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Seizure Outcome Relates to Prognostic and Histological Factors in Patients with FCD and HS Associated Partial Epilepsy

Research Article

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Abstract

Focal Cortical Dysplasia (FCD) and Hippocampal Sclerosis (HS) patients often present with seizures or pits which are drug resistant in nature. These patients can be seizure-free after lesion resection. However some still experience seizures after surgery. The present study aimed to analyze the clinical data of a group of FCD and HS allied partial epilepsy patients and evaluate their seizure outcomes and prognostic factors. Follow-up study involved clinical data collected from medical records of patients diagnosed with FCD and HS pathologically and underwent surgical resection in Department of Neurology, Krishna Institute of Medical Sciences (KIMS), Secunderabad. The seizure outcomes were evaluated based on the International League against Epilepsy (ILAE) classification. The prognostic factors were identified according to univariate and multivariate analysis. A total of 576 (FCD = 174; HS = 402) patients were included, with a mean age at surgery of 17.32 ± 8.34 years for FCD and 10.74 ± 7.24 years for HS. All patients were followed up at least for one year with a mean follow-up duration of 7.98 ± 3.84 years. At the final follow-up, 89 (51.6%) of FCD and 324 (80.5%) of HS patients achieved ILAE Class 1 or 2. Univariate and multivariate analyses revealed that the short duration of seizures and gross total resection were significant positive factors for seizure-free. Bilateral interictal or ictal epileptiform discharges in preoperative video-electroencephalogram (VEEG) were related to poor seizure outcomes. Surgical resection is an effective treatment for patients with FCD and HS associated partial epilepsy. The analysis of predictive factors could effectively guide clinical practice and evaluate the prognosis of drug resistant epilepsy.

Keywords: Focal Cortical Dysplasia; Hippocampal Sclerosis; Partial Epilepsy; Surgical Resection; Seizure Outcome; Prognostic Factors

Introduction

Epilepsy is the condition where spontaneous recurrent seizures happening and it is the major neurological disorders, with a prevalence of 6.38 % -7.60 % [1]. In the series of epilepsy surgery, FCD and HS of the CNS graded as the most common class of pathology leading to epilepsy with drug resistance [2]. Brain respective surgery is an efficient treatment for focal epilepsies with drug resistance of seizure freeness ranging from 60 % to 80 % within 01 % to 02 % follow-up years, 40 to 50 at 10 years of follow-up [3]. Added advantages in surgery are increased expectancy of [4], decreased sudden death risk [5], better life quality [6], mood improvement and regain of cognitive function [7]. All in all, these upshots are much better to the other choices of ablation, neuro modulation, and/or current medical therapy [3].

Nevertheless, almost 1/3 of patients persist to have convulsions after surgery, besides the resultant long term outcome is poorer than the immediate outcome, with 48% to 58% experience seizures continuing after 5 years of surgery [8, 9]. Hence it is urgency to reliable surgical outcomes predictors for HS and FCD linked epilepsies and choosing proper surgical patients remains a defy [10]. Some studies reported the threat reasons for postoperative surgery outcomes, but a section of these studies concentrated only on definite populations or on site specific focal lesions such as FCD and HS. Added to it, few articles reported only HS and FCD as a segment of the study object. In addition, previous results of research had only a certain worth to direct clinical work, as the research done with limited sample sizes. Herein, we studied a case strings engaging a total of 576 (FCD = 174; HS = 402) partial or focal epileptic patients to describe the clinico-histological characteristics and assess the outcome of surgery and predictors of prognosis. As per our familiarity, the current study is the largest group in the single study center.

Materials and Methods

Selection of Patients

This one institution study was agreed by the local committee of ethics. The criteria of inclusion were:

[i] Patients joined to Neurology Department, KIMS, Secunderabad from February 2010 to January 2018

[ii] Postoperatively confirmed the existence of FCDs and HS.

The rulings out criteria were:

[i] No seizures

[ii] A history of previous surgery

[iii] Clinical, electrophysiological, neuro radiological and pathological data not available to review

[iv] No surgical resection in patients

[v] Patients who lost during postoperatively. Medical records of patients' were reviewed retrospectively for detailed demographic, histological, clinical variables. The focal epilepsies allied with FCD and HS were classified according to the ILAE [11].

