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Surgical Strategies for Epilepsy in Developing Countries: Experience with SEEG in Temporal Lobe Epilepsy

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Abstract

Introduction: In this work we present the evidence that in a developing country, it is possible to perform surgical treatment for drug resistant temporal lobe epilepsy patients, including those cases that require SEEG, with a similar outcome than in developed countries.

Methods: We selected 19 consecutive drug resistant temporal lobe epilepsy patients, who underwent SEEG evaluation at El Cruce Hospital from 2014 to 2019. SEEG is performed due to failure to localize the Epileptogenic Zone (EZ) with non-invasive methods, when the hypothesis of EZ are suspected to involve extra temporal areas, negative MRI, suspected bilateral onset, bilateral hippocampal lesion, or with discrepancies between MRI findings and scalp Video-EEG monitoring. The implantation scheme was planned based on the EZ hypothesis, based on scalp Video-EEG, especially ictal clinical semiology, neuroimaging data and neuropsychological results. Between 6 and 12 multilead electrodes per patient were implanted, in temporal and extra temporal areas.

Results: Thirteen patients (68.4%) with unilateral EZ were found eligible for surgery after SEEG. Seven patients underwent a mesial temporal region resection (left N=3, right n=4). One patient underwent a frontotemporal corticectomy, one patient an insulectomy. Because of the pandemic situation, four patients are on a list for surgery. Six patients were formally excluded from surgery because of the bilateral (seizures originating independently or concomitantly in both temporal lobes) or multifocal origin of their seizures.

Conclusion: According to the results obtained in this case analysis, we consider SEEG to be an appropriate method to define EZ in patients with drug-resistant temporal epilepsy and the subsequent indication for surgery. We hope to encourage the multiplication of epilepsy surgery centers in the region that have specialist staff and financial resources. Despite the high costs, it is achievable development with the same quality as that carried out in developed countries.

Keywords: Temporal lobe epilepsy; Stereoelectroencephalography; Epilepsy surgery; Ictal clinical semiology; Ictal electrical semiology

Introduction

The epidemiological studies available from developing countries suggest a prevalence of comparable magnitude for drug-resistant epilepsy [1,2]. Epilepsy surgery is an important treatment option for people with drug-resistant temporal lobe epilepsy [3], there is a great need for alleviating the extremely difficult situation of people with epilepsy and their families. A recent review has demonstrated the availability of epilepsy surgery in a few low- and middle-income countries, and much less if it were necessary to perform intracerebral monitoring for definition of Epileptogenic Zone (EZ) in surgical candidates [2]. Stereoelectroencephalography (SEEG) was designed and developed in the 1960s in Paris, France by Talairach and Bancaud [4]. It is an invasive method of exploration for drug-resistant focal epilepsies, contributing of a tridimensional and temporally precise study of the epileptic discharge. It allows anatomo-electrical correlations and tailored surgeries [5-9].

The identification of EZ using SEEG has gained acceptance over the last decade in contrast to electrocorticography [10]. By using SEEG we can describe hypothetical epileptic networks in three-dimensions. In this study, we present our experience in Argentina since 2014.

In 1984, some members of our group began to perform acute intraoperative Stereoelectroencephalography (SEEG), and since 1994, SEEG with chronic extra operative

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recordings. Our Surgical Epilepsy Center was installed in a public hospital from 1984 to 2014. In 2014, the same professional team moved to another public hospital, continuing its research and educational activity. According to the Argentine health system, patients who have state coverage do not have to pay directly for medical services. In the case of other coverage patients, the cost is outsourced.

In our experience, the creation of local specialized epilepsy centers with the capability to perform pre-surgical evaluation and epilepsy surgery faces several challenges, including a critical view of technological advances and the need to support well-trained people who can evaluate and operate patients with relatively limited resources.

The history of modern medicine shows that the use of technological resources that initially have a high cost, and therefore are limited exclusively to countries with high income levels, as it begins to have a wider use, the costs decrease. Even this technology has begun to be manufactured in underdeveloped countries. However, the greatest challenge is the training of specialized human resources.

In this work we present the evidence, by analyzing a series of cases, that in our country it is possible to perform surgical treatment for patients with drug-resistant epilepsy, especially those cases that require SEEG, with a similar outcome than in developed countries.

Methods

Subjects

For this research, we selected 19 consecutive patients with drug resistant temporal lobe epilepsy who underwent SEEG evaluation at El Cruce Hospital from 2014 to 2019. All the patients were investigated and implanted with a similar protocol. Between March 2020 and August 2021, SEEG and surgeries were cancelled because of the pandemic situation.

In the selected group of patients we decided to continue with invasive studies due to failure to localize the EZ with non-invasive methods, when the hypothesis of epileptogenic zones are suspected to involve extra temporal areas, those patients with negative MRI, or with suspected bilateral onset, with bilateral hippocampal sclerosis, or with discrepancies between MRI findings and scalp Video-EEG monitoring.

The EZ for the selected patients was defined on the basis of ictal semiology and electrical findings, MR imaging, and neuropsychological testing.

Non-invasive phases

Phase I: Ictal data: Video-EEG recording with analysis of electro clinical correlations [11].

Interictal functional data: Neuropsychological and neurologic assessment, mental health evaluation, PET, if necessary (not always available).

Interictal morphologic data, with 3 Tesla MRI [12,13].

Invasive phase

Phase II: The anatomic targeting of electrodes is established individually, according to available noninvasive information and hypotheses about the localization of the epileptogenic zone, set in an interdisciplinary pre-surgical conference with epileptologists, neurosurgeons, neuroradiologist, neuropsychologists and psychiatrists.

Video SEEG

SEEG exploration was carried out during long-term monitoring (7 to 12 days/24 h). Video-SEEG recording was prolonged as long as necessary in order to record several of the patient's habitual seizures. A 64 to 128 channel Micrones, Brain Quick, SDLTM 64 express, at a 256 Hz sample rate was used.

