Periodic Lateralized Epileptiform Discharges (PLEDs):

Do they represent an ictal pattern, requiring treatment?

by

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Abstract

The goal of this report is to review periodic lateralized epileptiform discharges (PLEDs), especially their associated symptoms, the possibility that the pattern represents a focal status epilepticus and finally the usefulness of anti-epileptic drugs (AEDs). The associated symptoms often include an “altered state of consciousness” or “confusional state”, but also more specific symptoms have been noted, like nystagmus retractorius, cortical blindness, depression, apraxia, amnesia, hemianopsia, hemiparesis, gaze preference or deviation, dysphasia and speech impediment. PLEDs have often been referred to as an ictal pattern and many investigators have called the condition an example of subclinical status epilepticus. Intense hypermetabolism and increased blood flow from PET and SPECT scans have often been reported to support the ictal nature of this waveform. Although the pattern is difficult to treat, the AEDs that have been reported as successful include carbamazepine, midazolam, pentobarbital, sodium valproate and felbamate. Since only subtle symptoms are, at times, present and therefore may be missed and the pattern is known to be difficult to treat, epileptologists who view the PLED pattern as only an EEG curiosity and decide against treatment may wish to re-evaluate the electroclinical evidence related to this interesting and significant pattern.

I. Introduction

In 1964 Chatrian et al. [1] published an important study on periodic lateralized epileptiform discharges (PLEDs). During that same year Hughes and Schlagenhauff presented data to the American Epilepsy Society and later published [2] on the same pattern they called “periodically recurring focal discharges” that related the periodicity of the pattern to certain aspects of the electrocardiogram. Although the clinically evident epilepsy partialis continua, that may occasionally appear with the PLEDs, clearly establishes a focal status epilepticus, more often no obvious clinical symptoms may appear with the PLEDs. Also, Handforth et al. [3] published in 1994 data on PET scans that showed in these patients “intense hypermetabolism”, a condition usually associated with ictal patterns. However, some neurologists and even epileptologists do not view this waveform as an ictal pattern and may even recommend that no treatment is required. The fact that some of these patients can communicate and may not have obvious clinical symptoms also helps to convince some to consider the pattern as only an epiphenomenon or an EEG curiosity. The goal of this study is to review the world literature on the question of whether this waveform represents a status epilepticus, also to summarize the clinical changes associated with the PLED pattern and explore the usefulness of possible anti-epileptic drug (AED) treatment.

2. Method

The reviewer used Medline to identify publications dealing with PLEDs in the world medical literature.

3. Results

3.1 Symptoms associated with PLEDs

3.1.1 Altered consciousness

A few years after Young et al. [4] published a 1977 case of PLEDs associated with “nystagmus retractorius”, other authors [5] pointed out that the pattern was “usually associated with altered states of consciousness”. A similar point was made by Lee and Schauwecker [6] whose description was “frequent association of mental confusion”, also adding that focal neurologic signs and obvious seizures occurred. In 1991 Gras et al. [7] used the phrase “depression of consciousness” to relate to PLEDs, adding that “partial pure epileptic seizures” can also occur. It was the same altered level of consciousness emphasized by other authors [8]. Another study [9] referred to the change in mental states as “recurring confusional states”. Still others referred to “impaired level of consciousness” [10] or similarly [11] to “altered consciousness”, as did Westmoreland [12] and more specifically this type of symptom was called “underlying dementia” by Begum et al. [13]. From PLEDs on the occipital area, another study [14] described cortical blindness in a patient in an obtunded state.

3.1.2 Negative phenomena

Meador and Moser [15] were likely the first group to refer to “negative phenomena” linked to PLEDs. They referred to unusual ictal negative phenomena that included “neglect syndrome, catastrophic depression, apraxia, aphasia, amnesia, homonymous hemianopsia and hemiparesis”. The authors wisely advised that clinicians “could consider seizures in the setting of unexplained deficits, even if there are no positive ictal phenomena”. Five years later in 2005 Kaplan [16] also stated that PLEDs usually produced “negative” neurologic findings. He mentioned gaze preference, epileptic nystagmus and gaze deviation, which was the principal clinical feature of this PLED pattern. Finally, Calarese et al. [17] also confirmed that this ictal pattern may be associated with negative motor phenomena. Others [18] referred to the associated condition as “subtle status”.

Fushimi et al. [19] had an interesting approach that could add to the question of subtle status or negative phenomena by indicating that the P300 as an Event Related Potential (ERP) showed an increase in latency associated with an increase in the frequency of the PLEDs.

