

Classification and Serial Evolution of PLEDs

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Background and Purpose: Periodic lateralized epileptiform discharges (PLEDs) are defined as spikes or sharp waves occurring at an approximately regular interval. PLEDs are subdivided into PLEDs proper and PLEDs plus in Reiher's classification, but since this does not sufficiently reflect the pleomorphism of PLEDs, we propose a new subclassification scheme of PLEDs, and discuss the relationship between them and clinical prognoses.

Methods: Thirty-seven patients who had at least two available EEGs were included in this study. Each patient had structural brain lesions identified in brain CT/MRI: 237 EEGs from 37 patients were reviewed and the patterns of PLEDs were classified by electroencephalographic characteristics based on Reiher's classification. PLEDs proper of class 3 were subclassified into four categories: (1) simple, (2) benign, (3) vigorous, and (4) suppressed.

Results: Most of the PLEDs that started with the vigorous or suppressed pattern of class 3 evolved into the simple or benign pattern of class 3 and subsequently changed into class 1 or class 2, finally intermingling with the neighboring background waves. PLEDs that started with the benign or simple pattern of class 3 rapidly changed into class 1 or 2. Patients showing the benign or simple pattern of class 3 exhibited a better clinical prognosis.

Conclusions: PLEDs have five distinctive classes, and over time they evolve from malignant PLEDs plus to benign PLEDs proper before finally disappearing. It appears that those of class 3 have more diverse patterns, with the vigorous and suppressed patterns being the more malignant forms of PLEDs in this class.

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Key Words : PLEDs, EEG, Classification, Prognosis

INTRODUCTION

The term periodic lateralized epileptiform discharges (PLEDs), first coined by Chatrian and colleagues in 1964, is a peculiar electroencephalogram (EEG) pattern consisting of unilateral and focal spikes or sharp wave complexes that appear periodically, usually at the rate of 1~2 s.¹ Subsequent studies have described such variable periodic patterns as BIPLEDs (bilateral independent PLEDs), GPEDS (generalized periodic epileptiform discharges), SIRPIDs (stimulus-induced rhythmic, periodic, or ictal discharges), and subclassifications of PLEDs.²⁻⁵ Although the likelihood of neuronal injury from each

type of discharges in a given clinical setting has been emphasized, the categorization of the various types of PLEDs have been controversial. Furthermore, few studies have investigated temporal changes in the patterns of PLEDs.

Reiher et al. (1991) described the brief and low-amplitude focal stereotyped rhythmic discharges (RDs) closely associated in temporal and spatial distributions to higher amplitude interictal epileptiform discharges. They subdivided PLEDs into two categories: (1) PLEDs plus, which were associated with RDs and (2) PLEDs proper, which were not. In addition, PLEDs proper were subdivided into PLEDs of classes 1, 2, and 3 based on

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the metronomicity of the periodicity. Moreover, PLEDs plus could be subdivided into PLEDs of classes 4 and 5 based on the duration of RDs.⁵

We have found that characteristics of spikes or sharp waves and background activity differed considerably within the same PLEDs classes, and assumed that these differences reflect the degree of cerebral damage and recovery as well as variations in the electrophysiologic status of the brain. Therefore, in this study we aimed to subclassify PLEDs according to these observed differences and suggest a serial pattern of PLEDs using our new subclassification. We also analyzed the relationship between the classification of PLEDs and clinical prognoses.

MATERIALS AND METHODS

1. Subjects

Thirty-seven patients with PLEDs in the EEG were admitted to the Department of Neurology at Chungnam National University Hospital between January 2000 and August 2005. All the patients underwent EEG recording at least twice, and had structural lesions in their brains as indicated by MRI or CT. None of the patients had metabolic abnormalities.

