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Periodic epileptiform discharges in mesial temporal lobe epilepsy with hippocampal sclerosis

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ABSTRACT

Purpose: Periodic epileptiform discharges (PEDs) are an uncommon, abnormal EEG pattern seen usually in patients with acute diseases and less frequently in chronic conditions, such as mesial temporal lobe epilepsy (mTLE). Evaluate the clinical histories, neuroimaging findings, and serial electrophysiological studies prior to the appearance of PEDs in patients with mTLE secondary to hippocampal sclerosis (HS).
Methods: We searched 19,375 EEGs (2006–2012) for the presence of PEDs secondary to mTLE due to HS.
Results: 12 patients were included. The patients with PEDs had a high prevalence of psychiatric comorbilities, including major depression (50%), interictal psychosis (16%) and dementia (8%). All of the patients had intractable epilepsy with similar clinical findings. We observed a sequential neurophysiological worsening of the EEG patterns prior to the appearance of PEDs. Five patients with PEDs underwent epilepsy surgery and four were seizure free at follow-up 15 (±9) months.
Conclusions: PEDs are rare in patients with mTLE and HS and their presence in these cases could reflect clinical severity and neurophysiologic worsening, clinically manifested by intractable epilepsy and severe psychiatric comorbidities. The presence of PEDs in EEGs of patients with mTLE, however, was *not* associated with poor postsurgical seizure-freedom.

1. Introduction

Scalp electroencephalographic (EEG) findings in patients with temporal lobe epilepsy (TLE) commonly contain interictal blunt spikes, sharp waves, or sharp-slow waves complexes with maximal amplitude in basal anterior temporal electrodes (sphenoidal, zygomatic, mandibular notch $\geq$ T1/2 $\geq$ F7/8 $\geq$ T3/4).[1] These interictal epileptiform abnormalities are usually unilateral and may appear isolated or in short rhythmic trains lasting 1–2 s.[2] Other EEG patterns have also been reported in patients with TLE, such as interictal rhythmic delta activity[3] and frontal midline theta activity,[4] but the occurrence of interictal periodic epileptiform discharges (PEDs) in TLE is far less common.[5]

Periodic lateralized epileptiform discharges (PLEDs) were described initially by Chatrian et al.[6] and are considered abnormal indicating an increased risk for partial onset seizures.[7] Most often PEDs are found in patients with acute disease commonly caused by acute or subacute structural lesion of the cerebral cortex that can either diffuse or focal.[8,9] PEDs can also be observed in patients with static encephalopathy and epilepsy,[6,7,9] and some authors have postulated that chronic PLEDs may be a different entity than that occuring during acute illness.[10]

Studies have found PEDs in patients with symptomatic epilepsy,[9–12] with substantial controversy over whether PEDs and related discharges represent ictal phenomenon meriting aggressive treatment, or reflect a non-specific, self-remitting marker of brain injury.[9] To our knowledge no data has been

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published on the occurrence of PEDs in patients with mesial TLE (mTLE) with hippocampal sclerosis (HS), which is the most common pharmacoresistant form of human epilepsy observed at surgical epilepsy centers.[13]

The classical pattern of HS is characterized by greater loss of principal neurons in the Sommer sector (CA1 and prosubiculum), CA3, and the hilus of dentate gyrus than CA2 sector and subiculum, and often accompanied by astrogliosis and axonal reorganization.[14,15] In the present study, we describe the clinical and neuroimaging findings in patients with mTLE and HS, as well as electrophysiological changes prior to the appearance of PEDs.

2. Methods

This is a case series study, which was carried out using the printed records of all EEGs and video-EEGs performed from January 1st, 2006 to October 31st, 2012 at the Department of Neurophysiology from the National Institute of Neurology (NIN) in Mexico City. Among 19, 375 EEGs and video-EEGs we found that 12 had PEDs and mTLE with HS.

