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Does Neurological Examination Change With Resolution of PLEDs on EEG in Non-Anoxic Patients: A Prospective Observational Study

Jane Louie and Jaishree Narayanan

Departments of Neurology
Metrowest Medical Center, Framingham, MA (JL)
University of Massachusetts Medical Center, Worcester, MA (JN)

Abstract

We present a prospective observational study of 18 consecutive non-anoxic patients with Periodic Lateralized Epileptiform Discharges (PLEDs) on their EEG, who were followed acutely till resolution of their PLEDs. We followed their electroencephalographic and clinical courses. 13 of the 18 patients were discharged from the hospital at their baseline mental status, 3 died in the hospital and 2 patients did not show any clinical improvement. All the 13 patients who improved showed complete resolution of PLEDs on their follow-up EEG. The 3 patients who died showed severe diffuse cerebral dysfunction without PLEDs on their follow-up EEGs. Of the 2 patients with no improvement, one showed severe diffuse cerebral dysfunction and the other showed persistent intermittent PLEDs which were state dependent. All patients received anti-epileptic drugs (AEDs). Structural versus non-structural PLEDs etiology made no difference in terms of the discharged patients' outcome. Our study thus far suggests that a majority of the patients showed neurological improvement with resolution of PLEDs on their EEG. 4 of the 5 patients who did not improve showed severe diffuse cerebral dysfunction on their EEG and 1 showed intermittent PLEDs. All the patients who did poorly had initially presented with multiple convulsive generalized seizures and had multiple medical complications. We would like to see if this trend continues in a larger cohort of patients.

Correspondence to Jaishree Narayanan: narayanj@ummhc.org

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Introduction

The term periodic lateralized epileptiform discharges (PLEDs) is used to describe an EEG pattern consisting of lateralized sharp waves, spikes or other complex wave forms occurring in a periodic fashion.¹ This was initially described in the setting of an acute brain lesion, but now there have been descriptions of PLEDs in chronic brain lesions, patients with long standing epilepsy, and even in patients without any seizure disorder, although rare.²⁻⁵ Most of these patients have strokes, but PLEDs have been seen in patients with neoplasms, central nervous system infections as well as hemorrhages. Although these patients usually have seizures, the significance of this pattern is still controversial. It is also known that PLEDs can be a transient phenomenon. Presently to our knowledge, there are no prospective reports on whether there is any neurological improvement with resolution of PLEDs on EEG.

Methods

This is an ongoing prospective observational study of 18 patients from April 2008 to the present, whom we followed acutely after finding PLEDs on their EEGs. These were consecutive patients seen in an inpatient setting who got an EEG for altered sensorium, a new localizing neurological finding without an acute stroke, or seizures, and the EEG revealed PLEDs. PLEDs were defined as repetitive focal or hemispheric complexes consisting of spike, spike and wave, polyspike and sharp waves recurring periodically every 1-2 seconds with a return to background between discharges and occupying most of the recording.⁶ We excluded patients in whom PLEDs occurred after a post-anoxic cerebral injury or if there were Bilateral Periodic Epileptiform Discharges (BiPEDs), because this may carry a poor prognosis. We also exclu-

ded patients with PLEDs+ so as to have uniformity in EEG patterns. Data regarding their etiology, clinical course, physical findings, medications, brain imaging, and EEG were followed.

Results

Fifteen patients (83%) had structural lesions to account for PLEDs as seen in Table 1 (6 with neoplasm [33%], 1 with SDH, 1 with SDH and cryptococcal meningitis, 3 with stroke [17%], 1 with stroke and PRES, 2 with SAH, 1 with gliosis), and 3 (17%) with a nonstructural etiology.

The clinical presentations were varied as seen in Table 1: 6 patients (33%) presented with partial seizures followed by altered sensorium, 4 patients (22%) with multiple generalized seizures followed by unresponsiveness, 3 patients (17%) had altered sensorium without reported seizures, 3 patients (17%) with aphasia, 1 patient with Gerstmann's syndrome, and 1 patient with cognitive decline and staring episodes.

All patients were on anti epileptic drugs (AEDs). One patient was started on intravenous infusion of Propofol in low doses for sedation. One patient was started on low dose midazolam infusion for alcohol withdrawal. One patient needed to be started on Propofol infusion for control of ongoing partial seizures, and he died.

13 (72%) of the 18 patients were discharged from the hospital with resolution of their presenting symptoms and seizures, while 3 patients (17%) died in the hospital and 2 patients (11%) were discharged without much improvement. Of the 3 patients who died, 2 had subdural hematomas as their PLEDs etiology and 1 had acute on chronic ischemic stroke as his PLEDs etiology, but they also had multiple other medical complications

Table 1: Some relevant patient data from the study. AMS: Altered mental status.