2. Etiology

The etiologies were classified as ischemic cerebral infarction, hemorrhagic cerebral infarction, central nervous system infection, traumatic brain injury, central nervous system vasculitis, tumor, cerebral venous thrombosis, limbic encephalitis, or undetermined.^{6,7}

3. EEGs

A total of 237 EEGs were reviewed by two neurologists (Y.-S. Kim, J.-M. Kim). The mean number of EEG recordings per patient was six, and four patients had the minimum of two EEG recordings. The intervals between the EEG recordings varied due to this being a retrospective study; the mean interval was 4 days, and

two patients had continuous EEG monitoring. Every EEG showing PLEDs was classified according to Reiher's method. PLEDs proper of class 3 were sustained throughout the recording with a metronomic periodicity.⁵ In this study, PLEDs proper of class 3 were subclassified into four categories according to the characteristics of spikes or sharp waves and background activity. First, simple PLEDs proper of class 3 have focal spikes or sharp waves followed by relatively good background activity. The amplitudes and the duration of background activity are stable, but the amplitudes are significantly suppressed compared with the background activity in the contralateral hemisphere. Second, benign PLEDs proper of class 3 have more prominent background activity following spikes or sharp waves. The background activity is equivalent to that in the contralateral hemisphere, its duration being more or less variable. However, that is not against the rule of periodicity of PLEDs. Third, vigorous PLEDs proper of class 3 show spikes or sharp waves of higher amplitude than simple and benign PLEDs proper of class 3. The background activity has a high amplitude and is unstable and irregular compared with that in the contralateral hemisphere. Spikes or sharp waves frequently have at least two phases and are intermingled with high-amplitude background activity. It does not correspond to PLEDs plus, which has distinct background activity that is not mixed with spikes or sharp waves with RDs. Fourth, suppressed PLEDs proper of class 3 show high amplitude spikes or sharp waves followed by flat background activity (Fig. 1).

We measured the amplitudes, durations, and intervals between PLEDs complexes in three randomly selected different sites that had few artifacts and showed pure PLEDs without other epileptiform discharges. In addition, their average values were calculated and the temporal profiles of PLEDs were also analyzed.

4. Clinical analysis

The history of clinical aspects, physical findings, and seizure characteristics was obtained by chart review, with the final outcome confirmed by telephone inter-

