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Epileptogenicity and surgical outcome in post stroke drug resistant epilepsy in children and adults

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ABSTRACT

OBJECTIVE Post-stroke epilepsy (PSE) represents a rare etiology in patients undergoing pre-surgical evaluation for epilepsy. Refractory PSE has been traditionally surgically treated with hemispherotomy. The aim of this study was to define the electrophysiological features of epileptogenic zone (EZ) using stereoelectroencephalography (SEEG) recordings in patients with refractory PSE. *METHODS* We analyzed ictal SEEG recordings from 21 consecutive patients. Epileptogenicity was quantified using the "epileptogenicity index" (EI) method in distant and perilesional cortical structures. We identified different seizure onset patterns (SOP) through a visual and time-frequency analysis. *RESULTS* We found that 81% of patients showed a complex organization of EZ, involving remote and perilesional structures. EZ involved a significantly ($p < 0.01$) higher number of distant regions displaying a high epileptogenicity (EI ≥ 0.3). Low voltage fast activity (LFA) and high amplitude slow activity (HAS) patterns were observed respectively in 85.7% and 14.3% of patients. Surgery was proposed in 12/21 patients. Good surgical outcome (Engel Class I or II) was observed for all patients who underwent tailored functional disconnection based on SEEG results. Shorter epilepsy duration to surgery was found in the seizure-free group. *SIGNIFICANCE* Refractory PSE may present a complex organization of EZ. SEEG recordings are warranted to guide tailored hemispherectomy.

1. Introduction

Stroke is the most common cause of epilepsy after middle age (Tanaka et al., 2015). Long term cumulative risk of post-stroke epilepsy varies from 2 to 15% (Zelano, 2016). In children with perinatal arterial ischemic stroke epilepsy rates ranging from 0 to 50% were reported, depending mostly on age at stroke onset and presence of acute symptomatic seizures (Golomb et al., 2007; López-Espejo and Hernández-Chávez, 2017),(Laugesaar et al., 2018),(Billinghurst et al., 2017). Perinatal arterial ischemic stroke, defined as a focal disruption of cerebral blood flow occurring between 20 weeks of gestation and postnatal day 28, is the second most common etiology of neonatal seizures, after perinatal asphyxia (Fox et al., 2013). Intractable epilepsy could also represent a delayed presentation of perinatal stroke (Fitzgerald et al., 2007). Indeed, some authors have studied medically refractory epilepsy due to perinatal stroke in the context of childhood hemiparesis (Carreno et al., 2005; Prayson and Hannahoe, 2004; Smith et al., 2015).

Many studies have attempted to identify patients at high risk of seizures or epilepsy after stroke (Graham et al., 2013)(Galovic et al., 2018). Predictors of epilepsy within these patients seem to be hemorrhagic stroke, total anterior circulation infarction, stroke severity (in terms of functional outcome and size of stroke) and cortical or cortico-subcortical involvement. The role of acute seizures and of early age at first stroke remain ambiguous (Galovic et al., 2018; Lamy et al., 2003), (Pitkänen et al., 2016). An association between initial presentation of stroke with seizures and epileptogenesis has been clearly shown for

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children with perinatal stroke (Fox et al., 2013),(Fox et al., 2016). Furthermore, post-stroke seizures and epilepsy are independent predictors of vascular cognitive impairment and functional disability (Golomb et al., 2007; Pendlebury and Rothwell, 2009) as well as a risk factor for stroke relapse (Ryvlin et al., 2006).

The risk of developing post-stroke epilepsy (PSE) and severity of epilepsy seems also to depend on the affected brain regions. Notably, vascular damage of the parieto-temporal cortex, supramarginal gyrus and superior temporal gyrus was related to a higher risk of late seizures and epilepsy (Heuts-Van Raak et al., 1996). Around 25% of patients with PSE become drug-resistant (Ghatan et al., 2014; Wusthoff et al., 2011). These patients may need presurgical invasive investigations with intracranial recordings because of complex and widespread organization of the epileptogenic zone. Intracranial EEG in these patients showed seizure onset often remote from the early injured lobe or from the margin of the porencephaly (Carreno et al., 2005; Ghatan et al., 2014). Two main localizations of the epileptogenic zone (EZ) have been described in these patients, motor and posterior cortex, often showing bilateral involvement. Few populations of patients have been explored by intracranial EEG; in particular, to our knowledge, no homogeneous stereoelectroencephalography (SEEG) population has been reported in the literature (Kuchukhidze et al., 2008; Schilling et al., 2013; Usui et al., 2008).

For patients presenting an extensive EZ, different surgical techniques have been proposed such as multilobar disconnection, hemispherotomy and functional hemispherectomy (Dorfmüller and Delalande, 2013)(Scavarda et al., 2009). These procedures have proved to induce seizure control, but not improve functional outcome (Scavarda et al., 2009). More recently, more selective deconnexion has been proposed to replace the classical hemispherotomy (Scavarda et al., 2018).

The main objective of this study is to describe electrophysiological features of seizures (the organization of epileptogenic zone and the seizure onset pattern) among a cohort of patients with drug resistant epilepsy related to stroke, explored by SEEG recordings. In particular, we aim at quantifying the involvement of perilesional and not lesional cortical tissue at the seizure onset zone by using an objective measure, the “epileptogenicity index” (EI) (Bartolomei et al., 2008).