The protocol during the ictal and post-ictal period includes systematic patient assessment performed by qualified technical staff and, at the same time, patients are instructed to promptly advise the staff whenever they experience their first symptom.

By reviewing video-SEEG-recordings it has been possible to accurately identify every symptom and its precise time of onset, and associated ictal SEEG activity.

SEEG acquisition, recording and analysis

Between 6 and 12 multilead electrodes Ad Tech® were implanted per patient, in temporal and extra temporal areas depending on the suspected origin and region of early spreading of seizures. Electrodes were implanted perpendicular to the midline vertical plane with the patient's head fixed in the Talairach stereotactic frame. For mesial temporal lobe structures, depth electrodes were inserted through 2.5 mm diameter drill holes, using orthogonal orientation, usually targeting the amygdala, anterior and mid/posterior hippocampus locations. These enter the brain through the middle or inferior temporal gyrus and provide sampling from gyral and adjacent sulcal cortices (from superficial contacts) and mesial structures (deepest contacts). If necessary, another approach was used, recording the hippocampus with an electrode inserted occipitally and longitudinally, according to the hypotheses about the localization of the epileptogenic zone.

When the hypothesis of EZ involve extra temporal areas, other electrodes were implanted exploring extra temporal perisylvian region (the orbitofrontal cortex, the operculo-insular region through the frontal operculum, the temporal operculum), Other areas implanted were: Suprasylvian parietal area, anterior or posterior cingulo, in order to determine the extension of the EZ to these regions or to study the propagation of seizures. Oblique trajectories are used to reach the postero-medial orbitofrontal cortex.

Each electrodes consisted of: (a) 9 or 10 platinum contacts with 2.6 (Spencer) or 4.43 (Micro-Macro) mm inter-contact distance, contact length of 2.41 mm and 1.1 mm diameter (Spencer), or (b) 9 platinum contacts, 1.43 mm distance between the first and the second contact and 4.43 mm inter-electrode distance from the second to the last. Contact length was 1.57 mm and the electrode diameter was 1.28 mm. The SEEG clinical signal was low-pass filtered at 1000 Hz, sampled at 2000 Hz and recorded using the a 128-channel EEG System Micromed .

Simultaneously, 9 micro-wire platinum electrodes were implanted, with two purposes, to identify the EZ and research on memory systems, but still without clinical application yet, and these data will not be analyzed in this work [14]. (Ad-Tech Medical Instrument Corporation, USA and Micromed). Electrode locations in hippocampus (11 probes) and amygdala (8 probes) were based exclusively on clinical criteria. The signal electrodes were recorded using a 128-channel Micromed, Brain Quick. SD LTM Model 64 express, filtered between 0.3 and 7,500 Hz, and sampled at 30,000 Hz.

The exact position of each electrode was verified by post-implantation computed tomography-MRI co-registration. The

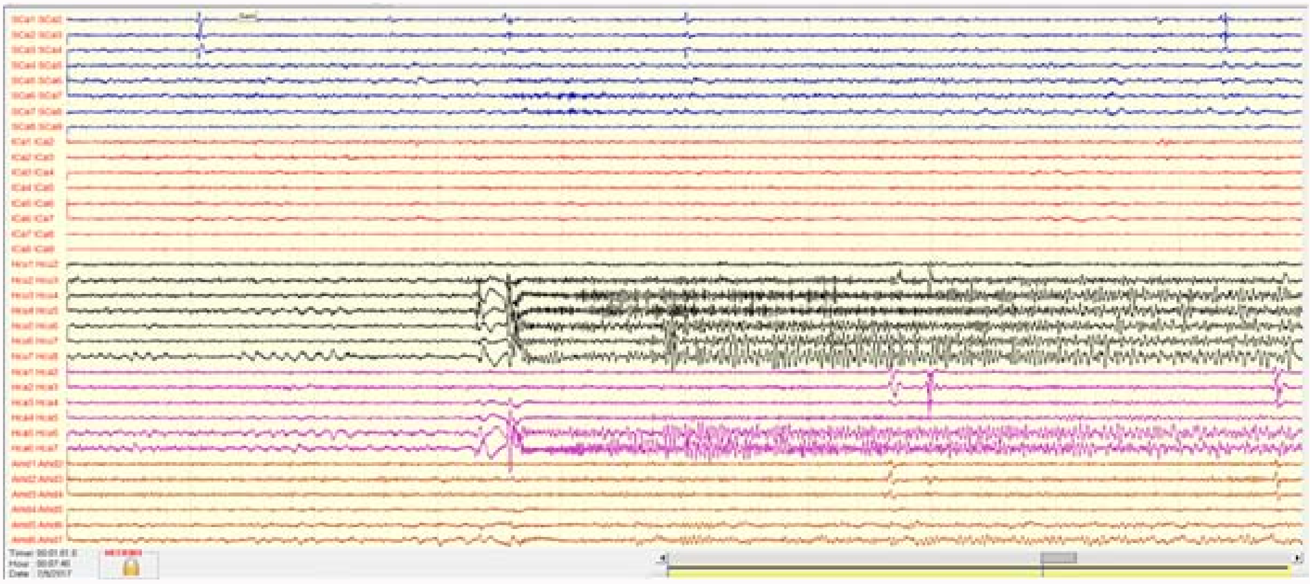

Figure 1a: Different patterns of seizures onset on SEEG recordings.