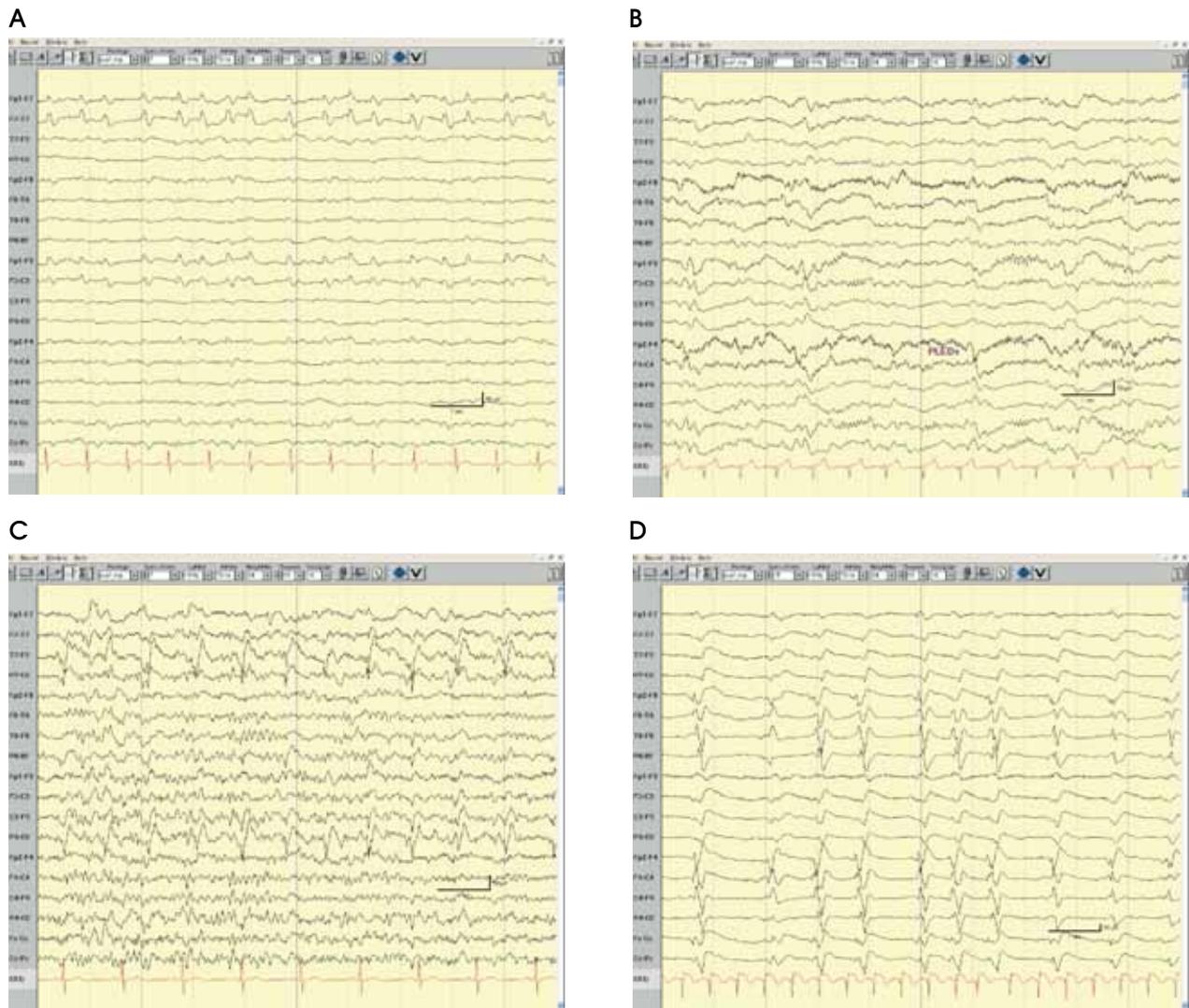


Figure 1. Representative EEG recordings showing diverse patterns of PLEDs proper of class 3: (A) simple, (B) benign, (C) vigorous, and (D) suppressed.

view. Parameters studied included the outcome (death or functional decline) and the time of disappearance of PLEDs. To determine the prognosis, the functional outcome was assessed at the time of discharge or within 2 months following discharge. The level of function was divided into three grades: totally independent, partially dependent, and totally dependent.⁸ A special emphasis was placed on the relationships between the classifications of PLEDs reported initially, at the outcome, and at the time of disappearance of PLEDs. In addition, we investigated whether the EEG seizure and the outcome were related. The time of disappearance of

PLEDs was confirmed based on follow-up EEG recordings.

5. Statistical analysis

The differences of amplitudes, durations, and intervals among the classifications of PLEDs were examined using one-way ANOVA. The chi-square test was used to determine the relationships between the classifications of PLEDs reported initially, at the outcome, and at the time of disappearance of PLEDs. Statistical analysis was performed using SPSS (version 10.0 for Windows), with

statistical significance defined at the $p < 0.05$ level.

RESULTS

1. Demographic features

Thirty-seven patients (12 women and 25 men) were included in the study. The mean age was 65.2 years (range, 20 to 89 years). The cause of PLEDs was ischemic cerebral infarction in 11 patients; hemorrhagic cerebral infarction, central nervous system infection, and tumor in 3 patients; traumatic brain injury in 2 patients; limbic encephalitis in 2 patients; central nervous system vasculitis in 1 patient; and cerebral venous infarction in 1 patient. The cause of PLEDs could not be determined in 11 patients. The causes and classification of PLEDs were not related. Thirty-five (94.6%) patients had clinical seizures. Fourteen patients (37.8%) died during their hospitalization or within 2 months of discharge.

2. EEGs

A total of 112 EEG recordings met the criteria for PLEDs (PLEDs proper, 100 EEGs; PLEDs plus, 12 EEGs), with 71 EEGs belonging to PLEDs proper of class 3. The morphologies and the number of patients of PLEDs class are listed in Table 1. Simple and benign PLEDs proper of class 3 rapidly evolved to PLEDs

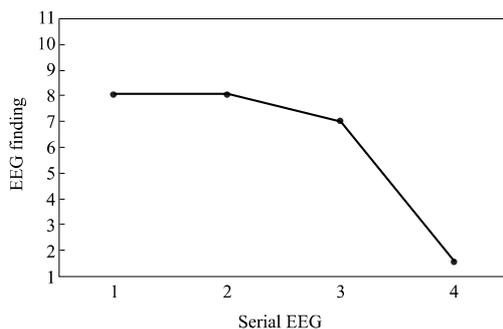


Figure 2. Average evolution of five patients with initial vigorous PLEDs proper of class 3. The X-axis represents the sequence of EEG recordings and the Y-axis represents the EEG findings: 1; slowing, 2; occasional sharp, 3; frequent sharp, 4; PLEDs proper of class 1, 5; PLEDs proper of class 2, 6; simple PLEDs proper of class 3, 7; benign PLEDs proper of class 3, 8; vigorous PLEDs proper of class 3, 9; suppressed PLEDs proper of class 3, 10; PLEDs plus of class 4, and 11; PLEDs plus of class 5.