3.1.3 Symptoms related to AEDs

Ono et al. [20] reported that there was a good correlation between PLEDs and dysphasia and also claimed valproate (VPA) was not an effective AED, but carbamazepine (CBZ) was successful. A similar symptom, namely, a progressive speech impediment, was the symptom mentioned by Ueki et al. [21]. Although a specific AED was not mentioned, these authors did indicate that the cortical symptoms improved after the administration of anti-convulsive agents, “thus establishing the diagnosis of non-convulsive status epilepticus (NSE)”. As was frequently mentioned in the previous section on symptoms associated with PLEDs, other authors [22] claimed that “consciousness disturbances” were found in all 22 of their patients and that the PLEDs were likely associated with epilepsy, specifically a manifestation of partial status epilepticus requiring AEDs. Another group [23] also specified “impaired consciousness” as the important relevant symptom and the results of functional neuroimaging supported the concept of PLEDs as an ictal pattern. These authors used midazolam to resolve both the pattern and the associated clinical symptoms.

3.1.4 Seizures

A number of studies have drawn conclusions regarding the PLED pattern associated with seizures. Schraeder and Singh [24] reported that clear clinical seizures usually occurred not only during, but also after the hospitalization. Therefore, the authors concluded that these patients needed AEDs. Similarly, Walsh and Brenner [25] reported the same distribution of seizures, namely before,

during and after hospitalization. From ictal scans (PET) and the results of regional cerebral blood flow, oxygen consumption and oxygen extractions ratios, other investigators [26] concluded that their results were similar to that seen in status epilepticus. Another group [27] referred to “the role of PLEDs as an intrinsic feature of the status epilepticus condition”. Handforth et al. [3] published a study that received great attention, showing that PET scans showed “intense hypermetabolism and that PLEDs represent partial status epilepticus”. A similar conclusion was reached by another group [28] that the hyperperfusion from the high regional cerebral blood flow was likely related to a partial status epilepticus. A number of other studies have also reported that hyperfusion occurs with PLEDs. Funakawa et al. [29] studied SPECT scans and the MRI and also Ali [30] reported on SPECT data, concluding that the pattern was likely ictal as did two other groups of investigators [31, 32]. Finally, others [33] concluded that the pattern was ictal and, if ictal, then it must be considered a status epilepticus, because the pattern is continuous. Fitzpatrick and Lowry [34] also emphasized that clinical seizures occur.

3.2 Medications

Other studies have reported on specific anti-epileptic drugs that were effective. Terzano et al. [35] indicated that CBZ was effective, concluding that PLEDs may represent a nonconvulsive status epilepticus. In that same study a correct response to a mental test was found at 0% when the PLEDs were 2/sec, increasing to 25% when they were 1 every 2 sec and a significant increase to 80% when they were gone. This study further supports the aforementioned reports, showing how this pattern can change the responsiveness of patients. Other authors [36] also used CBZ to normalize the “electroclinical status”. Barbiturates have also been successful. For example, Beydoun et al. [37] used pentobarbital coma for the recovery of their patient. Barbiturates or

phenytoin (PHT) were not helpful in the patient, described by Hughes and Fuller [38], who reported that their patient responded well to felbamate. Nor were barbiturates and PHT helpful in the patient described by Rejda et al. [39] who claimed that VPA abolished the PLEDs.

In certain medical conditions, specific medication, not usually considered as an AED, may be effective. For example, in a patient with herpes simplex encephalitis, acyclovir was administered and the PLEDs disappeared [40]. In a case of meningoencephalitis, "corticosteroid therapy was dramatically effective" [41]. Also, for PLEDs associated with multiple sclerosis, intravenous steroids were needed for complete recovery, although standard AEDs were partially effective [42].

4. Discussion

Section 3 of the results indicates that many clinical symptoms have been described that are associated with PLEDs. The most frequently mentioned symptom was an "altered state of consciousness", also called "confusional state" or "consciousness disturbance", etc. Altogether 8 studies emphasized such a disturbance and one other study mentioned 22 additional patients with the same kind of symptom. Also, more specific complaints included nystagmus retractorius, cortical blindness, depression, apraxia, aphasia, amnesia, hemianopsia, hemiparesis, gaze preference or deviation, nystagmus, dysphasia and speech impediment. Thus, many symptoms have been mentioned that are associated with PLEDs, especially subtle ones like a disturbance of consciousness. In addition, data on degrees of such a disturbance were shown to be associated with the frequency of the pattern with faster PLEDs related to greater disturbances of responsiveness. Especially because of the subtlety of this type of symptom, some clinicians may be unaware of these same symptoms in their patients and possibly view these patients in a clinically normal state.