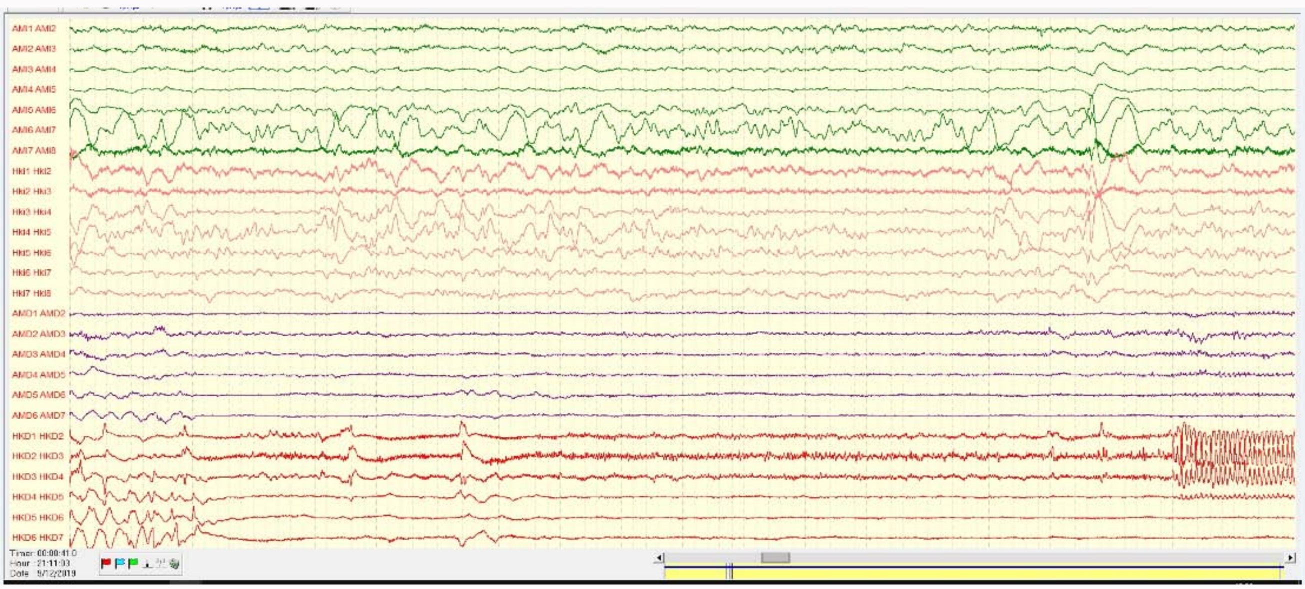

Figure 1b: Different patterns of seizures onset on SEEG recordings.

electrodes were left in place up to 12 days until sufficient information was obtained, including the recording of typical seizures.

The EEG activity is displayed using bipolar recordings between contiguous contacts and/or referential montages, in a global montage and in more selected channels, grouping adjacent and tightly connected regions and displaying them along rostrocaudal and/or dorsoventral axes, to provide an adequate overview for visual analysis. Synchrony and asynchrony between bursts of interictal activities from diverse areas are better identified. The electrocardiogram is systematically monitored.

For the purpose of this study, all SEEG recordings were reviewed by 3 qualified readers trained and experienced in video-EEG interpretation, and classified the ictal onset pattern. For inter-ictal analysis, approximately 2 h of EEG were reviewed each during day-time, night-time and sleeping states and significant epileptic discharges marked. Consensus was achieved by the 3 experts after discussion. The recording is daily reviewed to identify the background and paroxysmal activity.

Interictal abnormalities: The presence of slow activity, spikes, spike and wave, and fast discharges, was analyzed ictal activity. The first clear intracranial EEG sign of change from the background baseline that led to a clear seizure discharge without returning to the background baseline activity was identified as seizure-onset. The Seizure Onset Zone (SOZ) was identified visually on SEEG traces as the region where we identified the following activity occurred at the very onset of clinical seizures or before the earliest ictal manifestations: 1) Fast activity; 2) A high-amplitude slow synchronizing wave with fast activity superimposed; 3) Repetitive spikes or sharp waves in the preictal phase, followed by a fast activity (Figures 1a-1c).

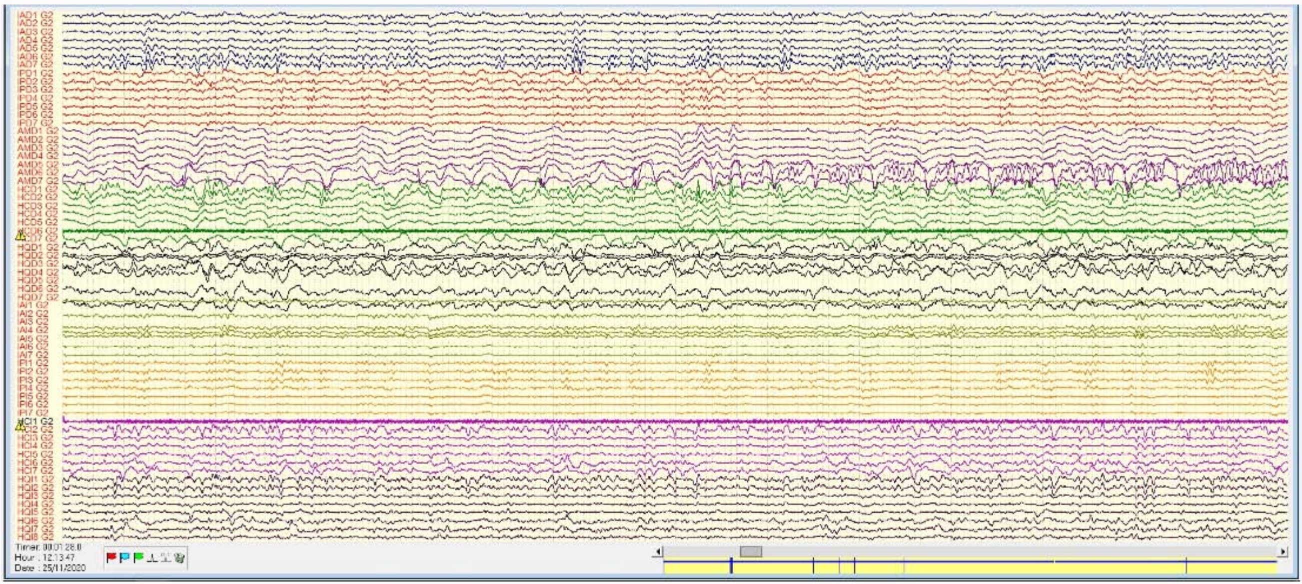

Figure 1c: Different patterns of seizures onset on SEEG recordings.