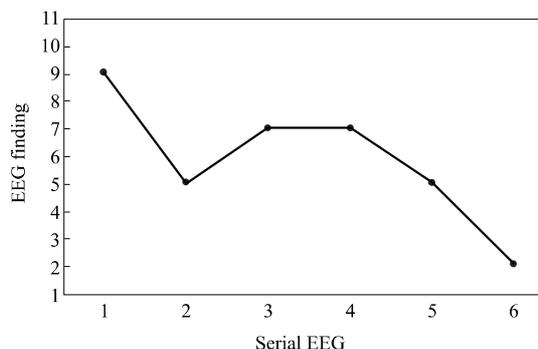


Figure 3. Average evolution of two patients with initial suppressed PLEDs proper of class 3 (axes as in Fig. 2).

Table 1. Characteristics of PLEDs

	Amplitude (μV)	Duration (ms)	Interval (s)	Number of EEG recordings
Class 1	46.6±4.9	0.3±0.0	3.9±0.7	8
Class 2	58.8±5.7	0.2±0.0	1.2±0.1	21
Class 3				
Simple	58.6±2.9	0.2±0.0	1.6±0.1	19
Benign	62.1±3.4	0.3±0.0	1.7±0.1	34
Vigorous	103.8±9.6	0.2±0.0	1.0±0.1	12
Suppressed	104.3±8.5	0.2±0.0	1.0±0.1	6
Class 4	72.1±7.0	0.4±0.1	1.2±0.1	9
Class 5	38.7±4.1	0.4±0.3	1.2±0.4	3
<i>p</i>	0.001	0.000	0.000	

Data are mean±standard deviation values. Class 1, PLEDs proper of class 1; class 2, PLEDs proper of class 2; simple class 3; simple PLEDs proper of class 3; benign class 3, benign PLEDs proper of class 3; vigorous class 3, vigorous PLEDs proper of class 3; suppressed class 3, suppressed PLEDs proper of class 3; class 4, PLEDs plus of class 4; class 5, PLEDs plus of class 5

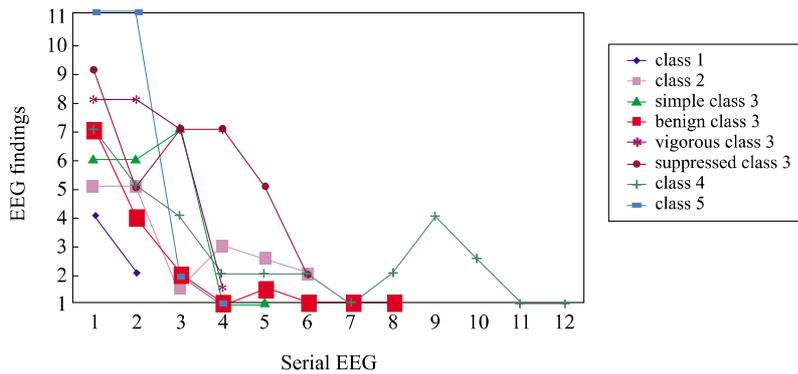


Figure 4. Stepwise evolution of PLEDs (axes as in Fig. 2).

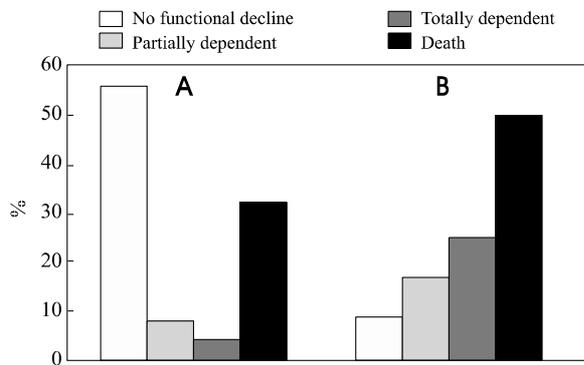


Figure 5. Relationship between PLEDs classification and functional status at follow-up: (A) benign group comprising PLEDs proper of classes 1 and 2, and simple or benign PLEDs proper of class 3 (n=25), and (B) malignant group comprising vigorous or suppressed PLEDs proper of class 3, and PLEDs plus of class 4 or 5 (n=17).

proper of class 2 or PLEDs proper of class 1, whereas vigorous or suppressed PLEDs proper of class 3 initially evolved to simple or benign PLEDs proper of class 3, and then changed to PLEDs proper of class 2 or PLEDs proper of class 1 (Fig. 2 and 3).