Pre-operative assessment

All patients subjected to non-invasive tests, including usual pre surgical valuations, such as detailed history, seizure semiology, brain MRI, neurological examination and long-term VEEG. MRI scans comprised T1-, T2- and FLAIR images. The lesion changes and epileptic site were analysed by neuro radiologist. The electrodes placed as per the standard 10 to 20 system with long-term 64 channels VEEG monitoring. IEDs or inter-ictal epileptiform discharges were named: a. Regional - IEDs involved 1 lobe or adjacent lobes; b. Unilateral - IEDs generated at ipsilateral hemisphere of the FCD or HS; c. Bilateral – IEDs in both hemispheres. Recorded ictal seizures from the patients were classified as a. Regional, b. unilateral and c. bilateral as per the IEDs. Neurologists and Electro physiologists teamed to spot the EZ (epileptogenic zone) depending on the observations of semiology and VEEG. Classification of seizure type was depending on the ILAE 2017 version [12]. Epilepsy surgery suitability was confirmed by a series of pre surgical examinations by a multi-disciplinary panel comprises of electro physiologists, neuro radiologists, neurosurgeons, and neurologists. In case the patient's VEEG depicted as the IEDs was localized and steady with the neuro imaging findings and symptomatological, usually the patient could directly proceed to the surgical stage. Other cases, patients require going into the 2nd stage of valuation.

Some particular non-invasive examinations need to be performed:

1. Magneto encephalography or MEG

2. Positron Emission Tomography-Computed Tomography or PET- CT. The EZ can be determined by non-invasive assessment in majority of the patients having FCD and HS. However in some patients the preoperative evaluation showed that the EZ was incompletely reliable with the lesion. In such cases, depth electrodes or subdural grids were implanted robotically to find the EZ.

Surgery procedure

The ultimate aim of surgery was the gross sum resection of the EZ with minimal or no complications. Neuro monitoring facilities like Intra-operative electro corticography or ECoG were conducted to define the EZ and found the functional regions. The surgical form was defined like: 1. GTR: No residual FCD or HS tissue identified on postoperative MRI

2. NTR: > 90% of the FCD/HS tissue was resected

3. STR: < 90% of the FCD/HS tissue was resected. Pathologists confirmed histopathology reports revealed that the tissues had an emblematic structure of FCD and HS.

Seizure Upshot during Follow-Up

All the patients who have undergone surgery for epilepsy were followed by the neurosurgeon in every 2 months at outpatient in the first year and annually after that. Scalp EEG and MRI were essential to find whether the EZ completely resected in all the patients at the 1st re-examination. The seizure upshots were recorded on far with the ILAE system for seizure outcome [13] with favorable or good outcomes defined as Class-I; unfavorable or poor outcomes as class-II-VI. All the patients resumed to get AEDs as prophylaxis post-surgically. EEG results and patients' surgery outcome decided whether to wean off or lessen the amounts of AEDs after surgery. Monotherapy patients would be able to wean off AEDs after the sugary gradually, if they: i. No convulsions for two years; ii. No IEDs in EEG; iii. No FCD/ HS lesions reappearance on MRI. Polytherapy Patients who met the above necessities could slowly reduce the dose of AEDs. Otherwise, the AEDs therapy should be planned as per the patients' test results.

Statistical Analysis

For the continuous variables, means, ranges and SD are represented. Frequencies and % are presented for definite data. The definite or categorical data was analysed by Fisher's z-test or Pearson X^2 test. Multivariate and/or univariate analyses were done to find the seizure outcome predictors. All statistical studies were performed with the SPSS software version 25 (IBM). P-value <0.05 is statistically significant.

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Results

Demographic Details

During February 2010 to January 2018, 576 (FCD = 174; HS = 402) patients (109 males and 65 females in FCD; 287 males and 115 females in HS) qualified the criteria of inclusion and enrolled for study. At the time of surgery, the average age was 17.32 ± 8.34 years for FCD and 10.74 ± 7.24 years for HS (Range: 1.5 – 67.0 for FCD; 1.2 – 69.0 for HS), the seizure onset average age was 11.54 ± 6.37 Y for FCD and 9.11 ± 7.17 Y for HS (Range: 1.0 – 65.0 for FCD; 0.9 – 67.0 for HS), seizures average duration was 5.78 ± 7.28 (where range = .1–20.3) Y for FCD and was 5.1 ± 6.8 (range, 0.1– 18.3) years for HS. The process of patient-selection was showed in (Figure I).

