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Ictal onset patterns of subdural intracranial electroencephalogram in children: How helpful for predicting epilepsy surgery outcome?

Aliza S. Alter[a,1], Ravi Dhamija[a], Tiffani L. McDonough[a], Stephie Shen[a], Danielle K. McBrian[a], Arthur M. Mandel[a], Guy M. McKhann[b], Neil A. Feldstein[b], Cigdem I. Akman[a,*]

[a] Department of Neurology, Division of Child Neurology, New York-Presbyterian Hospital/ Columbia University College of Physicians and Surgeons, 180 Fort Washington Avenue, New York, New York, USA
[b] Department of Neurological Surgery, Columbia University College of Physicians and Surgeons, 710 West 168th Street, New York, New York, USA

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ABSTRACT

Aims: We aimed to classify ictal onset patterns (IOPs) in pediatric patients undergoing intracranial electroencephalography (IEEG) to guide surgery for refractory epilepsy. We aimed to determine if morphology of IOPs can predict surgical outcome.

Materials and Methods: We performed a retrospective review of pediatric patients who underwent epilepsy surgery guided by subdural IEEG from 2007 to 2016. IEEG seizures were reviewed by a blinded epileptologist. Data was collected on outcomes.

Results: Twenty-three patients with 784 seizures were included. Age at seizure onset was 0.2–11 (mean 4.3, standard deviation 3.2) years. Age at time of IEEG was 4–20 (mean 13.5, standard deviation 4.4) years. Five distinct IOPs were seen at seizure onset: A) Low voltage fast activity (LVFA) with spread to adjacent electrodes (n = 7 patients, 30%), B) Burst of LVFA followed by electrodecrement (n = 12 patients, 52%), C) Burst of rhythmic spike waves (RSW) followed by electrodecrement (n = 9 patients, 39%), D) RSW followed by LVFA (n = 7 patients, 30%), E) Rhythmic spikes alone (n = 10 patients, 43%). Twelve patients (52%) had the same IOP type with all seizures. When the area of the IOP was resected, 14 patients (61%) had Engel I outcomes. Patients who had LVFA seen within their predominant IOP type were more likely to have good surgical outcomes (odds ratio 7.50, 95% confidence interval 1.02–55.0, p = 0.05). Patients who had only one IOP type were more likely to have good outcomes than patients who had multiple IOP types (odds ratio 12.6, 95% confidence interval 1.19–134, p = 0.04). Patients who had LVFA in their predominant IOP type were older than patients who did not have LVFA (mean age 15.0 vs. 9.9 years, p = 0.02).

Conclusions: LVFA at ictal onset and all seizures having the same IOP morphology are associated with increased likelihood of surgical success in children, but LVFA is less common in children who are younger at the time of IEEG.

1. Introduction

Although most children with epilepsy will be seizure-free with one antiepileptic drug, 13–24% of children with epilepsy will be drug-resistant, defined as poor seizure control despite trials of two antiepileptic drugs (Berg et al., 2006). Drug resistance is particularly common in children with focal epilepsy, with rates of intractability as high as 46.2% (Berg et al.). Epilepsy surgery is acknowledged as a therapeutic option for children whose seizures remain resistant to antiepileptic drug treatment (Spencer, 1986).

The presurgical evaluation aims to provide a comprehensive exploration to determine whether a patient diagnosed with drug-resistant epilepsy could receive benefit from epilepsy surgery treatment. The goal of presurgical evaluation is to identify the epileptogenic zone (Spencer, 1986). Seizure semiology, non-invasive EEG recording, neuroimaging and functional imaging data are the cornerstones of this evaluation. If the noninvasive evaluation is inconclusive, or incongruent, or if the epileptogenic zone overlaps with eloquent cortex, then

* Corresponding author at: 180 Fort Washington Avenue, 5th Floor, New York, NY 10032, USA.
E-mail addresses: aliza.alter@childrens.harvard.edu (A.S. Alter), ravi.b.dhamija@gmail.com (R. Dhamija), tiffani.mcdonough.md@gmail.com (T.L. McDonough), stephieshen@gmail.com (S. Shen), dkm23@cumc.columbia.edu (D.K. McBrian), amm28@cumc.columbia.edu (A.M. Mandel), gm317@cumc.columbia.edu (G.M. McKhann), naf6@cumc.columbia.edu (N.A. Feldstein), cia11@cumc.columbia.edu (C.I. Akman).
[1] Department of Neurology, Division of Epilepsy and Clinical Neurophysiology, Boston Children's Hospital, 300 Longwood Avenue, Boston, MA 02115.

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intracranial EEG monitoring (IEEG) is required for accurate localization and exploring the function of the epileptogenic cortex (Knowlton et al., 2008). Although data on IEEG in pediatric patients is limited, it is felt to be useful in a large majority of pediatric patients, particularly for localizing extratemporal or multilobar epileptogenic zones (Brna et al., 2015). However, only about half of children who have surgical resection guided by IEEG will achieve seizure freedom (Yang et al., 2014). Accurate identification of the epileptogenic zone is crucial for surgical success, but it remains unclear how best to identify the epileptogenic zone in children.

A number of studies have shown that low voltage fast activity (LVFA) or high-frequency oscillations at ictal onset on IEEG are associated with better surgical outcomes, particularly in adults (Faught et al., 1992; Jiménez-Jiménez et al., 2015; Lagarde et al., 2016; Nicholas M. Wetjen et al., 2009). Other ictal onset patterns (IOPs) are also identified on IEEG and used to guide surgical resection (Jiménez-Jiménez et al., 2015; Lagarde et al., 2016; Perucca et al., 2014; Singh et al., 2015). However, most of the published literature on this topic focuses on adult patients, or does not differentiate adults from children. Turkdogan et al (2005) reviewed both ictal and interictal IEEG patterns in 25 children and found that fast frequencies at ictal onset were more commonly seen in pediatric patients with dysplastic lesions but did not comment on the surgical outcome. Resection of regions with interictal high-frequency oscillations in children has been associated with better surgical outcome but without comment on ictal onset on IEEG (Akiyama et al., 2011). Overall, the literature on pediatric IEEG is sparse, and there is no published study evaluating the utility of IOPs to predict surgical outcome in an exclusively pediatric population.