For these 12 patients we reviewed and summarized clinical information (age, sex, physical findings, past history of febrile seizures, status epilepticus or perinatal hypoxia, age at onset of epilepsy, time since diagnosis of epilepsy, type of seizures, seizure frequency, psychiatric comorbilities, neuropsychological abnormalities, surgery, outcome, and time of follow-up). We used the Engel scale to describe the outcome in the follow-up.[16] The psychiatry department evaluated all patients with psychiatric comorbidities using a typical approach in the outpatient clinic not exactly during the time of EEG recordings showing PEDs.

Each patient had a workup that included routine laboratory tests, clinical neurological evaluation, neuroimaging, neuropsychological testing, nuclear medicine studies, interictal EEG and video-EEG. The neuropsychological testing and nuclear medicine studies were not performed simultaneously or on the same day as the EEG recordings showing PEDs. High-resolution 3.0 T MRI (T1, T2 and FLAIR acquisitions) was qualitatively reviewed using a standardized protocol by two neuroradiologists who were blinded to EEG findings. For each patient, seizure semiology was described using the Clinical and Electroencephalographic Classification of Epileptic Seizure, ILAE 1981.[17] Based on these results, all patients in the present study were diagnosed with unilateral mesial TLE with MRI evidence of mesial temporal sclerosis without other lesions. The pathological confirmation of HS was available only in the patients who underwent epilepsy surgery.

All patients had digital awake routine EEG (30 min) and video-EEGs recordings (6–72 h) with 24 scalp electrodes positioned according to the standard 10–20 system of electrode placement, reformatted to both bipolar and off-head referential montages. The filter setting were 0.3 s (0.53 Hz) and 70 Hz. All of the EEG and video-EEGs recordings (with 30–50% of antiepileptic withdrawals) were performed without sedative drugs. No patients had a seizure cluster within 48 h of the EEG or video-EEGs.

2.1. Patients with PEDs and mTLE with HS

All EEGs or video-EEGs that had been reported as repetitive or periodic discharges, PLEDs, PEDs or periodic epileptiform abnormalities were included in the present study. The following inclusion criteria were considered: (1) EEGs or video-EEGs that meet the criteria of PLEDs, bilateral independent PLEDS (BIPLEDs) or generalized periodic epileptiform discharge (GPEDs), (2) Both male and female patients aged more than 16 years and (3) complete clinical records and a follow-up until death or for at least one year. Patients with reports of triphasic sharp waves, status epilepticus, incomplete clinical records or with a follow-up of less than one year were excluded from the study. For each patient, we identified the first EEG or video-EEG study showing evidence of PEDs and then reviewed all previous EEG studies to evaluate changes in the previous EEGs done on the same patient.

For the purpose of this study, we classified PEDs as PLEDs, BIPLEDs or GPEDs, using strictly adhered-to definitions. PLEDs were characterized as lateralized or focal; periodic or near periodic; or spike, spike-wave, or sharp-wave complex presentations throughout most or all of the recording.[6] GPEDs were defined as the occurrence of periodic complexes occupying at least 50% of a standard 30-minute EEG over both hemispheres in a symmetric, diffuse, and synchronized manner[7,8,18] and BIPLEDs were defined as bilateral independent periodic lateralized epileptiform discharges.[7,19,20]

2.2. Statistics analysis

We used descriptive statistics, all the values are expressed in mean, percents and standard deviations.

3. Results

3.1. Patients with PEDs and mTLE with HS

From 2006 to 2012, we recorded 19, 375 EEGs and video-EEGs in inpatients and outpatients. We identified twelve patients who had EEGs that contained PEDs, and all had mTLE with HS based on EEG, neuroimaging and epileptic semiology. In these twelve patients, BIPLEDs, GPEDs, PLEDs or PLED-like activity were captured on at least 1 available EEG or video-EEG, which represents a prevalence of 0.061% among the inpatient and outpatient EEG and video-EEG recordings. Complete clinical information, EEGs, video-EEGs and neuroimaging findings were available in all the patients. Tables 1 and 2 show the clinical, neurophysiological and neuroimaging findings of these patients. All the patients with hypoperfusion in the SPECT study were concordant with the PEDs localization, ictal onset recorded in the video-EEG and the HS side indicated by brain MRI, except two patient with PLEDs that showed bi-temporal hypometabolism in the SPECT.