2. Materials and methods

2.1. Inclusion criteria

We retrospectively selected 21 consecutive patients affected by focal drug-resistant epilepsy secondary to vascular destructive brain lesion among 347 patients who underwent SEEG recording in our center between 2000 and 2016. During the same period, one patient had a complete hemispherotomy without prior SEEG due to an extensive lesion in one hemisphere.

We used the criteria of stroke established by Fox et colleagues(Fox et al., 2013) including (1) documented clinical presentation consistent with stroke, such as a sudden onset focal neurological deficit, headache or seizure; and (2) computed tomography or magnetic resonance imaging, showing a focal ischemic infarct or hemorrhage in a location and of a maturity consistent with the neurological signs and symptoms.

2.2. Pre-surgical evaluation

Prior to selection for SEEG, all patients underwent non-invasive assessment for drug resistant focal epilepsy, including detailed clinical history, neurological examination, neuropsychological evaluation, long-term video-EEG recording, brain structural magnetic resonance imaging (MRI), interictal 18-fluorodeoxyglucose-positron emission tomography (^{18}FDG-PET), and ictal single photon emission computed tomography (SPECT) when possible. Functional MRI for language and motor function or/and intracarotid amytal test, were carried out in selected patients. The degree of disability or dependence in daily activities was assessed using the modified Rankin scale (mRS) for stroke patients, adapted to evaluate children as well as adults (van Swieten et al., 1988).

2.3. SEEG recordings

SEEG recording was carried out during long-term video-SEEG monitoring in order to record several of each patient’s habitual seizures, following complete or partial withdrawal of anti-epileptic drugs. SEEG was indicated to define the EZ precisely when noninvasive data are inconclusive, to resolve divergence of noninvasive data pointing to two or more regions(Jayakar et al., 2016) (Isnard et al., 2018) SEEG exploration was performed using intracerebral multiple contacts electrodes (Dixi Medical™ (France) or Alcis™ (France); 10–15 contacts, length: 2 mm, diameter: 0.8 mm, 1.5 mm apart) placed intracranially according to Talairach’s stereotactic method. Implantation of intracerebral electrodes was performed in the neurosurgical department. Adequate localization of the electrodes in the cerebral space was checked using post-implantation 1.5 MRI or using a fusion of pre-implantation MRI and CT scan with electrodes in place. The anatomical targeting and number of necessary electrodes was established in each patient according to the hypotheses for localization of the epileptogenic zone determined by the clinical data and EEG recordings from phase 1. For all patients, at least one electrode was placed in the perilesional cortex.

Signals were recorded on a 196 channel Natus system, sampled at 512 Hz or 1024 Hz and recorded on hard disk (16bits/sample) using no digital filter. The only filter present in the acquisition process was a high-pass analog filter (cut-off frequency equal to 0.16 Hz) used to remove very slow non-physiological variations that sometimes contaminate the baseline. The video-EEG recordings were prolonged as long as necessary to capture several of the patient’s habitual seizures.

2.4. SEEG signal analysis: computation of the epileptogenicity index and seizure onset pattern

The epileptogenicity index (EI) is intended to quantify two important features of SEEG signals recorded during the transition from pre-ictal to ictal activity: (i) the redistribution of signal energy from lower frequency band (delta, theta, alpha) toward higher frequency band (beta, gamma) (energy ratio) and (ii) the delay of appearance of these high-frequency components in a given structure with respect to the first structure, itself involved in a “rapid discharge mode” (Bartolomei et al., 2008). In this respect, the EI is based on the same information as that used in visual review of SEEG seizure recordings.

In 3 cases, no fast activity characterized the seizure onset (cf. Seizure onset patterns). In these cases, the Energy ratio was changed in order to detect lower frequencies (gamma-beta-alpha/theta-delta).

In practice, we used a semiautomatic approach: a user-friendly graphical user interface allows the user to easily inspect and automatically validate detected change points, indicating the accurate onset of ictal rapid discharges. From this validation performed on a “structure-by-structure” basis, the EI was then computed. EI values are normalized with respect to the highest value across channels (ranging from 0 to 1). If there is no involvement of the brain structure, then EI = 0 whereas if the brain structure generates a rapid discharge and if the delay with respect to seizure onset is minimal, then EI = 1. An EI between 0 and 1 corresponds to variable values of epileptogenicity (for detailed methodology, see previous study (Bartolomei et al., 2008).

In order to determinate the epileptogenicity of analyzed brain areas, we selected several cortical structures that were crucial for understanding the anatomo-functional organization of involved systems. In agreement with the characteristics of our population, these structures differed from one patient to another (supplementary table, S1).

The EI was then calculated for each selected structure. We took

maximal EI values for both perilesional and distant regions for all seizures recorded in each patient.

An epileptogenic structure was defined as a cortical region initially involved in seizure generation (Bartolomei et al., 2008) and disclosing a EI ≥ 0.3. This cut-off was used to define regions with high epileptogenicity, according to previous reports (Bartolomei et al., 2011) (Lagarde et al., 2018b). The EI values obtained in sampled cortical regions were used to define different cerebral epileptogenic network.