The objective of this study was to classify the IOPs identified in a cohort of pediatric patients undergoing IEEG to guide surgery for refractory epilepsy. We hypothesized that the ictal onset patterns (IOPs) in children might differ from those commonly identified in adults. We sought to determine whether IOPs could be predictive of surgical outcome, and particularly whether LVFA at ictal onset in children may predict surgical success, as has been shown in adults (Lagarde et al., 2016).

2. Materials and methods

2.1. Patient selection

We performed a retrospective review of pediatric patients with refractory epilepsy who underwent IEEG monitoring at our institution from January 1, 2007 to October 31, 2016. We included patients who were aged 0–20 years at the time of IEEG and who had subsequent epilepsy surgery that was guided by IEEG findings. One patient who did not have any seizures captured on IEEG was excluded.

Inclusion criteria were 1) the diagnosis of focal epilepsy, 2) drug resistant clinical course, 3) consensus for epilepsy surgery evaluation reached at epilepsy surgery conference using intracranial subdural EEG electrode placement. The patients who had operations at another center, missed postoperative follow-up, or had intraoperative EEG and clinical data that were not retrievable were not included in the study.

This study was approved by the Columbia University Medical Center Institutional Review Board.

2.2. IEEG recordings and analysis

Recordings were performed using subdural electrodes on grids and/or strips, sometimes with the addition of multiple-contact depth electrodes. The recording was done on a Natus system® and saved on a Natus database as part of standard clinical care. Official IEEG reports were retrieved and reviewed to confirm the frequency and timing of seizures and seizure semiology. The IEEG files of reported seizures were selected for the analysis. Ictal EEG files were retrieved and clipped, then de-identified. Seizure clippings included at least 10 s prior to ictal onset and at least 20 s following ictal onset displayed using referential and/or bipolar montages. Ictal onset was defined as the first change seen on IEEG followed by sustained evolving rhythmic activity, either lasting at least 10 s (electrographic seizure) or with clinical symptoms (electroclinical seizure). The clipped IEEG seizures were reviewed independently by a board-certified epileptologist (CIA) who was blinded to patient clinical information. IOP was determined based on morphological characteristics seen visually at ictal onset.

The IOPs previously described by Singh et al (2015) were applied to classify the EEG findings for this cohort. These patterns included electrodecremental (ED), LVFA, ED plus LVFA, < 2 Hz rhythmic waves, < 2 Hz spikes, 2–4 Hz rhythmic waves, 2–4 Hz spikes, 5–7 Hz rhythmic waves, 5–7 Hz spikes, 8–13 Hz rhythmic waves, 8–13 Hz spikes, > 13 Hz spikes, repetitive spikes (no frequency specified), delta brush, and burst suppression.

The following terminology was used for IOP analysis: 1) Electroclinical seizure refers to a clinical change accompanied by evolving rhythmic activity on IEEG, 2) Electrographic seizure refers to evolving rhythmic activity on IEEG lasting at least 10 s but without any accompanying clinical changes. The predominant IOP type refers to the IOP type seen most frequently at the onset of a patient's electroclinical seizures.

2.3. Surgical outcomes and histological classification

Surgical outcome was assessed as part of regular follow-up. Surgical outcome was categorized using the Engel classification system (Engel, 1993). Post-surgical outcome was recorded at the time of the last visit and, when available, two years after the epilepsy surgery. Good outcome refers to Engel Class I outcome at the last follow-up; unfavorable outcome refers to Engel Classes II-IV. Histological classification was done at the time of resection by a neuropathologist. Focal cortical dysplasias were categorized according to the most recent ILAE classification scheme (Blumcke et al., 2011).

2.4. Statistical analysis

Statistical analyses were performed using Microsoft Excel. Due to small sample size, descriptive statistics were calculated. Odds ratios with 95% confidence intervals were calculated to compare the likelihood of Engel Class I outcome based on presence or absence of categorical variables. Paired t-tests were used to compare pre- and post-operative means. Unpaired t-tests were used to compare means between two groups of patients. Alpha was set at 0.05.

3. Results

3.1. Patient characteristics

Twenty-three patients (12 females) were included in this analysis (Table 1). Age range at time of IEEG was 4–20 (mean 13.5, standard deviation 4.43) years. Mean age at seizure onset was 4.3 (standard deviation 3.2, range 0.2–11) years. Mean time between seizure onset and IEEG was 9.2 (standard deviation 4.5, range 2–18) years. Twelve patients (52%) had MRI lesions thought to be relevant to their epilepsy; the other 11 had non-lesional MRI scans. Eight patients (35%) had temporal lobe epilepsy. Of these patients, three (patients 5, 12, and 14) had mesial temporal lobe epilepsy, four (patients 7, 10, 13, and 18) had lateral temporal lobe epilepsy, and one (patient 6) had involvement of the both mesial temporal lobe and lateral temporal neocortex. The other 15 patients had extra-temporal epilepsy. Mean post-operative follow up was 41.4 months after surgery (standard deviation 23.1 months, range 7–109 months).

Table 1
Pre-Operative Characteristics of Pediatric Patients Undergoing Subdural IEEG.

Pt No.	Sex	Age (Years) at Seizure Onset	Pre-Op Seizure Frequency	Pre-Op Anti-Seizure Medications	Lesion on MRI?	Suspected Epilepsy Localization	Age (Years) at IEEG
1	F	6	1/month to 4/day	CLZ, LEV, CBZ, ZNS	Y	L frontal	18
2	F	5	6/day	OXC, CLZ	N	L frontal	13
3	F	8	Several per week	LEV, LTG	Y	R frontal	19
4	F	5	many per day	OXC, CLZ, VPA	Y	R fronto-parietal-temporal	9
5	F	0.5	1-2/week	LEV, VPA	Y	R temporal	8
6	F	3	16-17/ month	LEV, OXC, TPM	Y	L temporal	19
7	M	5	1/week to 1/month	LEV, CBZ	N	L temporal	20
8	F	2	up to 40/day	VPA, ZNS, PGB	N	L orbitofrontal	16
9	M	11	every other week	LTG, ZNS, OXC	N	R frontal	15
10	F	3	Daily	LTG, CBZ	Y	L temporal	13
11	M	1.4	1-3/day	LAC, OXC	Y	R fronto-parietal-temporal	17
12	M	7	3/week to 3/day	PMD, PHT, LAC	N	R temporal	14.5
13	M	1.25	1/3 months	CLB	N	L temporal	19
14	F	8	every other day	LTG, LEV	Y	R temporal	13
15	M	0.17	2-3/night	VPA, LEV, OXC	N	L frontal	10
16	M	6	2-5/month	RUF, LEV	N	R frontal	17
17	F	5	2/week to many/day	OXC, LEV, ZNS, CLZ	N	mesial frontotemporallateralization unclear	8
18	M	1	2-3/week	OXC, LEV, CLB	N	L temporal	8
19	M	2	10-12/day	PHT, LEV, LAC, CLB, TPM	Y	L frontal	4
20	M	0.75	1/day, w/ extra clustering monthly	LEV, VPA, DZP, LAC	Y	L parietal	8
21	F	9	1/1-2 months	GBP, ZNS, VPA, CLB	Y	R fronto-parietal-temporal	14
22	M	0.3	2-3/week	CBZ, TPM	Y	R frontal	13
23	F	8	2-4/night	LEV, OXC	N	L fronto-parietal-temporal	14
Mean		4.3					13.5
StDev		3.2					4.4