The mean age of the patients was 39 (±12) year-old and 50% (6/12) were female. All patients were righthanded and 58% (7/12) of them had right mTLE. One patient with BIPLEDs had a past history of status epilepticus. The mean of the age at onset of epilepsy was 12 (±9) years old and the mean frequency of seizures monthly was 13 (±14). Also, all the patients had pharmacoresistant epilepsy and were taking 3 or more antiepileptics drugs, had normal physical and general neurological exams, but had moderate-to-severe neuropsychological deficits and were diagnosed with severe psychiatric diseases that included major depression 50% (6/12) or interictal psychosis 16% (2/12). Five patients underwent epilepsy surgery and four were seizure free at follow-up 15 (±9) months. The pathological analysis showed HS in these patients. Of the seven patients that had not had surgical treatment at the time of this study, two had interictal psychosis and dementia and their guardians declined surgical treatment, one patient refused the surgery, while the remaining four patients are scheduled for epilepsy surgery.

Fig. 1, illustrates the evolution of the EEG abnormalities before BiPLEDs were first observed. Table 2 shows the progression for an increase from slowing focal to generalized disturbances in the EEG of 5/12 patients. No patient had status epilepticus during the EEG recording. Among the 12 patients we had prior EEG or video-EEG recordings, which dated back to a median of 3 years (range 1–19 years). The PLEDs disappears in the postsurgical EEGs in patients who underwent epilepsy surgery.

Table 1
Clinical and neuroimaging findings of patients with periodic epileptiform discharges and mesial temporal epilepsy secondary to hippocampal sclerosis.

No. of patients	Age/sex	PED type	Past medical history				Side mTLE with HS (MRI)	Type of seizures (ILAE)	Frequency (mo)	Psychiatric comorbilities	Neuro-psychological deficits	Interictal SPECT	Surgery	Engel scale	Follow-up (months)
			Febrile seizures	Perinatal hypoxia	Age at onset of epilepsy (years)	Diagnosis of epilepsy (years)									
1	43/F	PLED		Yes	17	26	R	B1b,C2	5	Recurrent major depressive disorder, frequents postictal psychosis	Moderate verbal and visual memory deficits. Short-term memory deficit and long-term memory episodic dysfunction	Bilteral mesial temporal hypoperfusion	R AH and temporal anterior lobectomy	IA	27
2	33/F	PLED	Yes		1	32	L	B1b,C2	10	Major depressive disorder, generalized anxiety disorder	Moderate verbal and visual memory deficits	Left temporal hypoperfusion	L AH	IA	11
3	30/M	PLED	Yes		21	7	R	B1b,C2	4	Major depressive disorder	Moderate verbal and visual memory deficits	Bilteral R > L mesial temporal hypoperfusion	R AH and temporal anterior lobectomy	IA	22
4	33/M	PLED		Yes	28	4	L	B1b	53	Major depressive disorder	Semantic language,mild shortmemory verbal and visual deficits	Left fronto-temporal hypoperfusion	L AH and temporal anterior lobectomy	II	7
5	41/F	PLED			18	23	R	B1b,C2	4	Postictal psychosis, Interictal dysphoric disorder Major depressive disorder	Moderate verbal and visual memory deficities. Mini-mental Folstein 20/30				
6	42/M	PLED		Yes	1	41	R	B1b,C2	4	Interictal psychosis	Mini-mental Folstein 24/30				
7	72/F	PLED		Yes	6	65	R	B1b	4	Interictal psychosis	Apraxias, agnosias, severe visual and verbal memory deficities				
8	38/F	PLED		Yes	5	32	R	B1b,C2	10	Dementia Interictal dysphoric disorder	Moderate verbal and visual memory deficities				
9	25/M	PLED			10	15	L	C2,D	8						
10	27/F	PLED			12	15	R	A4b,C3	20	Major depressive disorder	Mild verbal and visual memory deficities		R AH and temporal anterior lobectomy	IA	8
11	40/M	BiPLED			20	20	L	A4b, B1b,C2	15	Interictal dysphoric disorder	Mild verbal memory deficits	Left temporal hypoperfusion			
12	47/M	BiPLED			4	42	L	B2b	16		Moderate verbal and mild visual memory deficities				

Table 2
Neurophysiological evolution of the previous electroencephalographic patterns of periodic epileptiform discharges in patients with mesial temporal epilepsy secondary to hippocampal sclerosis.