Electrical stimulation

Seizures triggered by Electrical Stimulation (ES) have an important diagnostic value when they reproduce the usual clinical pattern of the patient's seizures. Bipolar ES was carried out to map the eloquent areas and to evaluate the epileptic threshold in the epileptogenic cortex. If necessary, antiepileptic medication was progressively tapered during the SEEG monitoring [6,15,16].

Electrical stimulations were usually performed after recorded spontaneous seizures and performed between two contiguous contacts of the electrode using bipolar and biphasic current. Single bipolar pulse or train stimuli are used. The presence of after-discharges helped to differentiate non-epileptogenic from epileptogenic areas. The site from which a local after-discharge without any electrical or ictal clinical features can be triggered was considered to be outside the EZ.

We used two different parameters:

- Low frequency (shock stimulation) 1 Hz frequency, duration of 0.3 to 3 milliseconds, intensity of 0.5 to 5 milliamps, stimulation duration of 20 sec to 60 sec.
- High frequency (train stimulation): 50 Hz frequency, duration of 0.5 to 1 milliseconds, intensity of 0.5 to 5 milliamps, stimulation duration of 5 sec.

During stimulations, the following tasks were used: Naming, automatic speech (counting), repetition, reading aloud, and fluency.

MRI and CT Acquisition, electrodes localization

All subjects were scanned in a Philips Achieva 3T Magnet Unit, with final in-plane isotropic resolution of 1 mm. (TR/TE/TI=9.2/4.2/450 ms, matrix 256 × 256, bandwidth 31.2 kHz, FOV 256 mm × 256 mm, and 180 slices). We performed subject-specific anatomical segmentation, skull stripping and extraction of 3D pial surfaces for further analysis using the freesurfer image analysis (http://surfer.nmr.mgh.harvard.edu/). Non-contrast Computed Tomography (CT) (LSVCT GE, 64 detectors) scans was performed for each patient immediately after placement of electrodes in order to visualize IEs contacts and as part of the clinical evaluation.

Registration of MRI with post implanted CT and 3D models: For each patient, we registered the high-resolution preoperative T1 MR image and post-implanted CT, by using 3D Slicer open source medical image analysis platform (http://www.slicer.org). This procedure assured that the CT images and IEs were aligned with pre-implant MRI and all of the cerebral parcellations and 3D brain reconstructions provided by freesurfer as described in details by Princich et al. [12] (https://www.frontiersin.org/articles/10.3389/fnins.2013.00260/full).

PET

Our Hospital does not have Positron Emission Tomography (PET) equipment. In some patients we were able to perform interictal F-fluorodeoxyglucose (FDG) PET

Neuropsychological evaluation

The neuropsychological protocol used in this study was the same that was previously published by our group, and proved to be useful in locating and lateralizing EZ [17-21].

Neuropsychological evaluation was performed in three different stages: Before surgery, 6 months after resection, and a year afterwards. The protocol includes: (i) Attention: Forward And Backward Digit Span, WAIS, and Trail Making Test Part A; (ii) Verbal memory: Rey Auditory Verbal Learning Test (RAVLT) and List Learning Test; (iii) Visual memory: Rey-Osterrieth Complex Figure Test (RCFT); (iv) Executive function: Wisconsin Card Sorting Test (WCST), Trail Making Test Part B. Verbal Fluency (FAS); (v) Language: Boston Naming Test (BNT), Token Test (TT); (vi) Intelligence quotient (IQ); (vii) Handedness: Edinburgh Questionnaire (EHQ); (viii) Visuospatial Skills: Hooper tests; Judgment of Benton lines.

Psychiatric assessment

The psychiatric assessment is performed by trained psychiatrists, during the video-EEG monitoring (which usually lasts five days), according to a standardized protocol, with two main objectives: Diagnosis of comorbidities and psycho education for surgical treatment or invasive procedures [22-24]. Psychiatric evaluation is carried out when patients are lucid, able to answer all the questions.

If the patient has a seizure, the interview is interrupted until the postictal period ends. The psychiatric semiology is supplemented with structural interviews for present and past history of psychiatric disorders and personality disorders using standardized psychiatric assessments-the Structured Clinical Interview for Axis I diagnoses of DSM-IV (Structured Clinical Interview for DSM Disorders [SCID]-I and -II, respectively) [25]. In addition to these interviews, specific scales are used: Global Assessment of Functionality (GAF) [26], Beck Depression Inventory is used (BDI II) [27]. Barratt Impulsiveness Scale Factor structure of the Barratt impulsiveness scale [28].

Also, psychological the psychological evaluation included: McGill Illness Narrative Interview Schedule (MINI) [29], Brief Illness Perception Questionnaire [30], Quality of life in epilepsy-31 P inventory [31].

Surgery, follow-up and outcome

When the SEEG is finalized, electrode removal is carried out in the operating room. The surgical plan was finalized principally based on the results of the ictal SEEG and supported by results from other non-invasive evaluations, which helped to define the epileptogenic zone. All treatment recommendations were made within a multidisciplinary epilepsy conference. Surgery was performed in the same institution by the two same surgeons (P.S and E.S.). A histopathological examination of the resected tissue was performed in all operated patients. Post-operatively, patients were followed up by the surgeon (P.S.), as well as by epileptologists, neuropsychologists, psychiatrists and psychologists. All patients included in this study were followed up for at least one year. Seizure outcome was evaluated according to the ILAE classification system. Good and poor seizure outcomes were defined as ILAE class 1 to 3 and 4 to 6, respectively [32].

Statistical analysis

The data were analyzed using descriptive statistics. Nominal variables are presented as the number of subjects. Continuous variables are expressed as the median, minimum, and maximum. Analyses were performed using SPSS Statistics version 20.0 (IBM). This study was conducted with the approval of Institutional Review Boards of our Hospital.