Patient	Age	Gender	Reason for EEG	PLEDS location	Followup EEG	Clinical followup	Reason for PLEDs
1	84	F	Left-sided twitching, AMS	R temporal, central	Mild slow	Discharged, AMS resolved	Tumor
2	84	M	Generalized seizures, unresponsive	R posterior quad	Severe slowing attenuation	Expired	SDH
3	47	F	Partial seizure, AMS	Cz	mild slowing	Discharged, AMS resolved	No lesion
4	67	M	Generalized seizures, AMS	R frontal	severe slowing -> burst suppression	Expired	SDH
5	50	M	AMS	R temporal	Focal mild slowing	Discharged, AMS resolved	No lesion,
6	59	M	AMS, partial seizure	R temporal	Mild focal slowing	Discharged, AMS resolved	CVA- hemorrhagic
7	70	F	AMS, partial seizure	Left central	moderate slowing, triphasic	Discharged, AMS resolved	SAH
8	68	M	Aphasia	Left centro-temporal	Rare P3 spikes	Discharged, aphasia resolved	Tumor
9	65	M	Gerstmann's syndrome.	Left temporal	Left temporal sharps,	Discharged at baseline	Tumor
10	62	M	Aphasia	Left Frontopolar	left frontal sharps	Discharged, aphasia resolved	CVA
11	73	M	Multiple convulsive seizures, unresponsive	Left fronto-temporal	Severe slowing	Expired	CVA
12	3 y 8mon	M	Cognitive decline, staring episodes	Right hemispheric	Occ. right sharps,	Discharged, staring episodes resolved	Gliosis
13	71	F	AMS	Left temporal	Mild slowing,	Discharged, AMS resolved	CVA ? PRES
14	64	M	AMS, 1 seizure, left arm weakness	Right temporal	Right temporal slowing, occ. right temporal sharps	Discharged, AMS resolved	Tumor
15	64	F	AMS	Left central	Diffuse slowing left more than right, left sharps	CMO, AMS unchanged	Tumor
16	73	F	Convulsions, AMS	Left temp	Has left temp state dependent PLEDs	AMS unchanged	Tumor
17	39	F	Aphasia	Left Temp	Slowing	Aphasia resolved	No lesion
18	68	F	AMS eyebrow twitching	Right temporal	Slowing right	AMS resolved	SAH

including sepsis and metabolic problems. They all had convulsions followed by unresponsiveness at presentation. The 2 patients who did not improve had presented with convulsions followed by altered mental status. They both had neoplasm as PLEDs etiology.

Of the 13 patients who improved to their baseline neurological status and were discharged to home from the hospital, the 3 patients with aphasia had resolution of their aphasia with resolution of the PLEDs, the patient with Gerstmann's syndrome had resolution of his symptomatology with resolution of his PLEDs, the other 9 patients had complete resolution of their altered sensorium and confusion with resolution of their PLEDs. They had varied etiology for their PLEDs as seen in Table 1. Interestingly, 2 of these patients had recurrent aphasia few months after discharge with recurrence of PLEDs on their EEG in the setting of having missed AED doses. The aphasia resolved again with resolution of the PLEDs. The clinical improvement correlated with their EEGs in that as the EEG improved, the clinical condition also improved without significant time lag.

All patients obtained follow-up EEGs which were either serial multiple EEGs or continuous bed-side EEG monitoring in a few cases. 13 patients (72%) showed resolution of PLEDs with mild focal slowing on their EEG. 4 patients demonstrated severe diffuse cerebral dysfunction with burst suppression in 1 and delta range slowing with intermittent periods of no electrical activity in the other 3, although the PLEDs were not seen. 3 of these patients died and 1 patient was discharged to hospice without any neurological improvement. 1 patient showed persistence of PLEDs intermittently in a state dependent manner. This patient was discharged without any neurological improvement.

The 15 surviving patients were discharged on maintenance AEDs. 10 (56%) of these patients were seizure free on their first follow-up visit. 1 patient was lost to follow-up and 2 patients did not show any neurological improvement. 2 patients had recurrence of their aphasia a few months after discharge in the setting of having missed their AED doses with recurrence of the PLEDs on their EEG. They were re-loaded with their AED to attain therapeutic levels and the aphasia resolved with resolution of the PLEDs on the EEG. None of the patients had any adverse effects from treatment with the anti-epileptic medication in the acute condition.

Discussion

PLEDs in EEG are a well known phenomenon since their description by Chatrian in 1964, but their exact significance and management of patients with them still remains controversial. They are thought to be related to destructive structural lesions but are also known to be associated with seizures.²⁻⁵ The long term outcomes of treating patients who demonstrate PLEDs on their EEGs with anti-epileptic medications are still not definitively known. To our knowledge, there are no prospective randomized studies addressing this question. There is no data to our knowledge to suggest that resolution of PLEDs on EEG leads to improvement in the neurological status of the patient. It would be difficult to perform a double-blinded prospective randomized study, because one would have to withhold possibly beneficial medication from one set of the study patients. Conversely, there is also the risk of exposing patients to neurologically active medications that can have significant adverse effects. Lastly, one must consider the cost of treatment. There is literature that PLEDs can be ictal,^{2,7,8} including PET evidence of hypermetabolism coinciding with a similar localization of PLEDs on EEG, which suggests an

ictal nature.⁹ One of the reviews has suggested that seizures associated with PLEDs are difficult to control, and since they tend to resolve by themselves, it may not be worthwhile treating them from a practical point of view.¹⁰ A retrospective study by Schwartz et al., 1973 had shown that in 26 of 52 patients, the PLEDs resolved within days, in 23 within 4 weeks and in 3, the PLEDs persisted for months.¹¹ They state that the resolution was not a function of treatment of the encephalitis, but it is unclear from this study how many patients were treated with anti-epileptic medications. A majority of their patients had seizures, so it is likely that they did receive some anti-epileptic agent.