No. of patients	-19 years	-18 years	-11 years	-8 years	-6 years	-5 years	-3 years	-2 years	-1 year	Onset PEDs
1		3–4 Hz right focal temporal background slowing and sharp waves.	3–4 Hz right focal temporal background slowing and sharp waves.	3–4 Hz right focal temporal background slowing.	3–4 Hz right focal temporal background slowing and sharp waves.		3–4 Hz right focal temporal background slowing and sharp waves.	5–7 Hz generalized background slowing and 3–4 Hz right focal temporal paroxysmal slowing and sharp waves.	5–7 Hz generalized background slowing and 3–4 Hz right focal temporal background slowing and sharp waves.	√√5–7 Hz generalized background slowing and 3–4 Hz right focal temporal background slowing and PLEDs
2	3–5 Hz left temporal focal background slowing					Left fronto-temporal sharp waves	7–8 Hz generalized background slowing and 3–4 Hz left fronto-temporal focal background slowing and sharp waves.	7–8 Hz generalized background slowing and 3–4 Hz left fronto-temporal focal background slowing and sharp waves.	7–8 Hz generalized background slowing and 3–4 Hz left fronto-temporal focal background slowing and sharp waves.	√√7-8 Hz generalized background slowing and 3–4 Hz left fronto-background temporal focal slowing and PLEDs
3				Right fronto-temporal sharp waves		3–4 Hz right temporal paroxysmal focal slowing.			Right fronto-temporal sharp waves.	√√Right PLEDs
4									7–8 Hz generalized background slowing and 3–4 Hz left focal temporal background slowing and PLEDs	√√7-8 Hz generalized background slowing and 3–4 Hz focal left temporal background slowing and PLEDs
5									Right temporal sharp waves.	7–8 Hz generalized background slowing and 3–4 Hz right temporal focal background slowing and PLEDs
6									Right temporal sharp waves	Right PLEDs
7							4–6 Hz generalized background slowing and 3–4 Hz right temporal focal background slowing and sharp waves			4–6 Hz generalized background slowing and 3–4 Hz right temporal focal background slowing and PLEDs
8							4–6 Hz generalized slowing and 3–4 Hz right temporal focal slowing and sharp waves			4–6 Hz generalized slowing and 3–4 Hz right temporal focal slowing and PLEDs
9									5–6 Hz bi-temporal sharp waves and left PLEDs	Left PLEDs

10	Bi-frontal sharp waves	√√3–4 Hz bi-temporal background slowing and sharp waves.	√√7–8 Hz generalized background slowing, 5–6 Hz bi-temporal background slowing and right temporal PLEDs
11		√√6–7 Hz generalized, 5–6 Hz bi-temporal background slowing and left temporal PLEDs and right temporal sharp waves	√√4-6 Hz generalized background slowing and BiPLEDs
12		Bi-temporal sharp waves	√√7–8 Hz generalized background slowing and BiPLEDs

√√Inpatient video-EEG.

4. Discussion

Our results shows a prevalence of 0.061% of PLEDs due to mTLE and HS among the inpatient and outpatient EEG and video-EEG recoding in a neurological third level center. Their presence in these cases could reflect clinical severity and neurophysiologic worsening, clinically manifested by intractable epilepsy and severe psychiatric comorbidities. The presence of PEDs in EEGs of patients with mTLE, however, was *not* associated with poor postsurgical seizure-freedom.