Standard protocol approvals, and patient consents

Patients were fully informed about the aims and risks of electrode implantation, SEEG recordings and cortical stimulation procedures, and gave their written consent. Our epilepsy data register is approved by the local ethic committee.

Results

Between 2014 and 2021 we performed 233 Standard Anterior Temporal Lobectomies plus Amygdalohippocampectomy (SATL+AH), and a total of 47SEEG. We selected 19 patients who underwent SEEG, with a main EZ hypothesis located in the temporal lobe. In this group 126 spontaneous seizures (averaging 6.6-seizures/patient) were registered, and 30 provoked seizures during ES (average 3.3). The mean age was 29 years (range 18 to 43); the average duration of epilepsy was 14.3 years (range 5 to 44). Eleven patients (58%) were females and eight patients (42%) were male. None patient had a positive family history for epilepsy. One patient had a history of febrile seizures in infancy and two patients have a history of meningoencephalitis. Focal to bilateral tonic-clonic seizure was observed in 10 patients.

Pre-SEEG evaluation

For the analysis of the results, we divided the population into three groups according to the EZ hypothesis, diagnosed by non-invasive methods: A) Bilateral temporal; B) Unilateral temporal plus extratemporal; and C) Blateral temporal plus extra temporal.

Group A: Nine patients (47.3%), have a bilateral temporal implant. Interictal activity was as follows: Five patients have asynchronous bilateral temporal spikes, three patients, have asynchronous bilateral temporal and extra temporal spikes, three patients, have unilateral temporal spikes, and four patients have unilateral temporal and extra temporal spikes. MRI was normal in four patients, two patients have Bilateral Hippocampal Sclerosis (BHE), two patients have mild left mesial temporal changes that do not fulfill diagnostic criteria for Hippocampal Sclerosis (HS), and one patient has right HS associated with left amygdala enlargement. PET scan was performed in seven patients, five of these patients had bilateral hypometabolism, one patient has a normal PET scan, and one patient has a left temporal hypometabolism. Psychiatric assessment was normal in five patients and was abnormal in four patients. The most frequent psychiatric disorders observed were: Affective disorders, depression and anxiety disorders. In the neuropsychological assessment, almost half of patients presented both memory deficits (Table 1).

Group B: Seven patients (36.8%) have a unilateral temporal and extra temporal implant. Six patients have an interictal activity with unilateral temporal and extra temporal spikes and one patient has asynchronous temporal and extra temporal spikes. MRI findings were an insular lesion, a frontal heterotopia, a cingulate dysplasia, an occipital lesion, a temporal lobe oligodendroglioma, mild bilateral hippocampal changes, and one patient with a normal MRI. PET scan was performed in three patients, two of them have a right temporal lobe hypometabolism and one patient has a left temporal and parieto-occipital hypometabolism. Psychiatric assessment was normal in four patients and was abnormal in three patients. In the neuropsychological assessment almost half patients showed one type of memory deficit (Table 1).

Group C: Three patients (15.7%) have a bilateral temporal and extra temporal implant; interictal activity was asynchronous temporal and extra temporal bilateral spikes. MRI was normal in all of the patients, PET scan was performed in two patients, one patient has a right orbitofrontal and bilateral parietotemporal hypometabolism and the other patient has a bilateral frontotemporal hypometabolism. Psychiatric assessment was normal in two patients, in one patient was abnormal. Neuropsychological assessment showed bilateral memory deficits in two patients, the remaining patient has a non-verbal memory deficit (Table 1).

SEEG

Implantation scheme: The implantation scheme for the selected population was planned based on phase I methods (Table 1).

Group A: Bilateral temporal implantation was indicated in nine patients, targeting the amygdala, anterior and mid/posterior hippocampus locations. The defined EZ was mesial temporal in six patients: Left (n=4), right (n=2), and bilateral (n=3). Surgical treatment was indicated to the six patients with unilateral EZ.

Group B: In seven patients the EZ hypothesis included unilateral temporal and extra temporal areas. Patients underwent a unilateral and extra temporal implantation that included two or more of the following areas: The orbitofrontal cortex, the operculo-insular region

Table 1: Non-invasive evaluation.