A number of publications have considered the pattern as a “nonconvulsive status epilepticus”, “a subtle status” or “a partial status epilepticus”. Many other authors have also drawn the specific conclusion that PLEDs represent an ictal pattern and, if ictal, then it must be considered a status epilepticus because it is periodically continuous. Supporting the latter conclusion are the studies with SPECT and especially PET scans, showing an “intense hypermetabolism”, as noted with other ictal patterns. The hypermetabolism (and increased focal blood flow) during the PLEDs is in contrast to the hypometabolism usually seen with only the interictal discharges.

If neurologists/epileptologists do not test carefully for these types of subtle symptoms, like an altered state of nonconsciousness, they may not, of course, recognize the presence of these important symptoms. Mainly because most epileptologists understand that the PLED pattern is difficult to eradicate, this fact could lead some to disregard any treatment whatsoever. This reviewer had the experience of observing one neurologist, who was not well trained in EEG, claim that nothing should be done for his patient with 1/sec PLEDs which he viewed as only an EEG curiosity. Upon suddenly noting one muscle group jerking at 1/sec, he loudly claimed that immediate intravenous treatment was necessary for this focal status epilepticus. Whether these “final common pathways” to the peripheral muscles are activated or not should not be the deciding factor as to whether AEDs should be used to eliminate or control this ictal pattern.

Some reports have not mentioned the success or failure of some AEDs that were used, but other reports have specified that CBZ, pentobarbital, felbamate, midazolam and VPA have been successful. In two reports, PHT and phenobarbital were not effective, but the successful pentobarbital in one case required such a large dose to produce a comatose condition for its success. The point here is that, if one views PLEDs to represent a focal status epilepticus, the advice of Treiman [43] has often been that control over any status epilepticus condition may occasionally require sufficient medication that coma or the suppression burst EEG pattern may be needed. Thus, the frequent comment that PLEDs are difficult to treat is generally correct,

because any status epilepticus is difficult to treat. One reason for this problem of difficulty of treatment may well be that insufficient amounts of AEDs are often given and, if sufficient amounts were given, the PLEDs may well lose their reputation of being difficult to treat.

For those who view the PLED pattern as only an epiphenomenon without any clinical significance and therefore requiring no AEDs, they may claim that eliminating the EEG pattern is only an electrographic change, not related to any clinical effect. If correct, this situation may add further evidence in their view for the possible insignificance of PLEDs. However, many reports have included data that showed the resolution of the PLEDs occurred simultaneously with the elimination of the related symptoms. The references for these electroclinical correlations include the following 19 studies: 4, 9, 11-14,, 20-23, 27, 32, 35-37, 39-42. The parallel changes between the resolution of the PLEDs and the disappearance of the associated symptoms add further evidence that PLEDs likely represent an ictal or status epilepticus pattern. These parallel changes are not consistent with the view that the symptoms are related only to the usual cerebrovascular etiology and the EEG is only an epiphenomenon. If the latter were true, there should not be parallel electroclinical changes with recovery.

5. Summary

The goal of this study was first to evaluate the clinical symptoms associated with the periodic lateralized epileptiform discharges (PLEDs). Also, evidence is included as to whether the pattern represents an interictal or ictal event and whether it represents a focal status epilepticus. Finally, the report includes the medications that have been successful to eliminate the PLEDs and also their associated symptoms. Symptoms that have been reported have usually been an “altered state of consciousness”, also called “confusional state”, “consciousness disturbance”, etc. More specific symptoms have included nystagmus retractorius, cortical blindness, depression, apraxia, amnesia, hemianopsia, hemiparesis, gaze preference or deviation, nystagmus, dysphasia and speech impediment. A number of publications have

considered the pattern as a “nonconvulsive status epilepticus” “subtle status” or a “partial status epilepticus”. Supporting the latter conclusion were SPECT and PET scans showing intense blood flow and hypermetabolism, usually associated with ictal patterns. Specific AEDs that have been reported as successful include CBZ, pentobarbital, midazolam, felbamate and VPA.

Because the associated symptoms are often subtle and also the PLED pattern is usually difficult to treat, some epileptologists may fail to check on these possible subtle symptoms, and then disregard the EEG pattern. Therefore, they may fail to treat these patients, in part because of side effects of the treatment. However, the evidence in this report argues in favor of treatment and the failure to treat may be counter to the best interests of the patient who may remain in a “twilight” state. Finally, additional studies with appropriate controls may be needed in order to make more definitive decisions, especially about which AEDs would be helpful. However, these investigations should include a sufficient number of patients and medications to identify the drug(s) of choice.

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