Periodic epileptiform discharges are a rare EEG pattern. PLEDs prevalence varies from 0.1 to 1% in EEG laboratories.[6–8,21–26] However, the true incidence is likely higher as many patients with PLEDs may not undergo EEG, particularly those without a recent seizure or altered mental status.[26] Similarly, the true prevalence and incidence of BIPLEDs and GPEDs are also unknown, although studies report an incidence between 4% and 22% of BIPLEDs in patients in the intensive care unit[6,20,26] and a prevalence of 0.1% in routine EEG.[26] We did not found any patient with GPEDs and mTLE and HS. One possible reason is that GPEDS are usually seen in multifocal or diffuse cerebral injuries as anoxia, and herald a less favorable prognosis with higher mortality, though chronic GPEDs are now well recognized.[7] The prevalence of the PED in patients with mTLE and HS based in the criteria of clinical diagnosis is unknown.[27]

The present study describes the clinical characteristics and outcome of patients with PEDs and mTLE with HS. We found that our patients had the risk factors and natural history of patients with mTLE due to HS,[28] and all had intractable epilepsy with complex partial seizures sometimes with secondary generalization. Also, all of our patients had normal physical and neurological exams, but had moderate-to- severe neuropsychological deficits, which has been previously described in patients with mTLE and HS.[28] All had severe psychiatric comorbilities, including major depression, dementia or interictal psychosis with a prevalence higher than expected compared with patients with mTLE and HS without PEDs reported in other similar clinical case series.[29,30] One possible risk factor for this high prevalence is focus laterality in temporal lobe, our patients showed PLEDs more often on the right (66%). Currently, the type of affective disorder in relation to focus laterality in temporal lobe epilepsy is controversial.[31] Other predictors for development of interictal psychosis such as earlier age at onset of epilepsy, complex partial seizures or generalized tonic clonic seizures, and borderline intellectual functioning were similar to other studies.[32] Our descriptive study doesn't allow establishment of physiopathological or etiological associations between the cognitive dysfunctions and psychiatric conditions and the PEDs in mTLE with HS. Another limitation is the lack of serial neuropsychological evaluations during the follow-up.

Neuroimaging abnormalities occur in 90 to 100% of patients with PLEDs.[12] However, only one patient with chronic BIPLEDs and bilateral hippocampal injury has been published,[33] a 64 year-old man with bilateral hippocampal strokes with recurrent BIPLEDs. With respect to PLEDs and chronic subcortical lesions the prevalence reported in two separate studies had a range between 11 and 15%.[7,20]

Whether PEDs are an interictal or ictal activity remains unclear, despite reports of regional increases in cerebral blood flow, oxygen use, or hypermetabolism associated with PLEDs.[33–35] In contrast to previous studies, patients in the current study who had interictal SPECT studies showed mesial temporal hypometabolism, which was similar to a case that described a patient with chronic BIPLEDs with a benign prognosis who had bilateral hypoperfusion in the mesial temporal structures during the BIPLEDs recordings.[33] A possible explanation for the discrepancies among studies could be related to the stage of the underlying neurological condition. Our

