Luders, 2001; Wyllie et al., 2007). As a consequence, two-stage epilepsy surgery that relies on invasive recording of seizures from implanted subdural and/or depth electrodes has to be applied frequently and currently is the gold standard when non-invasive preoperative evaluation provides discordant or insufficient information. However, invasive intracranial recording requires at least two surgical procedures, thereby prolonging hospital stay and increasing the risk of (serious) adverse events, especially in infants and young children (Bansal et al., 2017).

Single-stage surgery guided by intraoperative electroencephalography (ECoG) might be a less invasive alternative to delineate the extent of tissue that has to be resected in order to render the patient seizure free (Bansal et al., 2017). These so-called tailoring searches for interictal activity before and after initial resection and can be repeated until no epileptiform abnormalities remain. However, results with respect to the usefulness of this approach to give exact information about the extent of tissue that has to be resected have been discussed controversially (Bansal et al., 2017; Knerlich-Lukoschus et al., 2017; Terra et al., 2014). Therefore, many neurosurgeons are still reluctant to rely on the results of intraoperative ECoGs.

In this prospective study, we investigated the relation between remaining epileptic discharges (EDs) in the intraoperative post-resection ECoGs and seizure outcomes 24 months after surgery in pediatric patients with drug-resistant structural focal epilepsies due to isolated Focal Cortical Dysplasia type II (FCD-II).

2. Methods

This prospective study was approved by the Medical University of Vienna Ethics Board (EK 978/2009). Informed consent was obtained from all patients and/or care-givers. Study inclusion criteria were: 1. Presurgical evaluation and epilepsy surgery at the study center before the age of 18 years, 2. MRI consistent with isolated FCD-II; 3. Planned single stage lesionectomy based on convergent non-invasive pre-surgical evaluation data and the consensual decision obtained at the interdisciplinary seizure conference. All lesionectomies were performed by the same two neurosurgeons (T.C and C.D) using intraoperative neuronavigation including 3D surface navigation (Stealth Station Cranial Treon or S7, Medtronic, CO, USA) (Mert et al., 2012). Intraoperative ECoGs were performed prior and immediately after resection and post-resection. ECoGs did not further influence or modify the primary decision concerning the extent of the resected tissue.

General anesthesia was performed using Propofol and Fentanyl (Drummond et al., 1992; Ferrier et al., 2006; Zijlmans et al., 2012). Propofol was stopped at least for 3 minutes before recordings (Drummond et al., 1992; Zijlmans et al., 2012).

Intraoperative ECoGs were performed prior to (baseline) and immediately after resection using a 32-channel system (© Sienna Digital EEG by EMS Biomedical) with steel or platinum strip- and/or grid electrodes. Low pass filter was 0.50 Hz, high pass filter was 70 Hz, 60 Hz notch was on and the paper speed was 30 mm/s. For the pre-resection ECoGs, both location and number of the electrodes were based on data collected during pre-surgical evaluation and the lesion visualized by MRI. For the post-resection ECoGs electrodes covered the margins of the resection and the surrounding tissue. Duration of the recordings depended on the individual decision of the paediatric neurophysiologist (G.G. and M.F.) with a minimum of five minutes per placement. Spikes were defined as transients with a mainly negative component, variable amplitude and duration of 20–70 ms, clearly distinguishable from the background activity (Niedermeyer, 2005) (Fig. 1). Fast activity