Abbreviations: IEEG = intracranial electroencephalography, CLZ = clonazepam, LEV = levetiracetam, CBZ = carbamazepine, ZNS = zonisamide, OXC = oxcarbazepine, LTG = lamotrigine, GBP = gabapentin, VPA = valproic acid, TPM = topiramate, LAC = lacosamide, PGB = pregabalin, CLB = clobazam, PHT = phenytoin, DZP = diazepam, PMD = primidone, RUF = rufinamide, L = Left, R = Right.

3.2. IEEG findings and ictal onset patterns

784 seizures were recorded (range 3–244 seizures per patient, mean 34.1 seizures/patient, standard deviation 53.4); 473 of these were electroclinical and 311 were electrographic seizures.

IEEG findings are shown in Table 2. Five distinct IOPs were seen at seizure onset (Fig. 1): A) Low voltage fast activity (LVFA) with spread to the adjacent electrodes (n = 7 patients, 30%), B) Burst of LVFA followed by an electrodecrement (n = 12 patients, 52%), C) Burst of rhythmic spike waves (RSW) followed by an electrodecrement (n = 9 patients, 39%), D) RSW followed by LVFA (n = 7 patients, 30%), E) Rhythmic spikes (RS) alone (n = 10 patients, 43%). Patterns that were described by Singh et al (2015) that were not seen in this cohort were electrodecrement alone, rhythmic waves alone at any frequency, delta brush, and burst suppression. Spikes alone were all classified together, regardless of frequency, due to small numbers of patients. Eleven patients (48%) had only one IOP type recorded, of whom one had seizures presenting with RS alone; the other ten had an IOP type that included LVFA and/or electrodecrement. Twelve patients (52%) had more than one IOP type recorded on IEEG.

The most common predominant IOP type was the burst of LVFA followed by electrodecrement (n = 10 patients, 43%). The next most common predominant IOP type was the burst of RSW followed by electrodecrement (n = 6 patients, 26%).

When combined, a burst of paroxysmal activity (RSW or LVFA) and subsequent electrodecrement was the predominant IOP type in a majority of patients (n = 16 patients, 70%). LVFA was seen at onset in the predominant IOP type in 16 patients (70%).

Patients who had LVFA at ictal onset within their predominant IOP were significantly older at the time of their IEEGs than those who did not have LVFA in their predominant IOP type (mean age 15.0, standard deviation 3.8, range 8–20 years in the LVFA group vs mean age 9.9, standard deviation 3.9, range 4–14.5 years in the group without LVFA, unpaired *t*-test p = 0.02, see Fig. 2). Patients who had epilepsy duration of 8 or more years at the time of their IEEG always had LVFA within their predominant IOP type, whereas patients with epilepsy duration of less than 8 years more often had RSW followed by electrodecrement or RS alone (Fig. 2). However, there was no difference in predominant IOP types when compared by age of seizure onset. Likewise, there was no significant difference in age of seizure onset when patients with LVFA within their predominant IOP type were compared to those without LVFA (mean age of seizure onset 4.1, standard deviation 3.2, range 0.2–11 years in the LVFA group vs mean age 4.7, standard deviation 3.4, range 0.8–9 years in the group without LVFA, unpaired *t*-test p = 0.71).

There was no difference in predominant IOP types in the patients who had lesions on magnetic resonance imaging (MRI) compared to those who did not have MRI lesions (Fig. 2).

3.3. Epilepsy surgery and post-surgery outcome

Surgical details, pathology, and outcomes are listed in Table 3.

When the area of the IOP was subsequently resected, an Engel Class I outcome was accomplished in 14 patients (61%). Epilepsy surgery decreased the frequency of seizures but failed to accomplish seizure freedom in three patients (Engel Classes II and III, 13%). Six patients had no significant benefit (Engel Class IV, 26%), three of whom had repeat epilepsy surgery at two years and at the time of the last follow-up.

There were no significant differences in the likelihood of Engel Class I outcome when patients were compared by the presence of IOP types. However, there was a significantly increased likelihood of Engel Class I outcome in the patients who had LVFA within their predominant IOP type compared to patients who did not (odds ratio 7.50, 95% confidence interval 1.02–55.0, p = 0.05, Figs. 2 and 3). Patients who had only one IOP type recorded that included LVFA and/or electrodecrement were also significantly more likely to have Engel Class I outcomes than patients who had multiple IOP types recorded (odds ratio 12.6, 95% confidence interval 1.19–134, p = 0.04, Fig. 3).

Patients who had Engel I outcomes also tended to be older than

Table 2
Ictal Onset Patterns Identified in Pediatric Patients on IEEG.