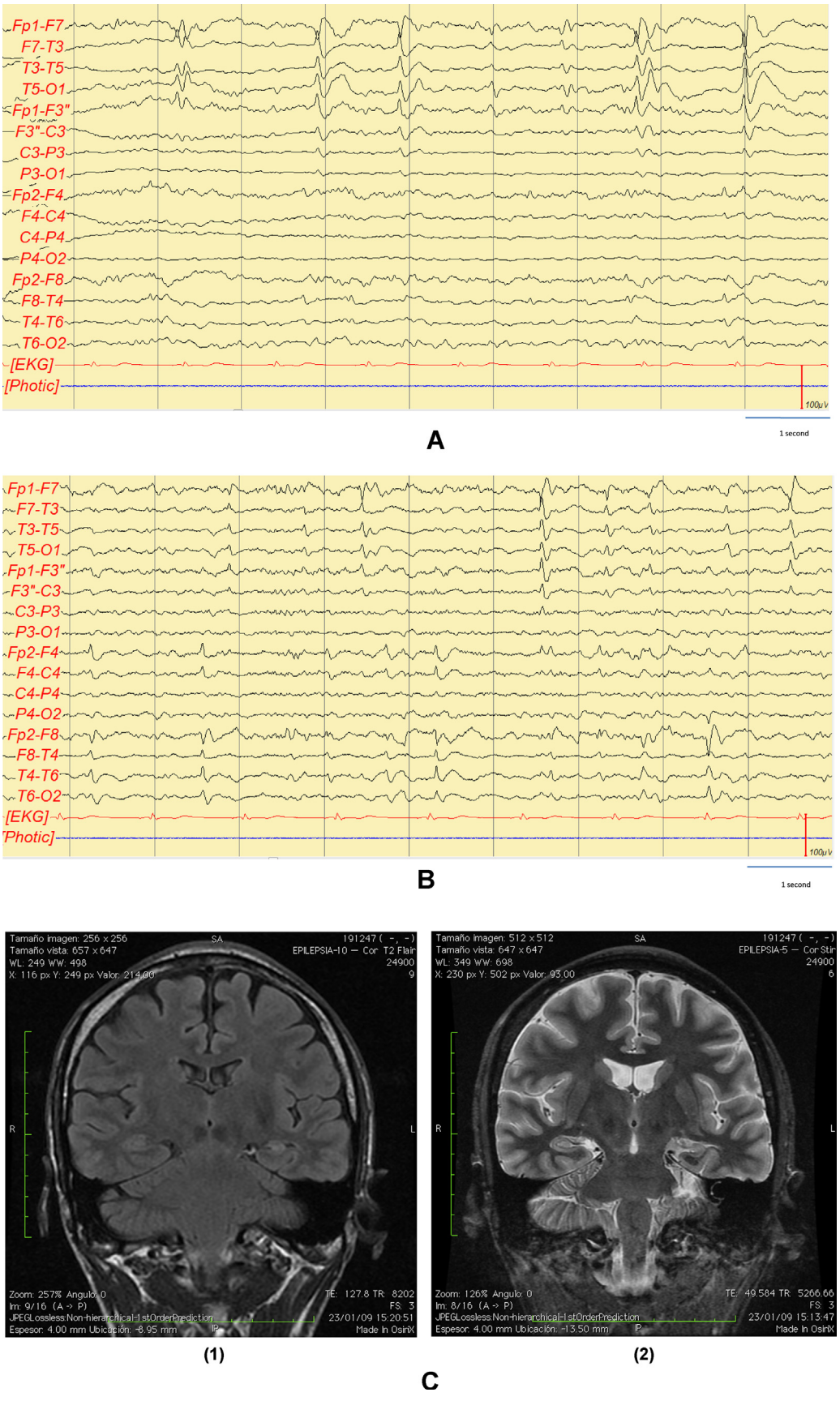

Fig. 1. Forty year-old male (Patient No. 11) with left mesial temporal epilepsy and hippocampal sclerosis. His video-EEG performed one year ago (A) showed 6–7 Hz generalized and 5–6 Hz bi-temporal slowing with periodic lateralized epileptiform discharges on the left temporal region and often sharp waves on the right temporal region. (B) In the follow-up the video-EEG shows Bi-PLEDs. These patterns were noted throughout or most of the total duration of the video-EEG recordings both during awake and sleep states. Low and high cut filters: 1–70 Hz. Notch: 60 Hz. Sensitivity: 100 μVp-p. (C) Cerebral MRI 3 T, (1) coronal T2 FLAIR and (2) STIR sequences showing left mesial temporal sclerosis. It's was perfomed the same year of the (A) video-EEG.