Patterns of seizure onset have been described using visual analysis combined to spectral time-frequency analysis. The seizure onset was defined as the first change of intracranial EEG signal leading to a rhythmic sustained discharge. The seizure onset pattern (SOP) was defined over the electrodes involved in the EZ. Six SOP were categorized as previously reported by our group (Lagarde et al., 2016) (supplementary Fig. S2).

2.5. Statistical analysis

Statistical analysis was performed to assess potential links between epileptogenic network features (as defined by EI values and SOP) and some clinical parameters (age at epilepsy onset, epilepsy duration, degree of disability, age at occurrence of stroke).

Statistical tests were performed on EI values estimated for all seizures recorded from each patient. In order to evaluate the relationship between epileptogenicity and distance between studied sites, we estimated contacts as being “perilesional” when they were localized near the bank of the vascular cavity or inside a zone showing neuroradiological signs of gliosis /necrosis. All other electrodes were considered as “distant”.

For each patient we considered the mean maximal value of EI among selected seizures in perilesional and distant areas. The epileptogenic zone organization was considered as being either “focal” or “network” (Aubert et al., 2009). Focal organization corresponded to a situation where seizures were generated by only one structure characterized by an EI value ≥ 0.3. Network organization was considered present in situations where seizures originated in at least two distant structures disclosing EI value ≥ 0.3.

Possible correlation between epilepsy duration, age at epilepsy onset, delay between stroke and epilepsy onset, disability and size of the EZ, as reflected by the number of structures disclosing high EI values (NEI ≥ 0.3), was investigated using a Spearman’s rank correlation coefficient. Statistical analysis was performed in order to compare the data between different groups using a non-parametric Mann-Whitney test. Fisher’s exact test was used for qualitative data. A *p*-value smaller or equal to 0.05 was considered to be statistically significant.

3. Results

3.1. Clinical and SEEG data

Clinical data are summarized in Table 1. Twenty-one patients were included in our study (8 F/13 M), representing 6% of all patients explored in SEEG in our center between 2000 and 2016.

Mean age at epilepsy onset was 7.1 years (range 0.7–20; SD ± 5,6) and mean delay between stroke and epilepsy onset was 4.9 years (range 0–18; SD ± 4.4). Mean epilepsy duration was 16.2 years (range 4–38.3; SD ± 8.9).

Among the twenty-one patients, fourteen had a perinatal and seven a postnatal stroke. Concerning the type of stroke, seventeen were ischemic stroke, three hemorrhagic (these two categories defined by MRI findings) and one was a post-infectious vascular event (clinical history). All patients had confirmation of stroke by MRI (radiological findings are described in Table 2). Localization of the vascular region is detailed in Table 2. Three patients did not present a motor deficit, five patients had a disability mRS score of 1, two had a score of 2, ten a scores of 3 and one had a score of 4. A total of 76 seizures were analyzed. Mean number of electrodes in SEEG recording was 10 (range 6–18; SD ± 2,8).

Following the SEEG 12/21 were subsequently operated. In 7 patients, surgery was contraindicated (two because of the risk of language impairment and three because bilateral epilepsy organization was found). One patient had a significant spontaneous clinical improvement after SEEG, and another one after thermocoagulation.

Among surgical patients, 7 underwent functional disconnection (see Table 1 and 2 for more details) and 5 surgical resection, associated to anterior intraventricular callosotomy for one (P12). The limits of the resection as well as the limits of disconnection were defined and tailored for each patient on the basis of the SEEG results. Interpretation of SEEG data was performed by visual and quantitative analysis. Cortical areas initially involved in seizure generation (showing high EI values) were included as much as possible in the resection or disconnection planning. Eloquent regions have been preserved in some cases, such as visual or language regions. In cases where partial disconnection has been performed, it has always disconnected the motor cortex because there was a clear hemiplegia before the surgery. The disconnection procedure is detailed in a previous report (Scavarda et al., 2018). Mean follow up was 3.7 years (range 2–7 y, SD ± 1.4 y). The surgical outcome was: Engel class IA for 8 patients (66.7%) including 6 cases of disconnection and 2 frontal cortectomies, for one patient class II (perinsular disconnection) (8,3%) and for 3 patients class III (25%) (all surgical resections) (Fig. 2). No difference was found in the age at epilepsy onset and the epilepsy duration between seizure free and not seizure free patients (p = 0.6 and 0.5 respectively). There was no visual field defect in their ophthalmological assessments before disconnection, except for patient 5 who finally underwent a classical hemispheric disconnection. For this patient data from not invasive evaluation (video-EEG, MRI) were not concordant, he presented a widespread lesion, a dual pathology (ischemic lesion + polymicrogyria + hippocampal/parahippocampal atrophy) and his ictal semeiology (loss of contact, urination) had not a high localizing value. The SEEG was indicated to decide whether a cortectomy (mono or multilobar) or a disconnection could be possible. The six patients undergoing a tailored suprainsular disconnection showed no visual or cognitive degradation after surgery and 5/6 showed improvement in social and behavioural status (see Table 3). In the postoperative period, pre-existing hemiplegia was worsened but a rapid improvement was observed for all the cases (see details in Scavarda et al, 018).