Pt No.	Days on IEEG	No. of IEEG Seizures	All IOP Types	Predominant IOP Type
1	5.5	10	Burst-LVFA→Edec	Burst-LVFA→Edec
2	3	8	Burst-LVFA→Edec	Burst-LVFA→Edec
3	7	112	Burst-LVFA→Edec	Burst-LVFA→Edec
4	18	46	1. Burst-RSW→LVFA 2. RS alone	Burst-RSW→LVFA
5	6.5	11	Burst-LVFA→Edec	Burst-LVFA→Edec
6	5.5	7	LVFA	LVFA
7	6	244	Burst-RSW→LVFA	Burst-RSW→LVFA
8	4	3	Burst-LVFA→Edec	Burst-LVFA→Edec
9	7	9	Burst-LVFA→Edec	Burst-LVFA→Edec
10	8	23	Burst-RSW→LVFA	Burst-RSW→LVFA
11	5.5	16	LVFA	LVFA
12	6.5	29	1. Burst-RSW→Edec 2. RS alone 3. Burst-RSW→LVFA	Burst-RSW→Edec
13	15	16	1. Burst-LVFA→Edec 2. RS alone 3. LVFA 4. Burst-RSW→Edec	Burst-LVFA→Edec
14	3	9	1. Burst-RSW→Edec 2. RS alone	Burst-RSW→Edec
15	14	11	1. Burst-RSW→LVFA 2. LVFA 3. Burst-LVFA→Edec 4. RS alone	Burst-RSW→LVFA
16	6	3	1. Burst-LVFA→Edec 2. Burst-RSW→LVFA 3. Burst-RSW→Edec	Burst-LVFA→Edec
17	8.5	58	1. Burst-RSW→Edec 2. RS alone 3. LVFA	Burst-RSW→Edec
18	7	3	RS alone	RS alone
19	7	34	1. Burst-RSW→Edec 2. LVFA 3. RS alone	Burst-RSW→Edec
20	9	4	1. Burst-RSW→Edec 2. Burst-RSW→LVFA	Burst-RSW→Edec
21	9	48	1. Burst-RSW→Edec 2. Burst-RSW→LVFA 3. RS alone 4. LVFA	Burst-RSW→Edec
22	6	77	1. Burst-LVFA→Edec 2. Burst-RSW→Edec 3. RS alone	Burst-LVFA→Edec
23	9	3	1. Burst-LVFA→Edec 2. RS alone	Burst-LVFA→Edec

Abbreviations: IEEG = intracranial electroencephalography, IOP = ictal onset pattern, LVFA = low voltage fast activity, Edec = Electrodecrement, RSW = rhythmic spike-waves, RS = rhythmic spikes.

those who had less favorable surgical outcomes, although this did not reach statistical significance (mean age 14.8, standard deviation 3.6, range 8–20 years in the Engel I group vs mean age 11.3, standard deviation 4.9, range 4–19 years in the Engel II—IV group, p = 0.09). There was no significant difference in mean time from seizure onset to IEEG between the group with Engel I outcomes and the group with less favorable surgical outcomes (mean time 9.8, standard deviation 4.0, range 4–16 years in the Engel I group vs mean time 8.2, standard deviation 5.4, range 2–18 years in the Engel II—IV group, p = 0.43).

Most patients remained on medication at two years and at the time of last post-operative follow-up; only one patient was able to discontinue all anti-seizure medications. Mean number of anti-seizure medications decreased from 2.7 medications pre-operatively (standard deviation 0.96, range 1–5 medications) to 2.3 anti-seizure medications at last post-operative follow-up (standard deviation 1.2, range 0–4 medications,).

3.4. Histopathology

The most common pathology described in the surgical substrates was focal cortical dysplasia (FCD), reported in 13 patients (57%), of which FCD I was reported in three (13%), FCD II in seven (30%), and FCD IIIA in another three patients (13%). Hippocampal sclerosis (HS) without FCD was reported in one. Other pathology included hyaline astrocytopathy in one patient, and gliosis in eight patients (35%, two of whom also had microscopic infarcts). No tumors were identified in the pathology of the patients in this cohort.

There was no significant association between surgical pathology and chance of an Engel Class I outcome (Table 3). There was also no significant association between types of IOP and surgical pathology (Fig. 2). FCD was seen in association with all IOP types except RS alone.

4. Discussion

The main objective of this study was to describe IOPs on pediatric intracranial EEG and determine if there was an association with surgical outcome, because no prior study has investigated this relationship in an exclusively pediatric cohort. We categorized 784 IEEG seizures in 23 pediatric patients, which is the largest report of its kind to our knowledge. We described five types of IOPs. We report a significantly increased chance of seizure freedom when LVFA is identified within the predominant IOP type. There was also a significant association between consistency of the IOP morphology and increased likelihood of surgical success.

4.1. Types of pediatric ictal onset patterns

Our findings show a spectrum of five types of ictal onset patterns that are seen on IEEG in children. The patterns that we found replicate some patterns that have been previously reported in adults or mixed cohorts. LVFA, burst of polyspikes followed by LVFA, rhythmic spikes, and spike-and-wave activity have been reported in association with FCD (Lagarde et al., 2016; Perucca et al., 2014; Sang-Ahm et al., 2000). Bursts of spikes or sharp waves have been reported immediately preceding fast activity at ictal onset, although some studies have not considered these bursts as part of the IOPs (Doležalová et al., 2013; Yitzhak et al., 1998). Electrodecrement has been reported in the adult literature (Jiménez-Jiménez et al., 2015; Singh et al., 2015), although this pattern has also been excluded from consideration as part of the ictal onset by some authors (Sang-Ahm et al., 2000). A burst of paroxysmal activity (either RSW or LVFA) followed by electrodecrement has not been well-described to date. This type of IOP was a very common finding in our pediatric cohort. As in the literature on adult patients, LVFA was the most frequently seen initial component of an IOP (Sang-Ahm et al., 2000; Singh et al., 2015). There were several types of IOPs which have been identified in adult patients but which we did not identify in our pediatric cohort; these include delta brush, burst suppression, sharp activity at 13 Hz or less, rhythmic waves in isolation, and electrodecrement in isolation (Lagarde et al., 2016; Perucca et al., 2014; Singh et al., 2015).

One important distinction about the types of IOPs seen in our cohort is that our cohort included primarily patients with neocortical epilepsy. Even among the eight patients with suspected temporal lobe epilepsy, only three had epilepsy limited to the mesial temporal lobe, which is dramatically different from most adult epilepsy surgical cohorts. Because only three patients had epilepsy limited to the mesial temporal lobe, and only five patients had mesial temporal electrodes during IEEG recording, we were unable to use our cohort to compare IOPs arising from the mesial temporal lobe compared to those arising from neocortical locations. However, hippocampal seizures have been described to produce distinct types of IOPs (Spencer et al., 1992), and this may be an important reason for differences in predominant IOP types when pediatric cohorts are compared to adult cohorts.