Initial PLEDs with metronomic periodicity and higher amplitude spikes or sharp waves progressed into a pattern of lower amplitude, longer duration spikes or sharp waves and finally changed into monomorphic, high-voltage slow waves. In contrast, the previously suppressed background activity recovered to an appropriate amplitude and frequency and eventually intermingled with transformed spikes or sharp waves. Through this process, PLEDs finally disappeared. This pattern was maintained regardless of the initial PLEDs

classification, with 35 (94.6%) patients showing this stereotyped serial evolution (Fig. 4).

3. Clinical analysis

Patients were divided into two groups according to the initial classification of PLEDs: (1) benign, comprising PLEDs proper of classes 1 and 2, and simple or benign PLEDs proper of class 3; and (2) malignant, comprising vigorous or suppressed PLEDs proper of class 3, and PLEDs plus of class 4 or 5. No functional decline or only partial dependence on family was present in 64% (n=16) and 25% (n=3) of patients in the benign and malignant groups, respectively (Fig. 5). Moreover, PLEDs disappeared at the first or second follow-up EEG recordings in 52% and 25% of patients in the benign and malignant groups, respectively (Fig. 6). In addition to the class of PLEDs, the presence of EEG seizure also affects prognosis: 57% of patients who did not experience EEG seizure were better than partially dependent, whereas 72% of patients having EEG seizure died during hospitalization or within 2 months of discharge (Fig. 7).

DISCUSSION

Whilst the hallmark of the PLEDs is their periodicity,⁷ they also exhibit diverse pleomorphic patterns. PLEDs proper of classes 1 and 2 do not correspond to the definition of PLEDs in Reiher's classification. In the same EEG recording, the morphologies of sharp waves

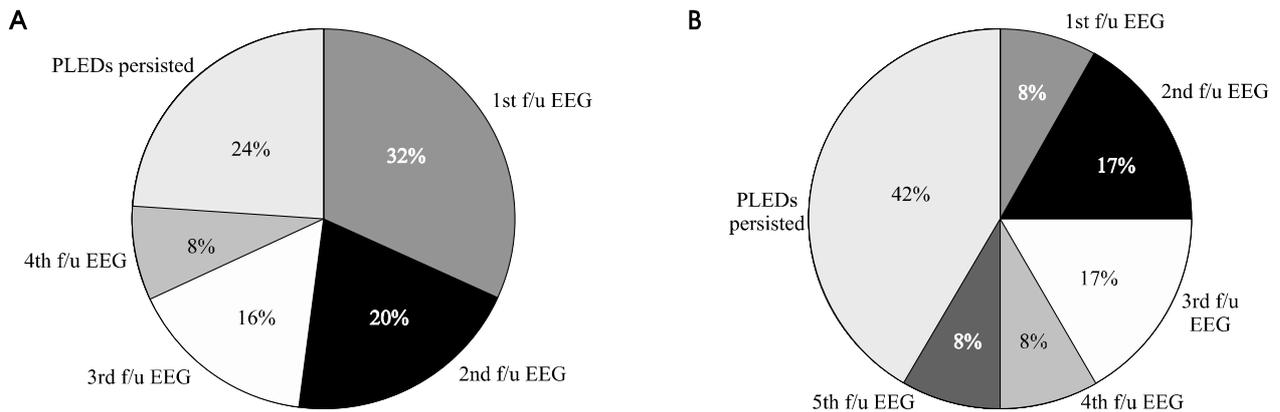


Figure 6. Resolution of PLEDs during the follow-up EEGs: (A) benign group and (B) malignant group. f/u; follow-up.