Group	Patients	Gender	Age (years)	Time of Evolution (years)	Interictal scalp pattern	NPS	PSY	MRI	PET SCAN	Scalp Video-EEG	Implant
A	1	M	19	5	Async bil T spikes	Anomias	Normal	Normal	Bil T Hypom	Bil Mesial T	Bilateral temporal
	2	M	19	5	Async bil T spikes	Normal	Normal	Normal	Bil T Hypom	Bil Mesial T	Bilateral temporal
	3	M	36	11	Unil T spikes	Bilateral memory deficit	Anormal	LH mild changes	Bil T Hypom	Bil Mesial T	Bilateral temporal
	4	F	18	12	Async bil T spikes	Bilateral memory deficit	Anormal	BHS	Bil T Hypom	Bil Mesial T	Bilateral temporal
	5	F	43	21	Async bil T spikes	Verbal memory deficit	anormal	BHS	No	Unil Mesial T	Bilateral temporal
	7	F	32	25	Unil T spikes	Bilateral memory deficit	Normal	RHS+left amygdala enlargement	No	Bil Mesial T	Bilateral temporal
	10	F	33	15	Unil T spikes	Non-verbal memory deficit	Anormal	Normal	Normal	Bil Mesial T	Bilateral temporal
	13	F	34	16	Async bil T spikes	Bilateral memory deficit	normal	Normal	L T hipom	Bil Mesial T	Bilateral temporal
	17	M	21	21	Async bil T spikes	Bilateral memory deficit	Normal	Mild left mesial changes + <temporal pole size	Bil T Hypom	Bil Mesial T	Bilateral temporal
B	8	M	22	10	Unil T/ExT spikes	Anomias	normal	LHS+ insula lesion	No	Unil T/ExT	Unilateral left: temporal+ant ins+parahippacampus
	9	F	28	12	Unil T/ExT spikes	Non-verbal memory deficit	Anormal	Frontal heterotopia/ temporal lateral secuelar lesion	No	Unil T/ExT	Unilateral left: temporal+F heterotopia+ant. cin +OF
	11	F	28	10	Async T/ExT bil spikes	Non-verbal memory deficit	Normal	Tumor	No	Unil T/ExT	Unilateral right: Heschl g.+fusiform g.+lingual g+ ant /post insula
	12	F	33	23	Unil T/ExT spikes	Verbal memory deficit	Normal	Occipital secuelar lesion	No	Unil T/ExT	Unilateral right: temporal + occipital
	15	M	36	14	Unil T/ExT spikes	Anomias	Normal	Mild mesial bilateral changes	LT+LPO hypom	Unil T/ExT	unilateral left: T+left OF+ ant ins
	16	F	22	12	Unil T/ExT spikes	Disexecutive deficit	Anormal	Cingular dysplasia	R T hipom	Unil T/ExT	Unilateral right: temporal+ ant/middle/ post cing
	18	F	42	44	Unil T/ExT spikes	Verbal memory deficit	Anormal	Normal	R T hipom	Unil T/ExT	Unilateral right: Temporal+ OF+ant cing +preFrontal
C	19	M	29	5	Async T/ExT bil spikes	Bilateral memory deficit	Normal	Normal	R Lat T In hypom	Bil T/ExT	Bilateral temporal +bilateral ant/post insula
	6	F	21	5	Async T/ExT bil spikes	Bilateral memory deficit	Anormal	Normal	no	Bil T/ExT	bilateral temporal+ ant ins+OF+post cing+sup parietal
	14	M	36	6	Async T/ExT bil spikes	Non-verbal memory deficit	Normal	Normal	Bil F T In hypom	Bil T/ExT	Bilateral temporal +post cing+OF+ant ins +parietal Op

References: Async: Asynchronous; bil: Bilateral; T: Temporal; Uni: Unilateral; EXT: Extratemporal; NPS: Neuropsychological Assessment; PSY: Psychiatric Assessment; LH: Left Hippocampal; BHS: Bilateral Hippocampal Sclerosis; RHS: Right Hippocampal Sclerosis; LHS: Left Hippocampal Sclerosis; Bil T: Bilateral Temporal Hypometabolism; Bil FT in: Bilateral Fronto-Temporal and insula hypometabolism; LT+LPO: Left Temporal and Left Parieto-occipital Hypometabolism; RT: Right Temporal Hypometabolism; R lat T in: Right Lateral Temporal and Insula Hypometabolism; bil mesial T: Bilateral mesial Temporal EZ; Unil mesial T: Unilateral Mesial Temporal Lobe EZ, bil T/Ext: bilateral temporal and extratemporal EZ, uni T/Ext: Unilateral temporal and extratemporal EZ; bilateral temporal+ ant ins+OF+postcing+sup parietal: Bilateral Temporal and Anterior insula and orbitofrontal and posterior cingulus and superior parietal area implantation.

through the frontal operculum or the temporal operculum, parietal operculum; the anterior cingulate gyrus or posterior cingulate gyrus, Heschl's Gyrus, lingual gyrus, pericalcarine area, prefrontal area. Surgical treatment was proposed to six patients; in five patients the EZ included the lesional zone (two patients temporal, two patients temporal and extra temporal, and one patient insula). In the patient with the occipital secular lesion, the EZ was located in the temporal mesial region. In one patient we found a multifocal origin of their seizures so he was excluded from surgery.

Group C: In three patients the EZ hypothesis included bilateral temporal and extra temporal areas, underwent a bitemporal and extra temporal implantation, including two or more of the following areas: orbitofrontal cortex, operculo-insular region through the frontal operculum, the temporal operculum, parietal operculum; the anterior cingulate gyrus or posterior cingulate gyrus. In one patient the EZ was defined in the right lateral temporal lobe, and one patient had a bilateral mesial temporal EZ and one patient a multifocal EZ. Surgical treatment was proposed to the patient with unilateral EZ.

Table 2: SEEG evaluation and follow up.