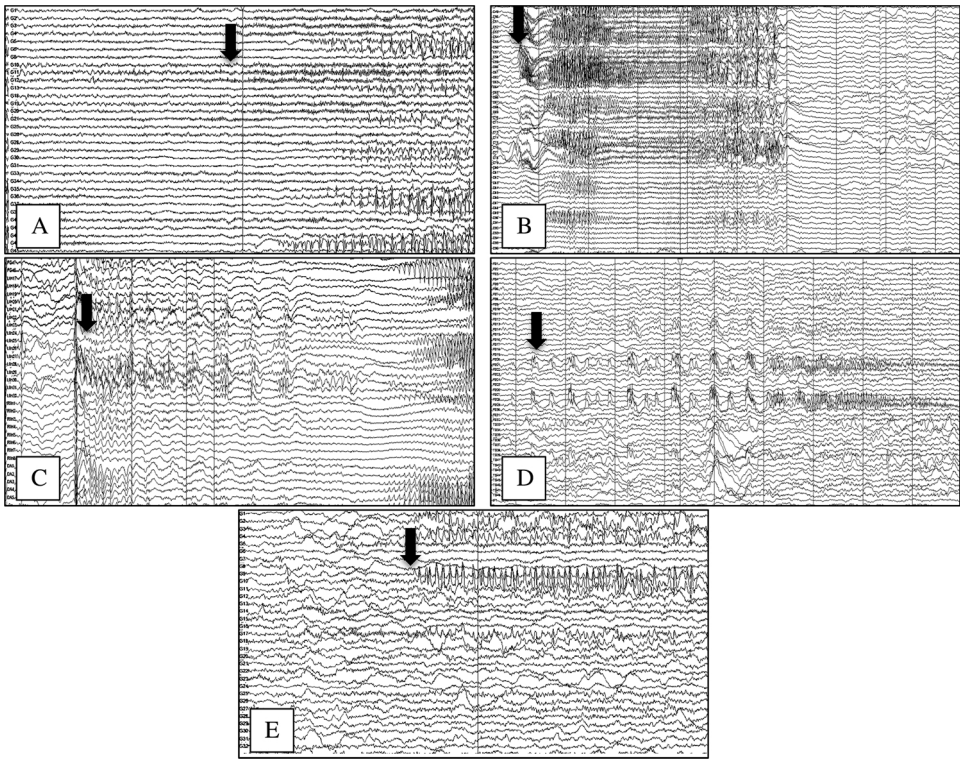

Fig. 1. Ictal Onset Pattern Types Identified on Pediatric IEEG.
Description: Ictal onset pattern types seen on subdural IEEG in pediatric patients. Arrows indicate ictal onset. A, LVFA with spread to adjacent electrodes. B, Burst of LVFA followed by electrodecrement. C, Burst of RSW followed by electrodecrement. D, Burst of RSW followed by LVFA. E, RS alone. Sensitivity is 70 u V/mm. Abbreviations: IEEG = intracranial electroencephalogram, LVFA = low voltage fast activity, RSW = rhythmic spike-waves, RS = rhythmic spikes.

We also found that patients who had LVFA identified at ictal onset in their predominant seizure type were older than patients who had RSW followed by electrodecrement or RS alone identified as their predominant IOP. There are many possible reasons for this age discrepancy. One possible reason could be that the types of focal epilepsy that present in younger children have different underlying pathophysiology than the types of focal epilepsy presenting in older children and adults. However, we did not find a difference in age of seizure onset in the patients who had LVFA compared to those who did not. Another possible reason for the age difference could be the remodeling of neural circuitry that occurs during development. It could be that younger children do not generate the same types of IOPs as older children even with the same epilepsy pathophysiology due to age-dependent differences in neural networks. Older children may therefore be more likely to have IOPs similar to adults because of the growth and remodeling that has already occurred, but the significance of these IOPs may not be able to be extrapolated to very young children being evaluated for epilepsy surgery. The uncertain significance of these IOP types in younger children may contribute to difficulty localizing the epileptogenic zone in patients with younger ages and is an important area for future research.

Another important characteristic of our cohort was time from seizure onset to IEEG, which was shorter on average in our cohort than in cohorts of older patients, although the minimum duration of epilepsy of 2 years was similar (Lagarde et al., 2016; Wetjen et al., 2009). Since it is not uncommon for adult patients to have epilepsy duration of 20 years or more prior to referral for epilepsy surgery (Berg et al., 2006), a pediatric cohort provides a unique opportunity to investigate a group of patients with comparatively early referral for epilepsy surgery. We did not find a difference in surgical outcomes based on duration of epilepsy prior to IEEG, but we did find that all patients with epilepsy duration of 8 years or more prior to IEEG had LVFA within their predominant IOP types. In contrast, patients with epilepsy duration less than 8 years at time of IEEG more frequently had RSW followed by electrodecrement or rhythmic spikes alone. It is possible that there is remodeling that occurs over the course of many years in response to seizures that contributes to the IOPs, such as LVFA, that are commonly reported in adult patients, and that patients with relatively shorter durations of epilepsy may be less likely to generate these IOPs. Therefore, another potential future direction would be a study of IOPs in patients undergoing IEEG within the first few years of seizure onset.

4.2. Associations with surgical outcome

Our rates of surgical success were comparable to other series reporting on pediatric epilepsy surgery (Yang et al., 2014), which are comparable to other series reporting on nonlesional neocortical epilepsy surgery (Kim et al., 2017). Similar to what has been observed in adults (Faught et al., 1992; Jiménez-Jiménez et al., 2015; Singh et al., 2015), and in mixed adult and pediatric cohorts (Lagarde et al., 2016), the identification of LVFA at ictal onset in a preponderance of seizures was predictive of increased likelihood of seizure freedom in children. However, younger children were less likely to have LVFA, which may be one factor making localization of the epileptogenic zone and postoperative seizure freedom more elusive in young children. Future studies on IOPs specifically in children under 14 years of age may be helpful for this group of patients.