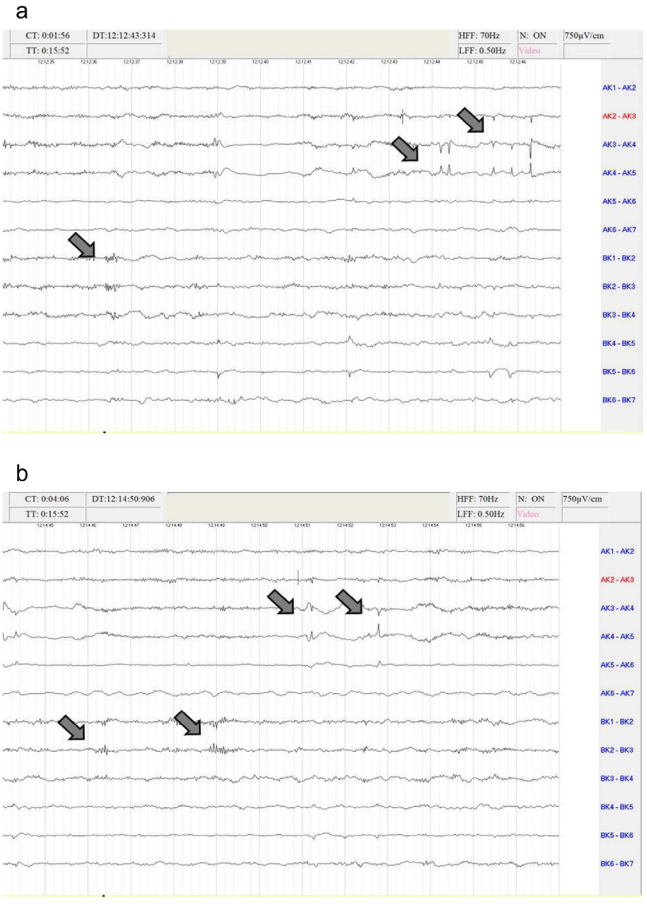

Fig. 1. (a and b) ECoGs in a bipolar montage (high frequency filter: 70 Hz, low frequency filter 0.50 Hz, 750 μV/cm) showing regional spikes and fast activity at the anterior and anterior/inferior margins of the resection of a left frontal focal cortical dysplasia type IIb in a 2 year old girl.

was defined as rhythmic bursts of polyspikes with changeable amplitude and a frequency between 13–30 Hz (Niedermeyer, 2005; Palmini et al., 1995; Terra et al., 2014) (Fig. 1). All ECoGs were analysed visually by two board certified neurophysiologists (GG, MF). To prevent bias, i.e. post-resection spikes caused by injury or isolation of the cortex during surgery (Schwartz et al., 2000) patients without ED in the pre-resection ECoGs (and de-novo occurring spikes and/or fast activity in the post-resection ECoGs) were not included into further analysis.

The presence of persistent spikes and fast activity in the post-resection ECoGs was correlated with postoperative seizure outcomes 24 months after surgery. Study endpoint was the reported seizure-frequency (i.e. seizure freedom versus ongoing seizures) 24 months after surgery.

Postoperative follow-up was documented on an inpatient basis, at three months after surgery and then every 12 months including 48 h prolonged video-EEG-monitoring, high-resolution MRI, neurological, neuro-ophthalmological, neuropsychological and psychiatric investigations. Seizure outcome was classified using the proposal of the International League Against Epilepsy (ILAE) (Wieser et al., 2001). For this study, two outcome groups were defined: Group1 – Seizure freedom from the day of surgery (Wieser 1a) and Group 2 – ongoing seizures after surgery (Wieser 1–5). Histological specimen were evaluated by one of the authors (A.M.) based on the International League Against Epilepsy (ILAE) classification proposal (Blümcke et al., 2011). Patients not fulfilling the definition criteria for FCD-II were excluded from further analysis.

Study hypothesis was that EDs (i.e. spikes and/or fast activity) recorded in the post resection ECoG predict unfavorable seizure outcomes.

2.1. Statistical analysis

Data were analysed using SPSS WIN 24.0 software (SPSS Inc, Chicago, Illinois, USA). Chi square tests were used to evaluate the relationship between the intraoperative spikes and fast activity and the postoperative seizure outcome. Descriptive methods were used for the analysis of demographic data.

3. Results

20 patients fulfilled the inclusion criteria. 2 patients had to be excluded from further analysis, because histological analysis revealed low grade tumors. No patient had to be excluded from further analysis due to the absence of EDs in the pre-resection ECoG. Outcome data from 18 patients were analyzed.