Group	Patient	Clinical Semiology	Interictal Activity	Ictal EEG	Localization	Lateralization	EZ	Surgery	ILAE outcame	Pathology
A	1	Epigastric sensation, loss of consciousness, OA, bil MA, behavioral arrest	Fast activity	Fast activity	Hippocampal body	Left	Mesial temporal	LTL	III	ILAE type I HE
	2	Deja vu, loss of consciousness, staring, OA	Spikes And spike and wave LH and	Repetitive spikes or sharp waves bilateral	Hippocampal body	Bilateral	Mesial temporal	No	No	no
	3	Epigastric sensation, loss of consciousness, behavioral arrest, OA	Spikes and spike and wave	Repetitive spikes or sharp waves	Amigdala + hippocampal body	Left	Mesial temporal	LTL	III	ILAE type I HE
	4	Epigastric sensation, nausea, loss of consciousness, OA, left MA	Spikes and spike and wave	Repetitive spikes or sharp waves	Hippocampal head	Left	Mesial temporal	LTL	III	ILAE type I HE
	5	Cognitive, auditory illusion, behavioral arrest, language impairment. With or without loss of consciousness	Spikes and spike and wave	Repetitive spikes	Amigdala + hippocampal head and body	Left	Mesial temporal	Pending	no	no
	7	Epigastric sensation, autonomic, loss of consciousness, bilateral manual dystonia	Spikes and spike and wave	fast activity	Hippocampal head	Right	Mesial temporal	RTL	II	ILAE type I HE
	10	Cogitive, cephalic, autonomic symptoms, loss of consciousness, behavioral arrest, bilateral MA, urinary incontinence, right head deviation.	Spikes and spike and wave	Fast activity	Lateral middle temporal cortex	Right	Mesial temporal	Pending	No	no
	13	Loss of consciousness, OA, bilateral MA, ambulatory automatisms, ictal language.	Bilateral spikes and spike and wave	Spikes and slow waves	Hippocampal head and body and lateral middle temporal gyrus	Bilateral	Mesial temporal	No	No	no
	17	Loss of consciousness, behavioral arrest	Slow waves	High-amplitude slow synchronizing wave	Hippocampal head	Bilateral	Mesial temporal	No	No	no
B	8	Laryngeal sensation, language impairment, aphasia, autonomic symptoms, loss of consciousness.	Fast activity	Fast activity	Ant. insula	Left	ant. insula	Insulectomy	III	type IIB cortical dysplasia
	9	Loss of consciousness, bilateral MA, ambulatory automatisms, ictal language	Slow activity	High-amplitude Slow synchronizing wave	fronto-obitario/ middle temporal gyrus	left	Fronto-obitario/ middle temporal gyrus	Frontal cortisec Tomy + temporal cortisectomy	IV	type IIB cortical dysplasia
	11	Cognitive, visual illusion, laryngeal sensation, loss of consciousness, pallor, behavioral arrest, OA, bilateral MA, ictal language, urinary incontinence, ictal flatulences.	Fast activity	Fast activity	Fusiform gyrus + heschl gyrus	Right	Mesial temporal	Pending	No	no
	12	Cognitive symptoms, auditory illusion, loss of consciusness, behavioural arrest, bilateral MA	Slow waves, spikes	Repetitive spikes or sharp waves followed by a fast activity	Hippocampal head and body	Right	Mesial temporal	RTL	IV	type IC cortical dysplasia
	15	Deja vu, loss of consciousness, staring, OA, bilateral MA.	Spikes and spike and wave	Repetitive spikes or sharp waves followed by a fast activity	Orbito-frontal+mesial temporal	Multifocal	Fronto-temporal	No	No	no
	16	Auditive illusion, cognitive, language impairment, loss of consciousness, staring, behavioral arrest, bilateral manual dystonia.	Slow waves	Repetitive spikes or sharp waves followed by a fast activity	Hippocampal head+cingulus	Right	Temporal mesial +cingulus	RTL+cingulus	III	type IC cortical dysplasia
	18	Deja vu, anguish, fear, loss of consciousness, OA, MA; ambulatory automatisms, pallos, ictal language.	spikes and spike and wave	High-amplitude slow synchronizing wave	Superior temporal cortex + hippocampal body	Right	Temp sup y mesial derecho	RTL	III	ILAE type I HE
C	6	Cognitive symptom, speech arrest, loss of consciousness. Bilateral tonic clonic seizure	Bilateral spikes and spike and wave	Repetitive spikes or sharp waves followed by a fast activity	Hippocampal head and body	Bilateral	Mesial temporal	No	No	No
	14	Epigastric sensation, deja vu, gustatory hallucination, pallor. Loss of consciousness, OA, MA, Ambulatory automatisms.	Bilateral spikes and spike and wave	Fast activity	Orbito-frontal / middle temporal gyrus	Multifocal	Fronto-temporal	No	No	No
	19	Humming, auditoy illusion, rigt leg paresthesias, loss of consciousness, left or rigt head deviation. Bilateral tonic clonic seizure.	Spikes and spike and wave	Repetitive spikes or sharp waves followed by a fast activity	Superior temporal gyrus + amigdala + hippocampal head and body	Right	Mesial temporal	Pending	No	No

References: OA: Oral Automatisms; MA: Manual Automatisms; Im C: Impaired Consciousness; Behavioral Arrest

SEEG results: Electro-clinical Semiology in relation to the established EZ: Patients with unilateral temporal EZ (n=10: Right mesial five patients, left mesial four patients, right lateral one patient) presented auras: Deja vu/cognitive five patients; epigastric sensation four patients; auditory hallucination/illusion three patients; others: cephalic sensation, laryngeal sensation, visual, emotional (one patient each aura). All patients presented aura and loss of consciousness. Most frequent symptoms observed were: Behavioral arrest (60%), bilateral manual automatisms (50%), autonomic symptoms (50%), and oral automatisms (40%). Forty percent had evolved to a bilateral tonic clonic seizure. The only two patients that presented urinary incontinence and ictal language had a right temporal EZ. The ictal patterns associated were: in four patients, fast activity, five patients' repetitive spikes and sharp waves followed by a fast activity and one patient a high-amplitude slow synchronizing wave with fast activity superimposed.

Patients with bilateral temporal EZ (n=4, 21%). Auras: two patients had a cognitive aura. All the patients presented loss of consciousness. The most frequent manifestations were behavioral arrest and oral automatisms. The ictal patterns associated were: In three patients' repetitive spikes and sharp waves followed by a fast activity and one patient a high-amplitude slow synchronizing wave with fast activity superimposed.

Patients with unilateral Temporal/extra-Temporal EZ (n=2: One patient left, one patient right EZ). Aura: Cognitive and auditory illusion one patient; without aura one patient. The two patients presented loss of consciousness and evolved to bilateral tonic clonic seizure. The ictal patterns associated were: in one patient repetitive spike and sharp waves followed by a fast activity, and the other patient a high-amplitude slow synchronizing wave with fast activity superimposed.

Patients with multifocal EZ (n=2, 10.5%). Auras: Epigastric sensation and cognitive aura. The two patients presented loss of consciousness, staring, bilateral manual automatisms, oral automatisms, and evolved to bilateral tonic clonic seizure. The ictal patterns associated were: One patient fast activity, the other patient a repetitive spikes and sharp waves followed by a fast activity.

Patient with anterior left insular EZ (n=1, 5%). Aura: Deja vu, anxiety sensation, followed by language impairment, loss of consciousness, autonomic symptoms. The ictal pattern associated was a fast activity at seizure onset (Table 2).