Patients who had only one IOP type recorded that included LVFA and/or electrodecrement were significantly more likely to have Engel Class I surgical outcomes than those who had multiple IOP types. Only five out of 12 patients (42%) with multiple IOP types achieved Engel Class I outcomes, which is in contrast to prior studies reporting good outcome in 58–82% of patients with multiple IOP types (Faught et al., 1992; Park et al., 1996). Faught et al (1992) found that multiple morphological sequences at ictal onset were not associated with worse surgical outcomes in a group of adult patients with mesial temporal epilepsy who underwent temporal lobectomy. Since Faught et al's inclusion criteria specified that all seizures appeared to originate from mesial temporal regions and that all patients had temporal lobectomy performed, it is possible that their patients would have had all seizure foci removed by the temporal lobectomy even if there were multiple temporal seizure foci. In contrast, our cohort included children with both temporal and extra-temporal epilepsy and with temporal and extra-temporal resections; only three of our patients had epilepsy

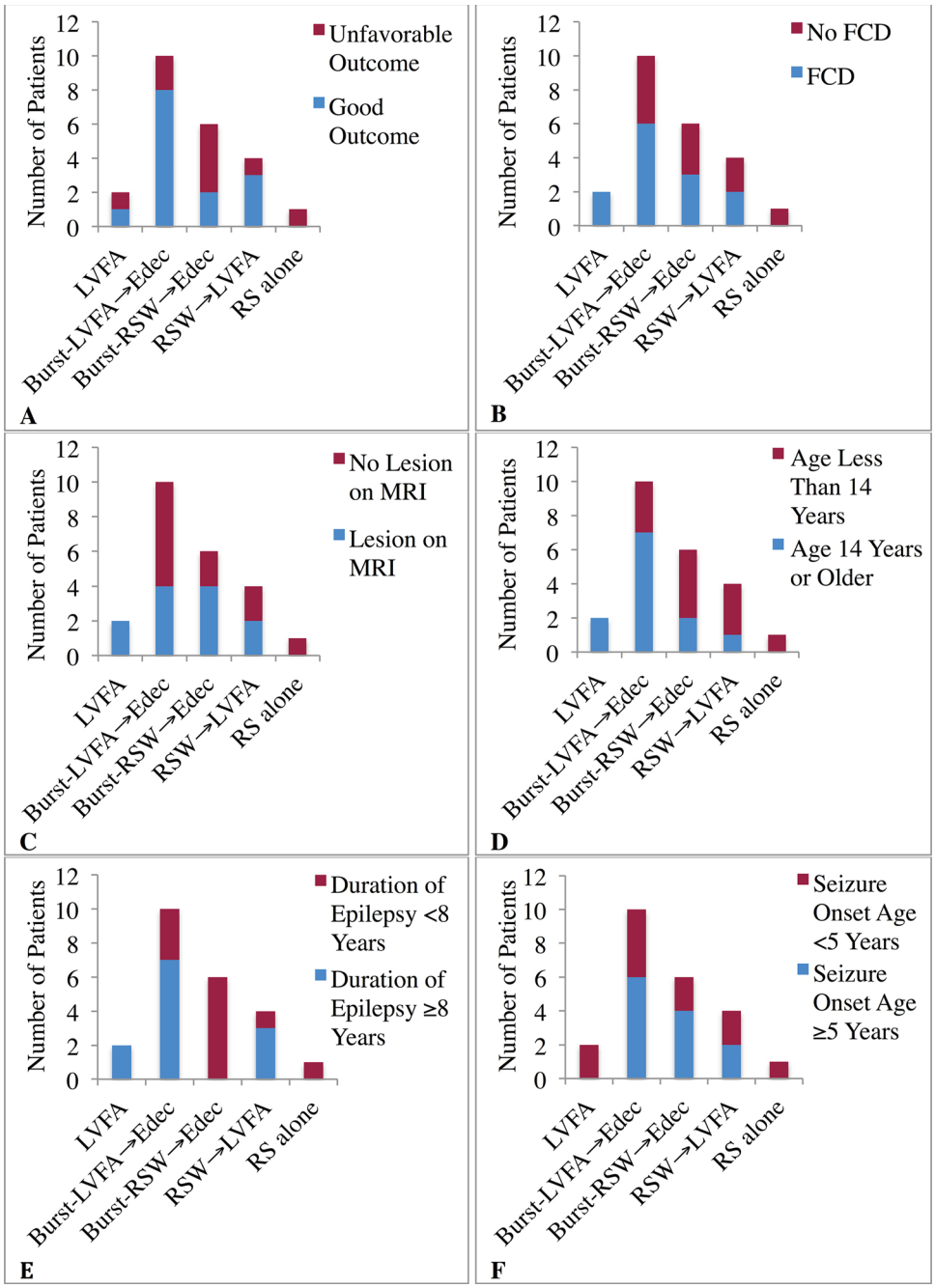

Fig. 2. Surgical Outcomes, Histopathology, MRI Findings, Age, Duration of Epilepsy, and Age at Seizure Onset By IOP Type in Pediatric Patients Undergoing Epilepsy Surgery Guided By IEEG.

Description: Numbers of patients with each ictal onset pattern type. A, Surgical outcome by predominant IOP type. Good outcomes, defined as Engel Class I, were seen with any predominant IOP type except for RS alone. Unfavorable outcome refers to Engel Classes II-IV. B, Histopathology by predominant IOP type. All IOP types were seen in association with FCD except for RS alone. C, MRI findings by predominant IOP type. There was no significant difference in predominant IOP type between the group who had lesions on MRI compared to those who did not. D, Age at time of IEEG by predominant IOP type. Younger patients were less likely to have LVFA seen within their predominant IOP type compared to older patients. E, Duration of epilepsy by predominant IOP type. All patients who had epilepsy for eight years or longer had LVFA within their predominant IOP type, whereas patients who had epilepsy for less than eight years more often had predominant IOP types without LVFA. Duration of epilepsy refers to time from seizure onset to age at IEEG. F, Age at seizure onset by predominant IOP type. There was no significant difference in predominant IOP type between the group who had seizure onset before school age compared to those who had seizure onset at school age or older. Abbreviations: IOP = ictal onset pattern, IEEG = intracranial electroencephalogram, LVFA = low voltage fast activity, Edec = electrodecrement, RSW = rhythmic spike-waves, RS = rhythmic spikes, FCD = focal cortical dysplasia, MRI = magnetic resonance imaging.

limited to the mesial temporal lobe. We therefore speculate that multiple IOPs are a poor prognostic factor particularly when seizures are not limited to the mesial temporal region. Multiple IOP types in these cases may be the neurophysiological equivalent to multiple seizure semiologies, which have previously been associated with poor surgical outcome in patients with FCD who underwent subdural IEEG (Widdess-Walsh et al., 2007). Multiple IOP types may suggest a multifocal epileptogenic zone even in the absence of multiple seizure semiologies; these multiple foci may be far apart or have intervening eloquent cortex, particularly when they are not all located in the mesial temporal region, which may make resection or physiologic disconnection of all seizure foci difficult. Multiple IOP types could also suggest that the recording electrodes are not sufficiently close to the epileptogenic focus to record the true ictal onset, and may instead be recording propagation patterns that have variability with different seizures.