Clinical Characteristics

(Table 1) presented clinical individualities of all patients, depicting that 334 (FCD: 85+HS: 249 = 57.9%) patients experienced an aura prior to the seizures. The seizure onset was recorded every day (daily) in 191 (FCD: 59+HS: 132 = 33.1%), weekly in 207 (FCD: 67+HS: 140=35.9%), monthly in 163 (FCD: 44+HS: 119=28.2%), and yearly in 15 (FCD: 4+HS: 11=2.8%) patients. In the cohort, 387 (FCD: 91+HS: 296=67.1%) had only focal-onset seizures, 87 (FCD: 41+HS: 46=15.10%) only had onset of generalized seizures, and the rest of the patients 102 (FCD: 42+HS: 60=17.7%) had duel seizure types. Sixty one (FCD: 26+HS: 35=10.6%) patients had no AEDs before surgery, perhaps due to the squat duration of epilepsy or the less frequency of seizures, 117 (FCD: 37+HS: 80=20.3%) were underwent monotherapy and 398 (FCD: 111+HS: 287=69.09%) patients undergone polytherapy. At the end of the follow-up, 123 (FCD: 41+HS: 82) of the 576 (21.3%) patients weaned off AEDs, 301 (FCD: 47+HS: 254=52.2%) patients underwent monotherapy, and the rest 152 (FCD: 86+HS: 66=26.3%) were still accepting polytherapy. The average AED number after surgery (0.99 ± 1.08) was greatly lesser than at baseline (3.56 ± 0.87) ($P < 0.005$).

All the patients had preoperative examination of MRI. HS in TL identified in 402 (69.7%) individuals. Patients with FCD located in TL, FL, PL and OL were found in 53 (9.2%), 77 (13.3%), 16 (2.7%) and 28 (4.8%) respectively (Figure-II).

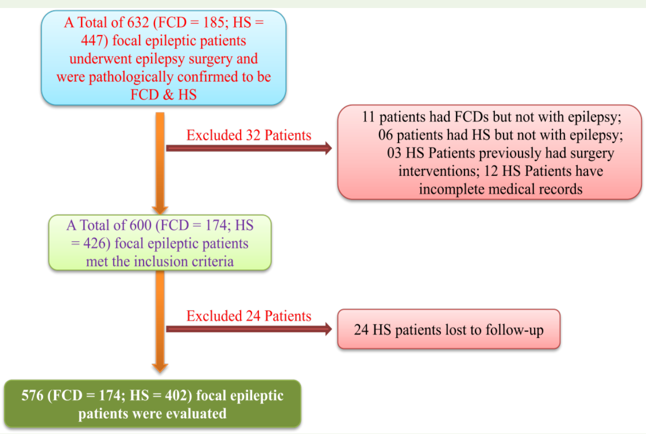

Figure 1: The process of patient's selection.

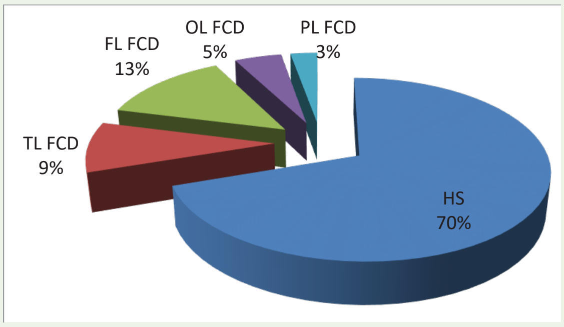

Figure 2: Location distribution of HS & FCD; Frontal lobe = FL; Temporal lobe = TL; Parietal lobe = PL; Occipital lobe = OL