3.2. Quantification of epileptogenicity and EZ organization

SEEG recordings permitted localization of the epileptogenic zone in all selected patients. The frontal lobe was the most frequently involved. Fourteen out of twenty-one showed an EZ involving the motor system, of which 6 patients presented involvement of central region (2/6 premotor and central). Central region was defined as cortical areas around the central sulcus, primary motor and somatosensory cortex and rolandic operculum. Five patients presented a premotor organization of EZ, 1 a prefrontal/premotor and 2 patients had an EZ located in the post-central region. Two patients showed an EZ involving the temporal lobe (1 temporo-mesial and 1 temporo-perisylvian). Among 5/21 of patients we defined an epileptogenic zone in the posterior region, all of whom having presented perinatal stroke.

Fig. 1 shows one example of SEEG exploration.

We analyzed a total number of 75 seizures (range 1–6/patient). The median number of epileptogenic structures (NEI ≥ 0.3) for each patient was 4. The median number of structures with EI ≥ 0.3 at distance of the lesion was 3, and 1 at perilesional area. In 17 (81%) patients, EZ involved remote and perilesional structures. One patient (4.8%) showed an EZ involving exclusively perilesional structures. For three patients (14.2%) the EZ involved only distant regions.

At the group level, no difference was found between mean maximal EI value between distant and perilesional regions ($p = 0.1$). We found

Table 1
Epileptological characteristics of included patients.

Patient No.	Age	Sex	Age at epilepsy onset	Epilepsy duration	Age at recordings	Seizure Onset Pattern	Epileptogenic zone localization/ organization	Surgery	Engel class	Follow-up (y)
1	22	M	6	9	15	pattern 2 (LAF)	PO/N	no (surgery contraindicated)	_	_
2	14	M	6	6	12	pattern 4 (LAF)	PreM/N	L central disconnection	IA	4,5
3	29	M	7	13	20	pattern 1 (LAF)	C_Pa/N	no (surgery contraindicated)	_	_
4	21	M	7	4	11	pattern 2 (LAF)	Pa/N	healed after SEEG	_	_
5	19	M	2	11	13	pattern 4 (LAF)	Pa_ant/N	L functional hemispherotomy	IA	4,5
6	41	M	0,7	38,3	39	pattern 2 (LAF)	PreM_Pa/N	L fronto-parietal disconnection	IA	3
7	26	F	1,5	23,5	25	pattern 1 (LAF)	PreM/F	L frontal disconnection (motor cortex)	IA	2,5
8	25	F	1,5	17,5	19	pattern 4 (LAF)	PreM/N	R frontal cortectomy (premotor cortex)	III	5
9	26	M	0,7	25,3	26	pattern 4 (LAF)	T plus/N	no (surgery contraindicated)		
10	18	F	8	10	18	pattern 6 (HAS)	PreM_C/N	L perinsular disconnection	II	2
11	37	M	6	23	29	pattern 1 (LAF)	Pa_post/N	no (surgery contraindicated)	_	_
12	46	M	7	31	38	pattern 5 (HAS)	PreM_PreF/N	L frontal cortectomy + anterior callosotomy	III	3,5
13	25	M	2	22	24	pattern 1 (LAF)	PT/N	improved after thermocoagulation	_	_
14	23	M	16	6	22	pattern 3 (LAF)	PreM_T/N	L frontal cortectomy	IA	2
15	15	F	7	6	13	pattern 3 (LAF)	PreM_preF/N	R functional perinsular, frontal and parietal disconnection (motor and sensorimotor cortices)	IA	3
16	32	F	8,5	16,5	25	pattern 2 (LAF)	POT/N	no (surgery contraindicated)	_	_
17	42	F	20	13	33	pattern 1 (LAF)	Tmes/N	R temporal lobectomy	III	7
18	21	F	3	13	16	pattern 4 (LAF)	C/N	no (surgery contraindicated)	_	_
19	33	M	18	12	30	pattern 3 (LAF)	PreM_PreF/N	R frontal cortectomy	IA	4
20	37	M	14	19	33	pattern 3 (LAF)	C/F	L frontal (motor cortex) and insular disconnection	IA	3
21	29	F	8	21	21	pattern 1 (LAF)	OT/N	no (surgery contraindicated)	_	_

Abbreviation: Pa = Parietal; PO = parieto-occipital; F = frontal; PreM = premotor; C = central; PreF = prefrontal; Tmes = temporo-mesial; T plus = temporal plus; OT = occipito-temporal; F = focal; N = network; L = left; R = right; LAF = low amplitude fast activities; HAS = high amplitude slow activities.

Table 2
Stroke and MRI features.