patients and the patient with benign BiPLEDs mentioned previously[33] had underlying chronic neurological conditions compared with the acute or subacute neurological conditions with PLEDs published elsewhere.[26,36] PLEDs may be observed for a prolonged period without the occurrence of either clinical seizures or electrographic evolution.[5,11] Positron emission tomographic studies have been undertaken in an attempt to clarify the ictal or interictal nature of PLEDs.[33] In some, increased local cerebral glucose metabolism could be found.[34] In contrast to the latter observation, other studies did not find an increase in either glucose metabolism or cerebral blood flow.[33,37] We consider in the present patients with mTLE and HS that PEDs are a marker of subcortical injury and not an ictal phenomena. Furthermore, the observation that the periodic discharges described resemble those found at a smaller scale when cortical dysplasias are invasively sampled and TLE PLEDs may arise in instances when the temporal neocortex is dysplastic,[26] is contradicted in our study because the histopathological findings in the neocortical sampled tissue were nonspecific. No patient was considered to have dual pathology, whereas the histopathological diagnosis of HS was evidenced in all cases submitted to surgery. The patient who underwent a left amigdalohippocampectomy (no neocortical resection) was also seizure free after surgery. Further, subsequent postsurgical EEGs showed no evidence of PEDS.

The pathophysiology associated with PEDs remains uncertain. For example, PLEDs can be generated from an acute or chronic cerebral injury and the location could be cortical, subcortical or both, although the most common substrate in PLEDs is an acute cerebral cortical and subcortical lesion.[7,11,20] However, some patients have normal neuroimaging studies when the PEDs are found.[7,24] One theory considers the spatially variable nature of brain lesions and proposes PLEDs can arise from different sites of the cortical-subcortical system prone to synchronous oscillations resulting from perturbation (i.e., lesion) of one or more sites.[20] Furthermore, changes in morphology and spatial patterns of PLEDs could arise from different sites within the network that generate different oscillations. Acute epilepsy animal models induced by bicuculline placed in the hippocampal-parahippocampal region of the isolated guinea pig brain found interictal and ictal epileptiform activities with variability of spatial propagation and time course in the olfactory-temporal region. In this model, arterial perfusion of bicuculline-induced periodic interictal spikes that originate in the piriform cortex, propagated to the entorrinal cortex and then sometimes spread to the CA1 region in the hippocampus.[38] However, ictal discharges are characterized by a peculiar pattern of fast activity that originates from the entorhinal/hippocampal region and only secondarily propagates to the perirhinal cortex. The results suggest that reiteration of ictal events may promote changes in the propagation pattern of epileptiform discharges that could act as trigger elements in the development of temporal lobe epilepsy.[38] Another interesting finding is that epileptiform ictal discharges are prevented by periodic interictal spiking in the piriform cortex[38] and olfactory cortex.[39] Invasive electroencephalography in patients with mesial temporal lobe epilepsy shows that the presence of periodic spikes before seizure onset has a significant correlation with reduced CA1 cell counts. This phenomenon is followed, in spontaneous seizures, by 13–25 Hz discharges in medial temporal lobe structures. Although hippocampus or entorhinal cortex are involved to a variable degree in mesial temporal epilepsy, the periodic spikes are more consistently seen in hippocampus.[40]

Mesial temporal lobe epilepsy with HS is a group of chronic disorders characterized by prominent neuronal loss and gliosis in the hippocampus and amygdala,[41] yet little is known about its 'natural' history from initial onset.[28] The course of the disorder is complex and may appear relatively benign at first with intractable seizures emerging only later.[28] Newly published data indicate that it may be a progressive disease, but the mechanism underlying the progressive nature remains unknown.[41] Ictal or inter-ictal chronic animal models of PEDS in temporal lobe epilepsy are lacking and the clinical evidence of chronic PLEDS in epileptic patients is rare.[9,10,12,36] Our patients are unique because PEDs are inter-ictal markers of subcortical injury, specifically in HS and provide a clinical opportunity to study the role of the inter-ictal PEDs in mesial temporal epilepsy with HS. The neurophysiological findings from previous EEGs of the same patients that later developed PEDs provides support that mTLE is a progressive disease.[41]

Other limitations of our study are the sample size, generalizability of our findings due to the potential sampling and selection bias of the referral patterns to our third level neurological center and the known limitations of retrospective studies.

5. Conclusion

In our study, PEDs were potential markers of clinical severity and neurophysiologic progression in patients with mTLE due to HS, clinically manifested by intractable epilepsy and severe psychiatric comorbilities, however, they did not impact the outcome after the epilepsy surgery. More studies with higher number of patients are needed to confirm these findings.

Conflict of interest statement

None.

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