To all patients, scalp EEG checking results were obtained. Regional IEDs found in 372 (FCD: 74+HS: 298 = 64.5%) patients, unilateral in 123 (FCD: 51+HS: 72 =21.3%), and bilateral in 81 (FCD: 49+HS: 32 =14.06%). Regional ictal onset rhythms found in 385 (FCD: 101+HS: 284 =66.8%), unilateral in 135 (FCD: 41+HS: 94 = 23.4%) and bilateral in 56 (FCD: 32+HS: 24 = 9.7%) individuals. The seizures onset could not captured due to insufficient time for monitoring of EEG in 93 (FCD: 22+HS: 71 = 16.1%) individuals. For precise localization of EZ, 398 (FCD: 125+HS: 273 =69.09%) patients underwent MEG, 141 (FCD: 41+HS: 100 =24.4%) underwent PET-CT, and 37 (FCD: 8+HS: 29 =6.4%) underwent intracranial electrode implantation. GTR of the focal lesion (FCD or HS) was achieved in 347 (FCD: 81+HS: 266 = 60.2%) cases, NTR was attained in 171 (FCD: 53+HS: 118 = 29.6%), and STR was achieved in 58 (FCD: 40 +HS: 18 = 10.06%) individuals. Histopathological records disclosed that the collected tissue samples had a representative structure of FCDs and HS. A total of 174 (FCD-IA: 25+FCD-1B: 31+FCD-IIA: 57+FCD-IIB: 36+FCD-III: 25 = 30.2%) were classified as various types of FCDs and the rest 402 were TLE-HS patients.

Surgical Difficulties

During this case strings, at the final follow-up no patient lost by seizure recurrence. A total of 96 (FCD: 61+HS: 35=16.6%) individuals had transitory neurological complications which did not influence their life quality, consist of 24 (FCD: 16+HS: 8=4.1%) with muscle weakness, 34 (FCD: 23+HS: 11=5.9%) with contra lateral quarter-quadrant hemianopia, 15 (FCD: 06+HS: 11=2.6%) with memory impairment, 8 (FCD: 05+HS: 03=1.3%) with transient dysphasia, 5 (FCD: 04+HS: 01=0.8%) with intracranial infection, 3 (FCD: 02+HS: 01=0.5%) with wound infection, and 6 (FCD: 04+HS: 2=1.04%) with CSF outflow. After comprehensive treatment, all 96 patients revisited to work or study. Added to it, 103 (FCD: 81+HS: 22=17.8%) patients suffered permanent neurological deficits, 43 (FCD: 31+HS: 12=7.4%) had hemi paresis, 18 (FCD: 11+HS: 07=3.1%) had facial paresis, 11 (FCD: 06+HS: 5=1.9%) had dysphasia, including 2 FCD (0.3%) patient with motor aphasia and 5 FCD (0.8%) patients with sensory aphasia, 3 FCD (0.5%) patients had hemianopia, and 1 HS (0.17%) patient with paresthesia. Even though the patients were subjected to postoperative healing training, they remain had signs that threaten their lives. It would be understand that the malfunction presented prior to treatment was excluded in the surgical impediments.

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Table 1: C linical, Demographic & Histological personalities of patients with focal epilepsies and association with surgery outcomes

Characteristics	Good Outcome	Poor Outcome	p-Value
	(ILAE-I)	(ILAE-II and Above)	(< 0.05* significant)
Sex:			
M: n = 109	81 (74.3%)	28 (25.7%)	
FCD			0.382
F: n = 65	48 (73.8%)	17 (26.2%)	
M: n = 287	223 (77.7%)	64 (22.3%)	
HS			0.274
F: n = 115	89 (77.3%)	26 (22.7%)	
Age at Seizure Onset:			
≤ 6Y: n = 101	72 (71.2%)	29 (28.8%)	
FCD			0.702
> 6Y: n = 73	51 (69.8%)	22 (30.2%)	
≤ 6Y: n = 212	193 (91.03%)	19 (8.97%)	
HS			0.364
> 6Y: n = 190	171 (90.0%)	19 (10%)	
Duration of Seizures:			
≤ 1Y: n = 37	22 (59.4%)	15 (40.6%)	
FCD			0.053*
> 1Y: n = 137	77 (56.2%)	60 (43.8%)	
≤ 1Y: n = 197	176 (89.3%)	21 (10.7%)	
HS			0.051*
> 1Y: n = 205	179 (87.3%)	26 (12.7%)	
Age at Surgery			
≤ 18Y: n = 78	52 (66.6%)	26 (33.4%)	
FCD			0.135
> 18Y: n = 96	79 (82.2%)	17 (17.8%)	
≤ 18Y: n = 207	179 (86.4%)	28 (13.6%)	
HS			0.151
> 18Y: n = 195	172 (88.2%)	23 (11.8%)	
Aura:			
Yes: n = 85	52 (61.1%)	33 (38.9%)	
FCD			0.183
No: n = 89	69 77.6%)	20 (22.4%)	
Yes: n = 249	183(73.4%)	66 (26.6%)	
HS			0.201
No: n = 153	132 (86.2%)	21 (13.8%)	
Seizure Frequency:			
FCD Daily: n = 59	43 (72.8%)	16 (17.2%)	0.173
Weekly: n = 67	44 (65.6%)	23 (34.4%)	
Monthly: n = 44	27 (61.3%)	17 (38.7%)	
Yearly: n = 04	03 (75.0%)	01 (25.0%)	
HS Daily: n = 132	103 (78.3%)	29 (21.7%)	0.096
Weekly: n = 140	107 (76.4%)	33 (23.6%)	
Monthly: n = 119	89 (74.7%)	30 (25.3%)	
Yearly: n = 11	09 (81.8%)	02 (18.2%)	
Seizure Types:			
FCD Focal only: n = 91	57 (62.6%)	34 (37.4%)	0.233
Generalized only:	24 (58.3%)	17 (41.7%)	
(n = 41)			
Both: n = 42	21 (50.0%)	21 (50.0%)	
HS Focal only: n = 296	213 (71.9%)	83 (38.1%)	0.196
Generalized only:	21 (45.6%)	25 (54.4%)	
(n = 46)			
Both: n = 60	39 (65.0%)	21 (35.0%)	