The significance of a burst of paroxysmal activity followed by electrodecrement remains unclear. In adults, electrodecrement as an IOP has sometimes been associated with poor surgical outcome (Doležalová et al., 2013; Jiménez-Jiménez et al., 2015; Singh et al., 2015). However, the electrodecrement that we noted, which followed a burst of paroxysmal activity and was often brief, was not necessarily associated with a poor surgical outcome. An association with good surgical outcome was seen in patients who had LVFA within their predominant IOP type regardless of whether electrodecrement was also present. It is therefore possible that this type of brief electrodecrement after a burst of paroxysmal activity may not be a clinically important component of IOPs. Given how common the electrodecremental pattern was in our cohort, we felt that it was important to include, but a potential future direction could be to develop and test a simplified classification scheme that eliminates electrodecrement from IOP classification. A classification scheme focused on distinguishing patterns with LVFA from those with RSW or rhythmic spikes only may be more

Table 3
Post-Operative Characteristics of Pediatric Patients After Subdural IEEG.

Pt No.	Type of Epilepsy Surgery	Surgical Pathology	Last Follow Up (months after surgery)	Engel Class	Anti-Seizure Meds at Last Follow Up	Repeat Epilepsy Surgery
1	L F resection	CD IIB	32	1a	LEV, CLZ	N
2	L F resection	CD IIB	47	1a	CLZ	N
3	R F lobectomy, partial CC	Gliosis	84	1a	LEV, LTG	N
4	R AT lobectomy, R F lobectomy, MST	CD IIA	60	1a	VPA, LCM	N
5	R T lobectomy	CD IIIA	14	1a	VPA	N
6	L AT lobectomy, L OF resection	CD IIIA	41	1a	LEV	N
7	L T resection	Gliosis	7	1a	LEV, CBZ	N
8	L inf F resection	Gliosis	38	1a	VPA, ZNS, PGB	N
9	R F lobectomy	CD I	32	1a	OXC, LTG	N
10	L FT resection	CD IIB	28	1a	CBZ, LTG	N
11	R P-O-T-F resection	CD IIB	3*	4	OXC, CLZ, LCM*	Y
12	R T lobectomy	Gliosis	31	1a	none	N
13	L T and OF resection	Gliosis	31*	4	LTG, CLB*	Y
14	R T lobectomy	CD IIIA	17	1a	LEV, LTG	N
15	R MF resection	Gliosis	44	3	VPA, LEV, OXC	N
16	R F resection	Hyaline astrocytopathy	34	1a	LEV	N
17	L MF resection	CD IB	26	4	CLZ, LEV, OXC, LAC	N
18	L AT resection	Gliosis, infarct	47	3	OXC, LEV, CLB, VPA	N
19	L F resection w stereotactic laser ablation	CD IIB	32	2	LEV, CLB, PHT, LAC	N
20	L F lobectomy	Gliosis, infarct	44	4	PHT, LAC, LEV, DZP	N
21	R T lobectomy, extra-T resection, MST	HS	63*	4	RUF, VPA, CLB, ZNS*	Y
22	R F lobectomy, R inf P resection	CD IIB	65	1a	CBZ	N
23	L F resection	CD I	18	4	LEV, OXC, LAC, LZP	N

* = at time of repeat epilepsy surgery; Abbreviations: IEEG = Intracranial electroencephalogram, IOP = Ictal Onset Pattern, LVFA = low voltage fast activity, L = Left, R = Right, F = Frontal, T = Temporal, P = Parietal, O = Occipital, AT = Anterior temporal, OF = Orbitofrontal, FT = Frontotemporal, MF = Medial frontal, CC = Corpus callosotomy, MST = multiple subpial transections, CD = Cortical Dysplasia, HS = Hippocampal sclerosis, CLZ = clonazepam, LEV = levetiracetam, CBZ = carbamazepine, ZNS = zonisamide, OXC = oxcarbazepine, LTG = lamotrigine, VPA = valproic acid, TPM = topiramate, LAC = lacosamide, PGB = pregabalin, CLB = clobazam, PHT = phenytoin, DZP = diazepam, LZP = lorazepam, RUF = rufinamide.

clinically meaningful and easier to apply than a classification scheme that also includes electrodecrement.

4.3. Associations with histopathology

FCD was found in association with all types of ictal onset patterns except for RS alone and was not exclusively associated with LVFA. This is similar to findings in other studies. No single EEG feature has been found to be absolutely diagnostic of dysplastic cerebral lesions in children, and multiple types of IOPs have previously been found in association with FCDs (Lagarde et al., 2016; Turkdogan et al., 2005). This study therefore confirms prior findings that IOPs cannot be reliably used to diagnose underlying pathology.