It is also unclear from the studies if the patients' neurological condition improved as the PLEDs resolved. As a first step, we thought that it would be worthwhile to try to answer this question. To get some preliminary data, we decided to perform a prospective observational study on patients with PLEDs of non-anoxic etiology. We did not include anoxic PLEDs since studies have shown a poor prognosis in this group.³ We also did not include patients in whom PLEDs coexisted with BiPEDS because this has also been shown to be associated with poor prognosis.^{4,12} Our study also did not include PLEDs+ to avoid variability in EEG patterns.

18 consecutive patients who had PLEDs on their EEG (structural and non-structural) were included in the study. They presented with neurological findings with or without seizures at admission. The patients either received multiple serial EEGs or were on continuous EEG monitoring to track their PLEDs. They had daily neurological evaluation to track their neurological status and deficits. They were all on AEDs. Three patients were also on intravenous infusion of Propofol or midazolam. The clinical course of all the patients was followed as inpatients

and also after discharge till their first follow-up outpatient visit except for 1 patient who was lost to follow-up.

From an etiological point of view, 83% of the patients had structural lesions in their brain, with the two most common diagnoses being tumors (33%) and CVA (17%). This is consistent with other studies, although we did not see patients with encephalitis and PLEDs during the time course of this study.²⁻⁵ 17% of our patients did not have any structural lesions.

The clinical presentations were varied as seen in Table 1. The most common presentations included patients with partial seizures followed by altered sensorium (33%), multiple generalized convulsions followed by unresponsiveness (22%), and altered sensorium without reported seizures (17%).

All patients received follow-up EEGs. 72% of the patients showed resolution of the PLEDs with mild focal slowing on their EEG in approximately 1 week. The neurological deficits resolved to the baseline level in these patients when the PLEDs resolved. This may suggest that the neurological deficits including the focal ones were possibly related to the PLEDs. This is also supported by the fact that in 2 of these patients the focal deficit recurred with recurrence of the PLEDs without any new structural lesion and resolved again with resolution of the PLEDs and that 1 patient who showed persistent, intermittent state dependent PLEDs did not show neurological improvement.

3 of the patients (17%) who died showed a pattern of severe diffuse cerebral dysfunction on their follow-up EEG. In 2 of them, the presumptive cause of their PLEDs was subdural hematoma which was evacuated and the third patient had acute on chronic ischemic stroke. All 3 patients had presented

with multiple generalized convulsive seizures followed by PLEDs on their EEG and had multiple medical complications. It can probably be surmised that their being critically ill contributed to the poor outcome in these cases.

Two patients (11%) were discharged without clinical improvement. One of these patients had severe diffuse (left more than right) cerebral dysfunction on her EEG and had multiple medical complications including sepsis and the other patient did not show resolution of PLEDs. Both of these patients had presented with multiple generalized convulsions followed by unresponsiveness. Multiple convulsions at presentation, multiple medical complications, and severe diffuse cerebral dysfunction on the follow-up EEG seemed to indicate poor prognosis for neurological recovery even if PLEDs resolved on the EEG. This is not surprising.

Among the patients who survived, there was no correlation between outcome and the presumptive etiology of the PLEDs. They uniformly did better as the PLEDs resolved. The 3 patients who did not have any structural lesion on their imaging also showed complete return to neurological baseline upon resolution of the PLEDs.

There was no correlation between outcome and age, location of PLEDs or the antiepileptics used. Most patients were treated acutely with fosphenytoin, Keppra, or both. Two patients were given phenobarbital and 2 patients were given Depakote. There was no correlation between the acute outcome and the anti-epileptic medication used. None of the patients had any adverse setbacks related to the anti-epileptic drug.

Conclusion

To our knowledge, there has been no study thus far that prospectively correlates the evolution of PLEDs with the neurological findings. This is a limited prospective observational study with a small sample size, but it seems to suggest that patients in whom the PLEDs resolved with some minor slowing on EEG show complete resolution of the presenting neurological deficit with resolution of the PLEDs. This is a small preliminary study but this could possibly suggest that the PLEDs may be linked to the neurological deficit although this is not definitive by any means. The study also suggests that multiple convulsions at presentation, multiple medical complications, and severe diffuse cerebral dysfunction on the follow-up EEG are poor prognostic signs for neurological recovery even if PLEDs resolve on EEG.

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