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	IEDs:			
FCD	Regional: n = 74	52 (70.27%)	22 (29.73%) 0.042*	
	Unilateral: n = 51	34 (66.6%)	17 (33.4%)	
	Bilateral: n = 49	25 (51.3%)	24 (48.7%)	
HS	Regional: n = 298	197 (66.1%)	101 (33.9%)	0.045*
	Unilateral: n = 72	47 (65.2%)	25 (34.8%)	
	Bilateral: n = 32	18 (56.2%)	14 (43.8%)	
	Surgical Type:			
FCD	GTR: n = 81	63 (77.7%)	18 (22.3%)	0.037*
	NTR: n = 53	37 (69.8%)	16 (33.4%)	
	STR: n = 18	09 (50.0%)	09 (50.0%)	
HS	GTR: n = 266	217 (81.5%)	49 (33.9%)	0.015*
	NTR: n = 118	67 (56.7%)	51 (43.3%)	
	STR: n = 40	21 (52.5%)	19 (47.5%)	
	Histopathology:			
FCD	IA: n = 25	14 (56%)	11 (44%)	0.087
	IB: n = 31	18 (58.06%)	13 (41.4%)	
	IIA: n = 57	39 (68.4%)	18 (31.6%)	
	IIB: n = 36	25 (69.4%)	11 (30.6%)	
	III: n = 25	15 (60%)	10 (40%)	
HS	n = 402	298 (74.1%)	104 (25.9%)	0.165
	Location Distribution:			
FCD	Frontal: n = 77	49 (63.6%)	28 (36.4%)	0.123
	Parietal: n = 16	08 (50%)	08 (50%)	
	Occipital: n = 28	16 (57.1%)	12 (42.9%)	
	Temporal: n = 53	35 (66.4%)	18 (33.6%)	
HS	n = 402	298 (74.1%)	104 (25.9%)	0.165

Outcome During Follow-Up

24 individuals went for reoperation. Fifteen of them subjected to FCD lesion deletion based on CT observations. Remaining 9 patients underwent HS removal that overlapped with functional areas. Ultimately, all of them achieved seizure-free, but 4 (FCD: 2 and HS: 2) of them had sensory aphasia and hemi paresis observed in two FCD individuals. At least for 1 Y, all the individuals were followed up with an average observation span of 7.98 ± 3.84 years. At the final follow-up, 89 (51.6%) of FCD and 324 (80.5%) of HS individuals achieved ILAE-I and II. Uni and multivariate analysis disclosed that the less span of seizures and GRT were significant supportive reasons for seizure-freeness. Among the 576 sufferers, 54 had convulsions only one time or rare auras even after missing of AEDs, included in the favorable outcome group.