Patient No.	Sex	Stroke timing /age (y)	Stroke type/MRI findings	Disability status (modified Rankin scale)
1	M	P	I/ L occipital mesial region	1
2	M	Po/5	I/ L MCA distribution	3
3	M	P	I/ R central/postcentral (parietal rolandic) porencephalic cyst	1
4	M	P	I/ L inferior parietal lobule poroencephalic cyst	2
5	M	P	I/ L hemispheric atrophy, especially of hippocampus and parahippocampal regions, micropolygyria of central and insula regions	4
6	M	P	I/ L porencephalic cyst frontal pole and insula; atrophy of CC and thalamus	3
7	F	P	I/ R fronto-temporo-parietal atrophy (MCA distribution?)	3
8	F	Po/ 1,5	N/ bilateral parieto-central infarcts (R > L)	3
9	M	P	I/R temporal necrosis	3
10	F	P	I/ L parieto-temporal porencephalic cavity and hemiatrophy	3
11	M	P	I/ R parietal operculum, insula, fronto-temporal regions (MCA territory)	0
12	M	P	I/ L frontal operculum atrophy, perisylvian hypersignal	1
13	M	P	I/ L border zone	1
14	M	Po/7	H/L fronto-mesial (premotor) (ACA territory)	1
15	F	Po/ 7	I/ R MCA territory	3
16	F	P	I/ L parietal infarcts (MCA territory)	2
17	F	Po/20	H/ R porencephalic fronto-parietal-temporal cyst (MCA territory)	3
18	F	P	I/ R central/postcentral porencephalic cyst (MCA)	3
19	M	Po	H/ R prefrontal (AVM sequel)	0
20	M	Po/ 6	I/ L MCA territory	3
21	F	P	I/ L post parieto-temporal lesion (MCA territory)	0

Abbreviation: P = perinatal; Po= postnatal; I = ischaemic; H = haemorragic; N= post-infectious vascular event; L = left; R = right; MCA = middle cerebral artery; ACA = anterior cerebral artery; AVM = arteriovenous malformation.

that EZ involved a significantly higher number of distant regions displaying a high epileptogenicity (NEI≥0.3) (p = 0.021; Wilcoxon test) (Fig. 3).

3.3. Seizure onset pattern

Concerning seizure onset patterns, the most prevalent patterns were slow wave or baseline shift followed by LVFA (pattern 4) and low voltage fast activity (LVFA)(pattern 1), both found in 5/21 patients (23.8%), followed by and preictal spiking with rhythmic spikes of low frequency high amplitude followed by LVFA (pattern 2) and burst of polyspikes of high frequency and amplitude followed by LVFA (pattern 3), both found in 4/21 patients (19%) then pattern of rhythmic spikes or spike-waves at lower frequency and with high amplitude(pattern 5), found in 2/21 patients (9.5%) and theta/alpha sharp activity with the low frequency and progressive increasing amplitude in 1 patient (pattern 6) (4.7%).

We divided seizure onset patterns into two categories based on the presence of low amplitude fast activity (LAF) or high amplitude slow activity (HAS)(Lagarde et al., 2016; Wang et al., 2017). We found 18/21 patients (85.7%) showing a seizure onset pattern including a fast discharge and 3/21 patients (14.3%) presenting a slow onset seizure pattern, without fast discharge (Fig. 4).

3.4. Relationship between clinical data and EZ neurophysiological features

We looked at whether the EZ organization was correlated with clinical parameters. We first looked for a correlation between epilepsy duration, age at epilepsy onset, degree of disability and the NEI ≥ 0.3 using a Spearman's correlation test. No significant correlation was found for epilepsy duration (p = 0.4), for age at epilepsy onset (p = 0.4) or degree of disability, mRankin scale (p = 0.9). In addition, when comparing perinatal versus post-natal stroke, the NEI ≥0.3 was not significantly different (p = 0.9, Mann-Whitney), nevertheless, we found a tendency to higher mean EI values in patients with perinatal stroke (p = 0.056, Mann-Whitney test).

In the same way, we did not find any differences in SOP between perinatal and post-natal stroke nor any correlation between slow or fast activities at seizure onset and extension of EZ, measured by NEI ≥ 0.3. Any statistical analysis was performed looking for surgical outcome influencing factors. Nevertheless, we observed that 1) the mean number of epileptogenic structures (NEI ≥ 0.3) was not different with regard to surgical outcome (SF = 4,1; NSF = 4,6); 2) concerning SOP, fast activities showed a higher rate in SF (Engel Class IA) patients (77.7% vs 66.6%).

4. Discussion

Stroke represents a rare cause of drug-resistant focal epilepsy referred to presurgical evaluation, accounting for only 6% of patients undergoing SEEG recordings in our tertiary center. To our knowledge, this is the first specific SEEG study among patients suffering from focal drug-resistant epilepsy related to perinatal/postnatal stroke. In this study we aimed to delineate the neurophysiological features of EZ, by quantifying epileptogenicity in perilesional, on the edge of the vascular lesion, and in remote cortical regions (distant). Furthermore, we describe seizure onset patterns among this etiology. These findings are crucial in choosing the better surgical approach.

5. Organization of EZ: quantification of epileptogenicity and seizure onset patterns

Looking at the general organization of EZ among this population, we confirmed a higher prevalence of anterior localization of EZ, localized in suprasylvian areas for 67% of patients, followed by a posterior cortex involvement in 24%. The latter localization was exclusively observed in patients with perinatal stroke. These findings are consistent with previous studies and correlate with the higher incidence of MCA stroke and susceptibility of posterior cortex insult in the immature brain (Menon and Shorvon, 2009; Usui et al., 2019).