Electrical stimulation

In nine patients (47.3%) ES triggered seizures (30 seizures), by stimulation applied between two adjacent leads of the EZ network. Seizures presented a similar clinical semiology and electrical pattern to spontaneous seizures, considering the spatial distribution and the evolution of the frequency features through the different areas. If a local after-discharge without any electrical or ictal clinical features was triggered, this particular site it was considered as being outside the EZ. In two patients (10.5%) auditory cortex was identified, and in both was outside the EZ.

Surgery

Thirteen patients (13/19, 68.4%) were found eligible for surgery. Seven patients underwent an Standard Anterior Temporal Lobectomy plus Amygdalo-Hippocampectomy (SATL+AH), in the dominant hemisphere was resected 3 cm and 5 cm from the temporal pole, in non-dominant cases was resected 4 cm from the temporal pole (left N=3, right n=4). One patient underwent a frontotemporal corticectomy. And one patient underwent an anterior insula resection. Because of the pandemic situation, four patients are on a list for surgery. Six patients were formally excluded from surgery because of the bilateral (seizures originating independently or concomitantly in both temporal lobes) or multifocal origin of their seizures (Table 2). None of the patients presented post-surgical complications.

Postsurgical outcome

Nine patients followed for at least 1 year, 7 patients showed a good outcome, all of them after SATL+AH, and 2 patients had a poor seizure outcome (Table 2).

Pathological anatomy

Pathological anatomy findings: Five patients (three left, two right) had hippocampal sclerosis type I (ILAE). Two patients have a type IC cortical dysplasia and two patients showed a type IIB cortical dysplasia (Table 2).

Discussion

The indication for surgery was performed in 68.4% of the cases analyzed. This finding is similar to that described in other epilepsy centers around the world. The use of SEEG monitoring in patients with temporal lobe epilepsy has specific indications. The central step in SEEG is to define a strategy for electrode placement. The integration of pre-surgical Video-EEG, especially ictal clinical semiology, neuroimaging and neuropsychological data results, allows us to define the EZ hypothesis and plan the SEEG scheme. For this instance, a well-trained multidisciplinary team that includes our staff epilepsy neurologists, psychiatrists, neuropsychologists, psychologists, neuroradiologist and neurosurgeons, constitutes the fundamental pillar. All the patients accepted surgery treatment when it was indicated. Our study protocol is very strict, only patients, who, in the psychiatric evaluation, reveal to be sure of receiving surgical treatment, underwent SEEG. A recent paper from an epilepsy center in United Kingdom [2], reports that only half of the adult patients with drug-resistant focal epilepsy who undergo pre-surgical evaluation, proceed with surgery.

Our SEEG electro-clinical findings have been similar to those described by other authors [15,33-35]. Clinical semiology plays a fundamental role for the implantation scheme, and electrical activity demonstrates the neural correlates during the evolution of the seizure. The stereotyped electro-clinical patterns observed, contribute in the definition of the EZ and to the knowledge about temporal lobe networks and its anatomical correlates. The identification of certain semiology sequences indicates its anatomical correlation, and the probable ictal trajectories in the brain in temporal and extra temporal seizures. These sequences were described in detail by Chauvel et al. [15], and we can confirm our findings. In 13 patients, we were able to define, following this methodology, the EZ hypothesis, including a patient with insular epilepsy that was included in this study because of the initial hypothesis of temporal epilepsy.

Despite the construction of strong pre-implantation hypotheses, some epilepsy localizations may be associated with bilateral EZs. There is controversy about surgical treatment in patients with bitemporal lobe epilepsy. Didato et al. [36] concluded "that surgical treatment should be discarded in patients with Bilateral Temporal Lobe Epilepsy (BTLE), as identified on ictal scalp VEEG". In a review, Aghakhani et al. [37] reported “the results of a meta-analysis of literature data on surgery outcome in 1,403 patients with presumed BTLE on the basis of scalp EEG recordings”. The main conclusion of this study was “that intracranial EEG (iEEG) revealed that temporal epilepsy was lateralized in 73% of these patients, and that 67% of them had a good outcome (Engel’s class I and II) after temporal lobectomy. Conversely when iEEG confirmed the bilaterality of seizures (“true BTLE”), by showing independent right and left seizures, only 45% of patients had a good outcome after unilateral temporal lobectomy”. On the other hand, Di Vito et al. [38] demonstrated that SEEG after unilateral resection in patients with bilateral origin of seizures with a good surgical outcome was useful to identify independent seizure onsets on one of the temporal lobe, and to choose the side of surgery. In our group of patients with bilateral independent seizure onset we discarded surgery treatment, considering the poor outcome reported in these cases. Also, other two patients were strictly accepted from surgery because of the multifocal origin of their seizures.

An important aspect to consider in countries with limited resources like ours, are high direct costs of surgery, and especially when it is necessary to perform SEEG, to date there is no other therapeutic alternative for this population, so we believe that it should be included in the diagnosis and treatment protocols of all the epilepsy centers of the world. In our center, we conducted a study of direct costs of hospitalization in the video-EEG Unit, conventional surgery, and SEEG, resulting in an approximate between 9000 and 12000 USD per patient [39]. Recent studies performed on developed countries, have demonstrated surgical intervention compared with non-intervention and the cost-effectiveness of SEEG [38,40]. Other authors have evaluated the direct costs of different SEEG techniques and a cost-effectiveness analysis where they conclude a total cost of 8000 Euros. The high costs of these procedures and treatments are significantly offset by the improvement in patient outcomes.

Based on the results presented in this study, we hope to encourage the multiplication of epilepsy surgery centers in the region, define the technical requirements and, despite the high costs of the electrodes and technical equipment, the possibility of their development with the same quality as that carried out in developed countries [1]. It is expected that, as has happened with other technological resources, the increase in their use will encourage the development of our own resources, with the same level and technical security, but a significant reduction in costs, a crucial aspect in our region.

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