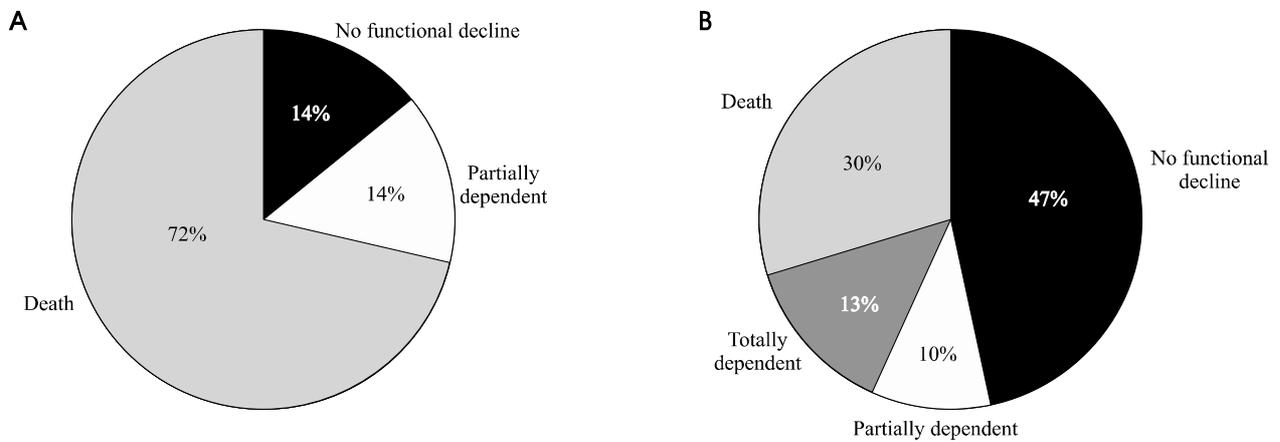


Figure 7. EEG seizure and functional status at follow-up: (A) with EEG seizure (n=7) and (B) without EEG seizure (n=30).

vary continuously along ictal and interictal periods in the single cycle and these reflect the spectrum of cerebral excitatory and inhibitory drives, and hence also pleomorphic changes of PLEDs. In our study, PLEDs proper of classes 1 and 2, and simple or benign PLEDs proper of class 3 showed rather stable amplitude and periodicity, but vigorous or suppressed PLEDs proper of class 3 showed higher amplitude spikes or sharp waves. In PLEDs plus of classes 4 and 5, the amplitude of PLEDs complexes decreased. These phenomena suggest the presence of underlying pathophysiologic responses during the evolution of PLEDs. That is, brain damage associated with evolving PLEDs was maximized during the period of vigorous or suppressed PLEDs proper of class 3, with the eventual prominently suppressed background activity and the decreased amplitude of PLEDs

plus of classes 4 and 5 reflecting extremely increased inhibitory drive in the brain. This hypothesis coincided with the description of Treiman and colleagues of a progressive sequence of electroencephalographic changes during generalized convulsive status epilepticus.⁹ From this we suggest that PLEDs, especially PLEDs plus, is a late phase of status epilepticus.

We have revealed diverse patterns of PLEDs proper of class 3, of which vigorous and suppressed PLEDs proper of class 3 appear to be more malignant considering the outcome and time of disappearance of PLEDs. These were considered to be pre-PLEDs plus, which evolved to PLEDs plus from PLEDs proper.

Many previous studies have strongly associated PLEDs with seizures,^{6-8,10} especially status epilepticus, and a poor prognosis.¹¹ But it is still controversial

whether antiepileptic drugs are needed in patients with PLEDs or, if treatment is initiated, how long it should be maintained for. All of the patients in our study were managed by antiepileptic drugs. Although there is no consensus, many studies have suggested that it would be reasonable to administer antiepileptic drugs for 3 to 12 months for those with PLEDs and seizures in the acute setting.^{12,13} Because vigorous and suppressed PLEDs proper of class 3 appeared to be a turning point in the evolution to malignant PLEDs plus in our study, aggressive treatment may be necessary during that period.

In conclusion, our study has revealed a regular serial pattern of evolution of PLEDs that results in a more diverse subclassification of PLEDs proper of class 3 compared to previous studies. This subclassification can help clinicians to detect the progression of PLEDs and to determine the appropriate time to start treatment.

Our study was subject to a few limitations. Subsequent EEGs recordings were obtained irregularly, and the intervals between serial EEGs were irregular. Therefore, we were unable to observe the final morphology of PLEDs and determine their actual time of disappearance. Future prospective studies with better designs should employ newly developed imaging and neurophysiologic techniques to improve our understanding of the nature of PLEDs.

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