Predictive Causes

The possible predictive factors allied with seizure upshot by univariate analysis were as follows:

Seizures duration (FCD: P = 0.053; HS: P = 0.051), IEDs (FCD: P = 0.042; HS: P = 0.045), Type of surgery (FCD: P = 0.037; HS: P = 0.015). Remaining factors that may not involve in the outcome are cataloged in (Table 1)

Discussion

Focal lesions of the brain, FCD and HS are the most common causes for the drug resistant epilepsies [2]. Surgery is generally used to combat seizures in these cases but post-surgical outcome is not upto the mark, reasons are unclear, and might be multifactorial [3]. Several studies have been done to relate clinical factors with the post-surgical seizure free outcome provided conflicting results due to its less sample size [13, 14, 10, 16]. The present study involved 576 patients (FCD: 174; HS: 402) who underwent epilepsy surgery. As per our familiarity, this is the largest case series on focal epilepsies from a single epileptic centre. Based on our studies more male than female identified for focal seizures with no difference in ILAE-I and II outcome (FCD: P = 0.382; HS: P = 0.274) conflicting with the previous studies [17]. More patients were identified with FCD allied focal epilepsies at < 6 years of age but HS allied epilepsies showed good outcome (FCD: P = 0.702; HS: P = 0.364) contrasting with earlier studies [18]. Surgery age >18 years have more ILAE-I and II outcome in FCD allied epilepsies (P = 0.135). Whereas surgery age has no influence on outcome of HS allied epilepsies (P = 0.151) supported earlier studies [19]. Most of the HS allied epilepsies had pre-operational auras, but more seizure free outcome was found in FCD and HS epilepsies with no pre-operational auras (FCD: P = 0.183; HS: P = 0.201), conflicting with the previous studies [20]. Daily and weekly seizure patients were more in FCD epilepsies, where as daily, weekly and monthly seizure patients were more in HS epilepsies. However in both the focal epilepsies, the seizure free outcome more in the daily and yearly cases (FCD: P = 0.173; HS: P = 0.096) supported by earlier studies [21, 22]. Epileptic patients with focal seizures showed good post-surgical outcome both in FCD (P = 0.223) and HS (P = 0.196) correlating with the previous studies [23]. Our study demonstrated TLE associated with HS offered good post-surgical outcome (P = 0.165) followed by FCD-IIB, IIA, III, IB and IA (P = 0.087) however, earlier studies have diverse

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opinions on histopathology based surgical outcome [3, 24, 25, 26, 27, 28 , 29]. Based on our study, FCD located in temporal lobe and frontal lobe offered good post-surgical outcome, irrespective of the FCD subtypes (P = 0.123) in correlation with the previous studies [30, 31]. Our study revealed that the above described clinical and histological factors have no influence on the seizure free outcome as they are statistically insignificant (P value is > 0.05). Based on the analysis (univariate), the possible and significant predictive factors allied with surgery outcome in FCD and HS epilepsies were seizure durations (FCD: P = 0.053; HS: P = 0.051), IEDs (FCD: P = 0.042; HS: P = 0.045) and surgical type (FCD: P = 0.037; HS: P = 0.015). Seizure duration is the time gap between seizure onset and the age of surgery. Both in FCD and HS, majorly in HS, the seizure duration of < 1 year exhibited more ILAE-I and II outcome. One conceivable supposition is that an enduring seizures cause an epileptogenic fuel processes such as synaptic plasticity, cell proliferation, cell death, inflammation and immune responses, that finally triggers new epileptic foci, consequently lower the chance to be seizure free after epilepsy surgery [14]. IEDs or inter-ictal spikes are bulky flashing electrophysiological actions found between seizures in epileptic patients. Even though IEDs happen more regularly than seizures, they are less studied and the connection to seizures unclear. Generally IEDs happen outside the brain tissue where the actual site of seizure onset and circulate toward it, representing that the dissemination of IEDs provides helpful information to localize EZ [32]. Several exposition studies depicted that dissecting brain areas of more IEDs improved surgical upshots in DRE patients [33]. Our studies revealed that patients with regional and unilateral IEDs got more favorable outcome in case of HS, whereas in case of FCD, regional IEDs provided good outcome. Complete resection of epileptic foci (GTR) offered good post-surgical outcome both in FCD and HS allied epilepsies. Furthermore our data fairly support the existence of an ongoing epileptogenic process managed by variety of biochemical and molecular factors, triggered by frequent seizures, traces of epileptic lesion and IEDs.

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