A large majority of patients (81%) showed a complex organization of EZ, involving both perilesional and distant structures. Other possible scenarios were isolated involvement of distant (14.2%) or perilesional regions (4.8%). Moreover, distant regions showed a greater epileptogenicity, in terms of extension, NEI ≥ 0.3, and of maximal EI values. Previous literature on drug resistant PSE have reported widespread epileptogenicity, often affecting remote regions. These previous reports defined the EZ mainly through scalp-EEG, MEG and Eco-EEG recordings

Table 3
Clinical data pre/post Op of the patients who underwent functional disconnection (Tailored suprainsular partial and functional hemispherotomy).

pt.	2	5	6	7	10	15	20
Surgical technique	L central disconnection	L functional hemisperotomy	L fronto-parietal disconnection	L frontal disconnection (motor cortex)	L periinsular disconnection	R functional periinsular, frontal and parietal disconnection (motor and sensorimotor cortices)	L frontal (motor cortex) and insular disconnection
preOp mRS score	3	4	3	3	3	3	3
postOp mRS score	1	ND	1	1	1	1	2
preOp VIQ/NVIQ	103/63	46	ND	76/58	76/58	88/67	ND
postOp VIQ/NVIQ	99/63	ND	ND	ND	ND	88/67	ND
Others preOp functional deficits (visual/language)	None	HH	None	None	None	None	Moderate anomia
Others postop Functional deficits (visual/language)	None	HH	None	None	None	None	Moderate anomia
postOp social 1 behavioral status	improved	ND	not changed	greatly improved	improved	improved	improved

Abbreviation: preOp= before surgery; posOp= after surgery; ND= not determined; VIQ= verbal IQ; NVIQ= not verbal IQ; GIQ = global IQ; HH=homonymous hemianopsia.

(Carreno et al., 2005; Ghatan et al., 2014; Kuchukhidze et al., 2008; Usui et al., 2008),(Bennett-Back et al., 2014). Major neuroanatomical changes and collateral sprouting of the injured cortex, followed by plastic rearrangements in remote regions, have been proposed as possible pathogenetic mechanisms of late seizures and PSE in animal models and humans (Menon and Shorvon, 2009). In animal models of neonatal strokes non-adaptive neurogenesis in contralateral hippocampus was reported, potentially implicated in secondary epileptogenesis (Kadam et al., 2010). Ghatan and colleagues speculated that early injury of associative regions could explain the kindling of multiple and distant cortical areas(Ghatan et al., 2014). In our series, EZ in the majority of cases (57%) involved highly connected associative areas (parietal, TPO junction or cingulate cortices) and in remaining patients premotor or motor cortex was involved. Connectivity studies in patients with motor cortex stroke showed acute disruption and successive recovery and increase of interhemispheric integration (Lee et al., 2018).

5.1. Seizure onset patterns

We also described SOP according to previous classification proposed by our group(Lagarde et al., 2016)(Lagarde et al., 2018a). We confirmed a prevalence of patterns including LVFA at seizure onset as described in previous series (Lagarde et al., 2016; Perucca et al., 2014; Singh et al., 2015)(Lagarde et al., 2018a). The pattern slow wave or baseline shift followed by LVFA has been mainly correlated with hippocampal sclerosis as etiology. HAS were reported as most frequently associated with atrophy, neuronal loss gliosis, notably diffuse gliosis (Perucca et al., 2014; Singh et al., 2015; Spanedda et al., 1997). However the number of analyzed patients in this series is limited, we confirm either a shorter epilepsy duration in patients presenting fast activities as SOP, as previously reported (Singh et al., 2015; Wang et al., 2017).

5.2. Surgical approach and outcome

Several surgical options have been reported in patients with drug-resistant PSE, from porencephalic cyst “uncapping”(Guzzetta et al., 2006), focal or large cortical resection(T Pascoal et al., 2013a),(Iida et al., 2005), functional disconnection(Scavarda et al., 2009), hemispherotomy (Carreno et al., 2005; Ghatan et al., 2014) and callosotomy (Dorfmüller and Delalande, 2013). Postoperative seizure outcome varies; Engel Class I has been reported in 60% of patients undergoing simple resection of gliotic scar around the cyst (Guzzetta et al., 2006), whereas variable outcome rates have been observed for cortical resection, depending on EZ localization, association with hippocampal sclerosis and perioperative electrocorticographic monitoring findings (Carreno et al., 2005; Ghatan et al., 2014; Iida et al., 2005)(Pascoal et al., 2013b). The best seizure outcome has been reported in patients undergoing functional hemispherectomy (up to 90% Engel Class I (Carreno et al., 2005; Dorfmüller and Delalande, 2013; Ghatan et al., 2014; Scavarda et al., 2009). In 6 of our patients, excellent outcome was observed after tailored suprainsular disconnection. This new technique has been recently reported (Scavarda et al., 2018) and is an efficient technique avoiding language, memory and visual consequences of classical hemispherotomy. A majority of patients who underwent TSIPH showed an improvement on their social behavior and no one presented a functional (motor or cognitive) degradation. This surgery was based on the results of SEEG which demonstrated a main role for premotor and precentral cortex, variably extending to the prefrontal cortex and the parietal cortex. This information, along with other clinical and imaging data, allowed disconnection of the EZ to be performed according to the specific pattern in each case.