3.1. Demographic data (Table 1)

The median age at onset of epilepsy was 18.5 months (+36.0 months, range: one to 136 months, interquartile range: 25% 1.75 to 75% 44.25). The median age at surgery was 72.5 months (+66.0 months, range: nine to 194 months, interquartile range: 25% 37.5 to 75% 173.0). The median duration of epilepsy before surgery was 45.5 months (+46.7 months, range: seven to 161 months, interquartile range: 25% 28.25 to 75% 98.75). Seizure frequencies prior to surgery were high in all patients (median: 4–10 seizures per day; range 4 seizures per year to more than 10 seizures per day). The epileptogenic lesion was located in the right hemisphere in 66.6% (10/18), and extra-temporally in 94.5% of the patients: in the frontal lobe in 77.8% (14/18), in the parietal lobe in 11.0% (2/18), in the occipital lobe in 5.6% (1/18) and in the temporal lobe in only 5.6% (1/18). Histology displayed FCD-IIa in 5.6% (1/18) and FCD-IIb in 94.4% (17/18) of the patients. All patients included had both spikes and fast activity within and over the lesion in their pre-resection ECoGs.

3.2. Post-resection ECoGs seizure outcomes 24 months after surgery and prognostic value of ECoG (Table 1)

55.6% (10/18) of the patients had EDs in their post-resection ECoGs. In 55.6% (10/18) of the patients spikes were documented and in 27.8% (5/18) of the patients fast activity was seen. All patients with fast activity also had spikes.

There was no significant difference between pre- and post-resection ECoGs with respect to spike morphology and amplitude. There was also no difference with respect to the duration of fast activity. We also did not detect significant differences between age groups.

Twenty-four months after surgery 66.7% (12/18) of the patients were seizure free.

There was a significant correlation between remaining fast activity documented in the post resection ECoGs and unfavourable postoperative seizure outcomes ($p = 0.009$, 1/12 seizure free patients vs 4/6 patients with ongoing seizures).

There was however no correlation between spikes in the post resection ECoGs and postoperative seizure outcomes ($p = 0.502$, 6/12 patients seizure free vs 4/6 patients with ongoing seizures at 24 months after surgery). There was no significant difference between patients who were seizure free and those who were not, neither with respect to spike morphology or amplitude nor with respect to the duration of fast activity. We also did not detect significant differences between age groups.

4. Discussion

Single stage surgery guided by intraoperative ECoG has been controversially debated with respect to its potential to avoid the necessity of two-stage invasive procedures and their potential complications (Bansal et al., 2017).

In this prospective single-centre study we found a significant correlation between fast activity recorded in the post-resection ECoGs and unfavourable seizure outcomes at 24 months after surgery. In contrast, spikes alone did not seem to be informative in this respect.

The close relationship between surgical outcomes and the occurrence of rhythmic epileptiform activity (i.e. repetitive electrographic seizures, repetitive bursting discharges, or continuous or quasicontinuous rhythmic spiking) in both surface EEGs and intraoperative ECoGs in patients with cortical dysplastic lesions has been documented (Palmini et al., 1995; Ferrier et al., 2006; Gambardella et al., 1996; Noachtar et al., 2008). Intraoperative ECoG identification of epileptogenic dysplastic cortical tissue seems therefore crucial to decide the extent of excision necessary for complete seizure control (Palmini et al., 1995). Our results are also in line with those reported by Knerlich-Lukoschus et al. (2017) who investigated the impact of clinical data, electrophysiological results and immunohistochemical analysis on the postoperative seizure outcomes of children with extratemporal epilepsy due to FCD-II. The authors concluded that ECoG might help to improve the identification of the epileptogenic tissue that has to be resected in order to get the patient seizure-free. However, this study did not differentiate between different types of epileptic discharges.