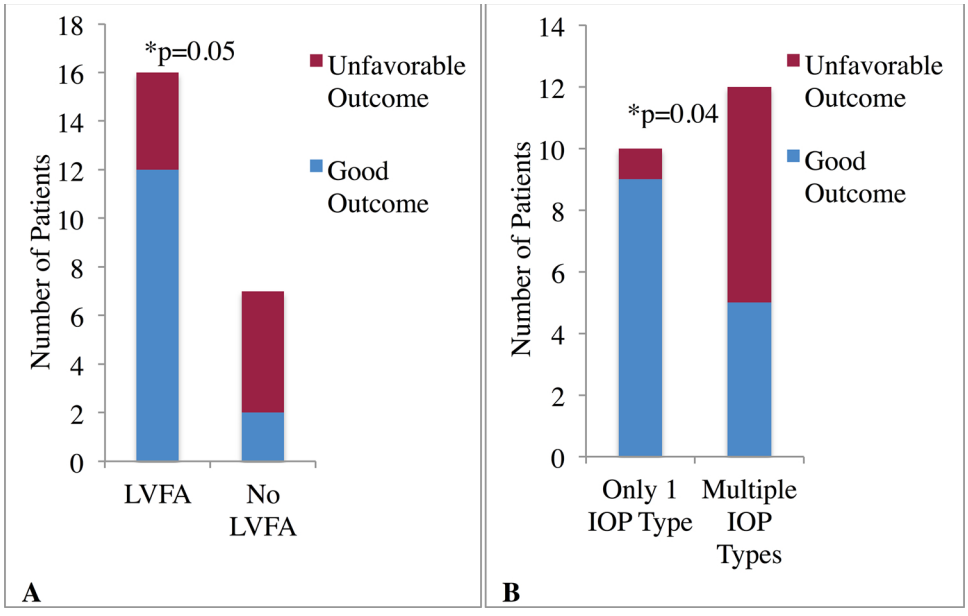

Fig. 3. Surgical Outcomes By Presence of LVFA in Predominant IOP and By Consistency of IOP Morphology.
Description: A, Surgical outcome in patients who had LVFA within their predominant IOP compared to patients who did not have LVFA in the predominant IOP type. Patients who had LVFA within their predominant IOP were more likely to have good outcomes (odds ratio 7.50, 95% confidence interval 1.02–55.0, p = 0.05). B, Surgical outcomes in patients with only one IOP type containing LVFA and/or electrodecrement compared to patients with multiple IOP types. One patient who had only one IOP type of rhythmic spikes alone was excluded, as rhythmic spikes alone were felt to be a propagation pattern rather than a true IOP. Patients with only one IOP type were significantly more likely to have good outcomes compared to patients who had multiple IOP types (odds ratio 12.6, 95% confidence interval 1.19–134, p = 0.04). Good outcome refers to Engel Class I. Unfavorable outcome refers to Engel Classes II-IV. * = Statistically significant at alpha < 0.05. Abbreviations: IOP = ictal onset pattern, LVFA = low voltage fast activity.

4.4. Study limitations

There are some limitations of our study that require mentioning. The present study describes IEEG findings of 23 pediatric patients from a single epilepsy center. This is the largest collection of seizures from an exclusively pediatric IEEG cohort used to investigate IOPs to our knowledge, but still the sample size is small enough that there may be Type II statistical errors. Multicenter collaboration is necessary to reach a larger number of patients diagnosed with drug resistant epilepsy as a result of various etiologies. Although brain tumors are among the most common pathologies described in pediatric epilepsy surgery patients, brain tumors were not reported in this cohort.

We also encountered difficulty with classification of the IEEG ictal data for this cohort. The description of IEEG findings and classification is limited and often described in adult epilepsy patients. For this study, therefore, we adopted variations of the classifications summarized by Singh et al (2015). Furthermore, we examined the seizures and accepted the seizure onset as officially reported by the epilepsy team assigned to the case previously. In this study, our aim was not to dispute or confirm the interpretation of IEEG data, although we are aware of the fact that the interpretation of IEEG is complex and may vary based on the experience of the interpreting physician. For example, the epilepsy team originally assigned to the case had access to video of the electroclinical seizures, and therefore they may have been biased to call a pattern an ictal onset because it occurred prior to a clinical seizure, when that same pattern in a different clinical circumstance could have been interpreted as an interictal pattern. Inter-rater reliability is another important potential confounding factor for IEEG interpretation and remains to be addressed. Indeed literature on inter-rater reliability for interpreting IOPs is limited (Singh et al., 2015). Further studies on inter-rater reliability and the development of a clinically reliable classification scheme for pediatric ictal onset pattern morphology would facilitate further research on this topic and has the potential to improve epilepsy surgical planning in children.

Another limitation is that electrodecrement and LVFA could be difficult to visually distinguish from each other. Clear standards for differentiating LVFA from electrodecrement would be helpful to better characterize both the electrodecrement and LVFA that we often noted after a paroxysmal burst at ictal onset, and to determine in what settings this finding may have clinical utility.

We also were challenged by the fact that many patients had multiple types of ictal onset patterns. Some prior studies have been limited in that they often only analyzed patients based on predominant IOP type but did not account for non-dominant IOP types (Jiménez-Jiménez et al., 2015). We sought to address this limitation by also including data based on whether each IOP type was present or not, in addition to analyses based on predominant IOP type. However, we did not account for the frequency with which the non-dominant IOP types occurred in each patient, and this may impact how clinically significant a non-dominant IOP type is. We also did not analyze the timing of emergence of multiple IOPs on the IEEG recordings. Future studies on the timing of emergence of different IOPs and relationship to timing of medication tapers may be beneficial to determine the clinical significance of late-emerging IOPs as well as how long patients should be recorded on IEEG and how to optimize capture of multiple IOPs when present.

We also limited this study to analyzing morphology at seizure onset only. Interictal high-frequency oscillations, interictal spikes, or a combination of spikes and high-frequency oscillations may be used to help identify the epileptogenic zone (Akiyama et al., 2011; Nicolas et al., 2018). However, the role of interictal high-frequency oscillations in the planning of epilepsy surgery remains incompletely understood (Gloss et al., 2014; Nicolas et al., 2018). We therefore chose to focus on ictal onset alone, so we did not analyze potential contributions of these types of interictal findings to epilepsy surgical planning and outcomes.

5. Conclusions

Children undergoing IEEG monitoring have a distinct set of IOP types. There is overlap with some of the IOP types seen in adults, but not all types of IOPs seen in adults are observed in children. Children are often observed to have a burst of paroxysmal activity followed by electrodecrement at ictal onset, which is an IOP type not well-described in adults. Older children are more likely to have LVFA at ictal onset than younger children. LVFA within the ictal onset on pediatric IEEG is significantly associated with increased likelihood of surgical success, All seizures having the same IOP morphology was also significantly associated with increased likelihood of surgical success, and therefore consistency of the IOP may be useful for prognostication and surgical planning. As a next step, we aim to address the questions if seizure propagation pattern and changes in IOP during the medication taper predict the postsurgical outcome in the pediatric age group.

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Declarations of interest

None.

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