This innovative approach tailors disconnections based on SEEG data in this way allows a truly functional surgical approach, targeting the epileptogenic zone and avoiding resection/disconnection of non-epileptogenic and functional areas (Scavarda et al., 2018).

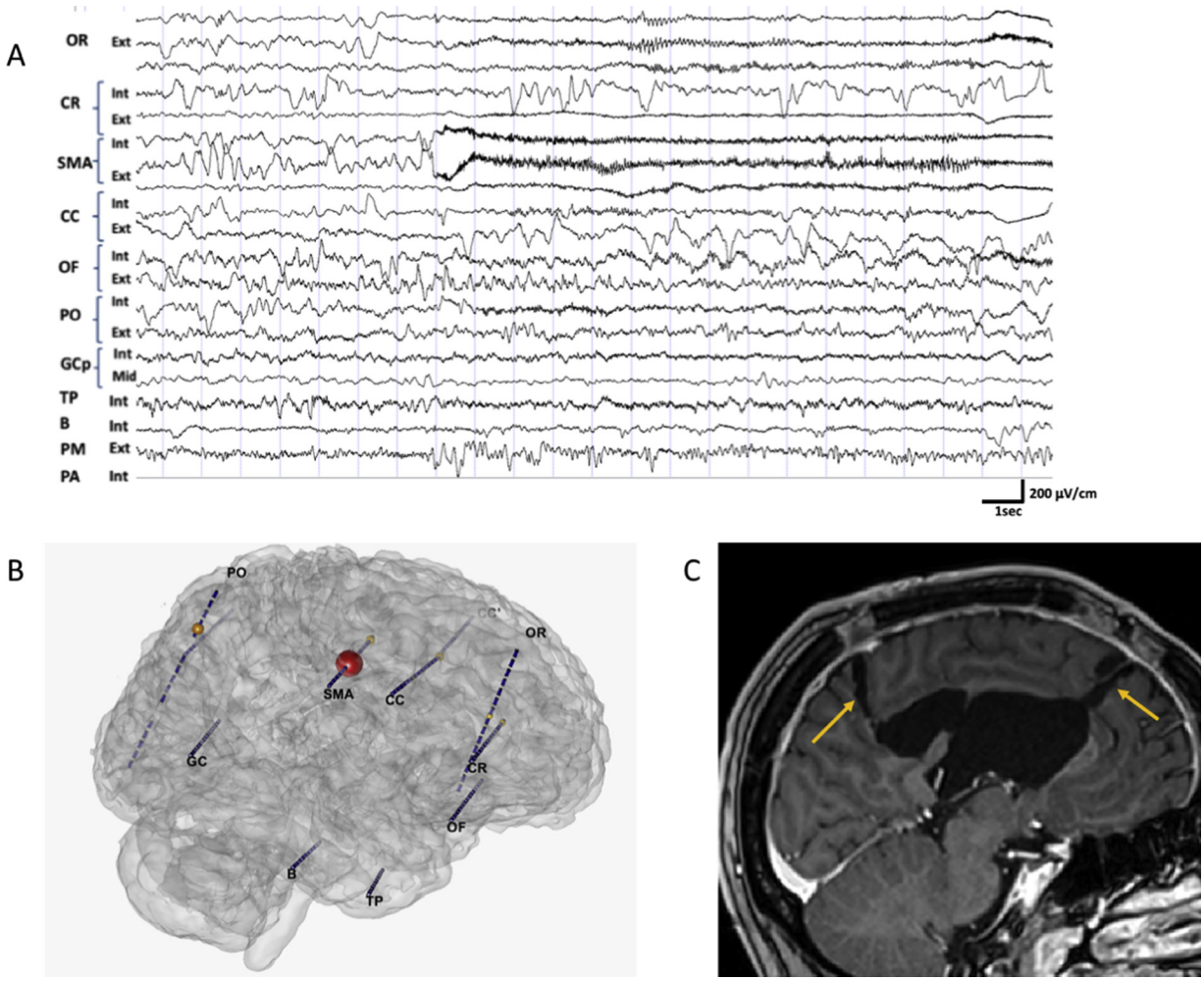

Fig. 1. Example of SEEG exploration in patient 7. A. SEEG traces of one typical seizure. The rapid discharge appears rapidly distributed over different regions but was prominent on the premotor (SMA electrode), as well the anterior cingulate cortex (CC electrode), the lateral contacts of electrode OR and of electrode PO. B. SEEG implantation showing the electrodes on a 3D MRI with the projection of the epileptogenicity index values as red and yellow spheres. C. MRI (sagittal plan) showing the disconnection.

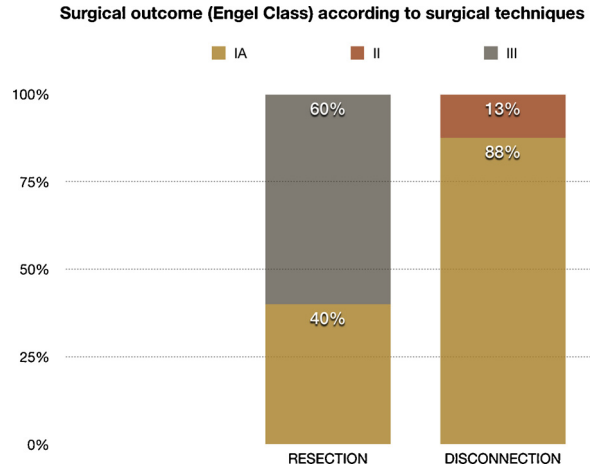

Fig. 2. Distribution of surgical outcome expressed in Engel Class according to surgical techniques. The frequency is expressed as a percentage of the total number of patients.