In contrast, Terra et al. (2014) analysed 78 patients with FCD-associated chronic epilepsies and found that seizure outcomes after respective surgery did not differ between those who had tailored resections based on intraoperative ECoGs and those who had lesionectomies without ECoG. Based on this result, the authors

Table 1
Patients characteristics.

	Sex	Age surgery (months)	Disease duration (months)	Side of surgery	Lobe	FCD II Sub-type	Post-resective ECoG – spikes	Post- respective ECoG – fast activity	Seizure outcome (Wieser)
1	M	194	146	Right	Frontal	IIb	Yes	No	Wieser 1a
2	M	66	66	Right	Frontal	IIb	Yes	No	Wieser 1a
3	m	79	43	Left	Frontal	IIb	No	No	Wieser 1a
4	m	162	161	Left	Frontal	IIb	No	No	Wieser 5
5	w	61	32	Left	Frontal	IIb	Yes	No	Wieser 1a
6	m	183	48	Left	Occipital	IIb	Yes	No	Wieser 1a
7	w	41	35	Left	Frontal	IIb	No	No	Wieser 1a
8	m	172	129	Right	Frontal	IIb	Yes	Yes	Wieser 4
9	m	96	72	Right	Frontal	IIb	No	No	Wieser 1a
10	m	9	7	Right	Frontal	IIa	No	No	Wieser 1a
11	m	42	29	Left	Parietal	IIb	No	No	Wieser 1a
12	w	27	26	Right	Temporal	IIb	Yes	No	Wieser 1a
13	w	177	93	Right	Frontal	IIb	No	No	Wieser 1a
14	M	24	23	Left	Frontal	IIb	Yes	Yes	Wieser 1
15	M	44	41	Right	Frontal	IIb	Yes	Yes	Wieser 5
16	W	24	20	Left	Frontal	IIb	Yes	Yes	Wieser 4
17	M	176	116	Right	Parietal	IIb	Yes	Yes	Wieser 1a
18	M	113	89	Right	Frontal	IIb	No	No	Wieser 4

concluded that intraoperative ECoG is not beneficial to delineate the extent of tissue that has to be resected in order to render patients seizure free.

There is a growing body of literature indicating, that fast activity recorded in the post-resection ECoG seems to be a good indicator of remnant epileptogenic tissue and by this can serve as a reliable tool to optimize the result of single stage lesionectomy in children with FCD II. Due to technical limitations we were not able to record true high frequency oscillations (HFOs), but our results are in line with those reported by van 't Klooster et al. (2017). They investigated HFOs in 54 patients and concluded that HFOs seem to be better biomarkers for epileptogenic tissue than spikes. Our results add to this and suggest further, that – similar as reported for HFOs – fast activity recorded with a relatively simple ECoG equipment seems also to have prognostic significance and by this might be an alternative to HFOs recorded with highly sophisticated and expensive technologies.

However, because of the small sample size and the absence of a control group (i.e. patients in whom the technique is used to tailor the resections), our results have to be interpreted with caution and further studies have to be performed to corroborate our findings. This might be of importance in times of decreasing resources.

General anesthesia was performed using Propofol and Fentanyl (Drummond et al., 1992; Ferrier et al., 2006; Zijlmans et al., 2012). As Propofol has been reported to influence the occurrence and the frequency of epileptic discharges, it was stopped at least for three minutes before ECoG recordings were started (respectively, until a continuous ECoG background pattern was observed without waking up the patient). Similar protocols were used by others (Drummond et al., 1992; Ferrier et al., 2006; Zijlmans et al, 2012).

5. Conclusion

Even when recorded with non-sophisticated techniques, presence of fast activity in post-resection ECoGs might be a valid negative outcome-predictor after surgery in paediatric patients with FCD-II associated drug-resistant epilepsies.

6. Disclosure

None of the authors has any conflicts of interest to disclose. The authors have stated that they had no interests which might be perceived as posing a conflict or bias. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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