Lack of concordance between extent of the vascular lesion and the complexity of EZ could explain a lower efficacy of surgical approaches that are unable to disrupt a widespread epileptogenic network.

A formal assessment of surgical outcome predictors or a comparison between different surgical approaches in our study was impracticable, due to the limited number of patients proceeding to surgery.

Nevertheless, our findings supported 1) the key role of SEEG in delineating the complexity of EZ network and accurately defining the limits of disconnection; 2) an excellent seizure and functional outcome for patients undergoing personalized tailored disconnections based on SEEG results.

Further studies of a larger population are needed to compare functional outcome between patients undergoing different surgical approaches.

Moreover, to our knowledge the disconnection approach was mainly employed in children in this etiology (Scavarda et al., 2009). Our population corroborates the possibility of using this technique in adults.

Finally, disconnection procedures are aimed at interrupting epileptogenic pathways and isolating the EZ. Interruption of aberrant connections could explain potential improvement of motor function, as recently reported in an elegant case report in a patient treated by a disconnection of the contralateral sensorimotor cortex(Pascoal et al., 2013a,b). These findings need to be confirmed in a larger series. Otherwise, they highlight the need to consider surgery in patients with drug-resistant PSE and to delineate surgical limits through SEEG findings.

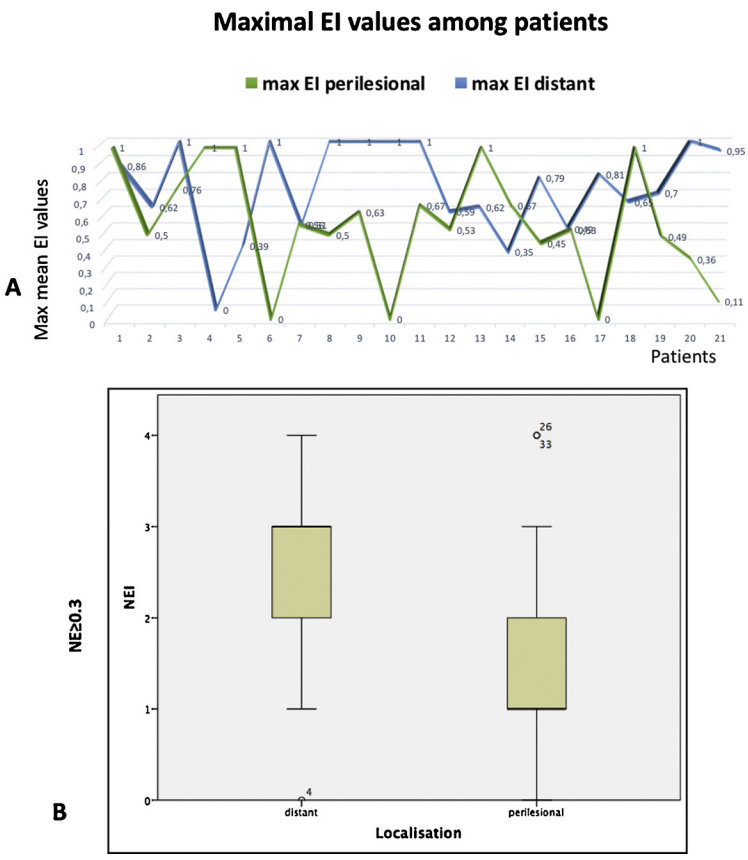

Fig. 3. A. Comparative profiles of epileptogenicity in the perilesional and distant cortical regions among 21 patients. For each subregion, we kept the highest EI value obtained in one perilesional region and the highest EI obtained in one distant area. **B.** Box-plots showing NEI ≥ 0.3 in perilesional and distant regions.

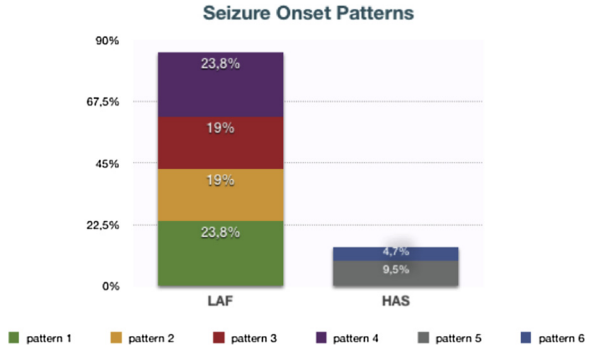

Fig. 4. Frequency of different seizure-onset patterns. The frequency is expressed in percentage of the total number of patients. Different seizure onset patterns are: 1)Low voltage fast activity (LVFA); 2) preictal spiking followed by LVFA, 3) burst of polyspikes followed by LVFA 4) slow wave or baseline shift followed by LVFA, 5) rhythmic slow spikes, 6) sharp theta/alpha activity.

Disclosure

The authors have no conflicts of interest to report. 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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