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Can diffusion-weighted imaging be used as a tool to predict seizures in patients with PLEDS?

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ABSTRACT – It is unclear which patients with PLEDs will have associated seizures and therefore will need to be treated aggressively with antiepileptic medications. We present a prospective observational study of ten consecutive non-anoxic patients with PLEDs based on continuous 24-hour EEG monitoring. According to the EEG, five of the patients had seizures associated with PLEDs and five had PLEDs but no seizures.
The aetiology included: neoplasm (*n*=1), cortical dysplasia (*n*=1), acute head trauma (*n*=1), encephalomalacia related to healed abscess (*n*=1), intraparenchymal haemorrhage (*n*=1), and no structural lesion (*n*=5). All patients underwent brain MRI using diffusion-weighted imaging (DWI). We found that the five patients who had seizures with PLEDs on continuous EEG had restricted diffusion on DWI. In contrast, the five patients who had PLEDs but no seizures on continuous EEG did not show a restricted diffusion pattern on DWI. We will continue to prospectively assess DWI findings in this group of patients and encourage other centres to also review similar data. If our observation is replicated, this would indicate that restricted diffusion on brain MRI may be a useful marker to identify patients with PLEDs on their EEG who are likely to have associated seizures.

Key words: periodic lateralized epileptiform discharges, PLEDs, diffusion-weighted imaging, DWI, EEG

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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 (Chatrian *et al*., 1964). This was initially described in the setting of an acute brain lesion, but descriptions of PLEDs in patients with chronic brain lesions, long-standing epilepsy, and even without any seizure disorder have been reported (Brenner, 2002; García-Morales *et al*., 2002; Chong and Hirsch, 2005; Fitzpatrick and Lowry, 2007). Many of these patients also had strokes. PLEDs are also seen in patients with neoplasms, central nervous system infections, as well

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as haemorrhages. Although these patients usually have seizures, the significance of this pattern is still controversial, and PLEDs are also known to be sometimes a transient phenomenon.

It is unclear which patients with PLEDs will have associated seizures, and this information is of great value regarding the management of PLEDs and decisions concerning which patients need to be treated aggressively with antiepileptic medications. In the observational study described here, we set out to determine whether there are any MRI findings that correlate with PLEDs associated with seizures.

Case studies

This is an ongoing prospective observational study of ten consecutive patients from August 2014 to the present, who were followed acutely after finding PLEDs on their EEGs. The patients received continuous EEG monitoring for 24 hours for altered sensorium or a new localizing neurological finding, such as aphasia or focal weakness. The patients who had altered sensorium had had it for 12 hours or so, involving very significant change from their baseline neurological status. Patients 4-10 were monitored in the intensive care unit, whereas Patients 1-3 were monitored elsewhere. The cause of seizures in the patients with no structural lesion was not entirely clear, except in Patient 10, who probably had encephalitis. Patients 6, 8 and 9 had follow-up brain MRI after discharge from hospital showing resolution of the DWI changes, and these patients recovered to their baseline neurological status. Patient 7 expired.

PLEDs were defined as repetitive focal or hemispheric complexes, consisting of spike, spike and wave, and polyspike and sharp waves recurring periodically every 1-2 seconds, with a return to background between discharges and occupying most of the recording (Pohlmann-Eden *et al*, 1996). Electrographic seizures were defined as a build-up of rhythmic activity evolving in frequency and amplitude for a duration of more than ten seconds. To be consistent, we only considered PLEDs for this study when the epileptiform discharges occurred once every 1-2 seconds. 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. Data regarding EEG, aetiology, and MRI findings were followed. Brain MRI was performed using a 1.5T MRI machine with and without contrast, using standard sequences including DWI and ADC. The MRI was performed either just before the EEG monitoring started or by discontinuing the EEG monitoring for the duration of the MRI. The MRI was reviewed by multiple readers to confirm consistent reading of the DWI changes. None of the restricted diffusion changes in any of the patients were considered to be consistent with artefact, for instance T2 shine-through artefact, by any of the readers.

All the patients underwent 24 hours of continuous EEG monitoring for altered mental status. They did not have overt clinical manifestations of seizures, such as convulsions, rhythmic nystagmus, version, eye deviation, *etc*. All ten patients had PLEDS on their EEGs, occurring every 1-2 seconds throughout the 24-hour period.

Figure 1A shows example EEGs of two of the patients in the study; one with right frontotemporal PLEDs and the other with right parietal PLEDs.

Figure 1B shows an evolving left frontal seizure in one of the patients in the study.

Four patients had left temporal or frontotemporal PLEDs, two patients had right temporal or frontotemporal PLEDs, one patient had right parietal PLEDs, one patient had left frontal PLEDs, one patient had right anterior quadrant PLEDs, and one patient had bilateral independent temporal PLEDs (*table 1*). Patients 1-5 had no electrographic seizure patterns on their EEGs. Patients 6-10 had PLEDs, as well as electrographic seizure patterns, on their EEGs. The patients with seizures showed 2-10 seizures within the 24-hour period. These patients did not show any clear overt clinical manifestations of seizures.

All the patients received concurrent MRI of the brain. Five of the patients had structural lesions corresponding to the region of the PLEDs. One patient had brain neoplasm, one had cortical dysplasia, one had head trauma, one had intra-parenchymal bleed, and one had a healed abscess. The other five patients did not have a clear structural lesion. The five patients who had electrographic seizure patterns on EEG (Patients 6-10) showed a restricted diffusion pattern in the region of the PLEDs (*figure 1C*). The pattern consisted of increased signal intensity in the gyrus on DWI sequences in the region corresponding to the PLEDS and seizures, and did not follow a vascular territory (*figure 1C*). Conversely, the other five patients who did not have any electrographic seizures on their EEG (Patients 1-5) did not show any DWI changes on brain MRI.

Discussion

PLEDs on EEG are a well-known phenomenon since their description by Chatrian *et al*. (1964), but their exact significance and management remains controversial. PLEDs are thought to be related to destructive structural lesions, but are also known to be associated with seizures (Pohlmann-Eden *et al*., 1996; Brenner, 2002; García-Morales *et al*., 2002; Chong and Hirsch,

2005; Fitzpatrick and Lowry, 2007). The exact clinical significance of PLEDs on the EEG is not entirely clear, although they have been associated with seizures and increased metabolism. It is not clear which patients are likely to have seizures and need to be treated aggressively with anti-seizure medications (Handforth *et al*., 1994; Pohlmann-Eden *et al*., 1996). The long-term outcomes of treating patients who demonstrate PLEDs on EEG with antiepileptic medications are still not definitively known, and, to our knowledge, there are no prospective randomised studies addressing this question. Clinically, it would be very useful to know which of the patients with PLEDs are likely to have associated seizures and need to be treated aggressively with antiepileptic medications if there are no overt clinical manifestations of seizures. Brain MRI is provided for most patients as part of the diagnostic workup once PLEDs are confirmed on the EEG. In this study, we attempted to correlate MRI findings with the presence or absence of seizures during 24-hour continuous EEG monitoring of these patients.

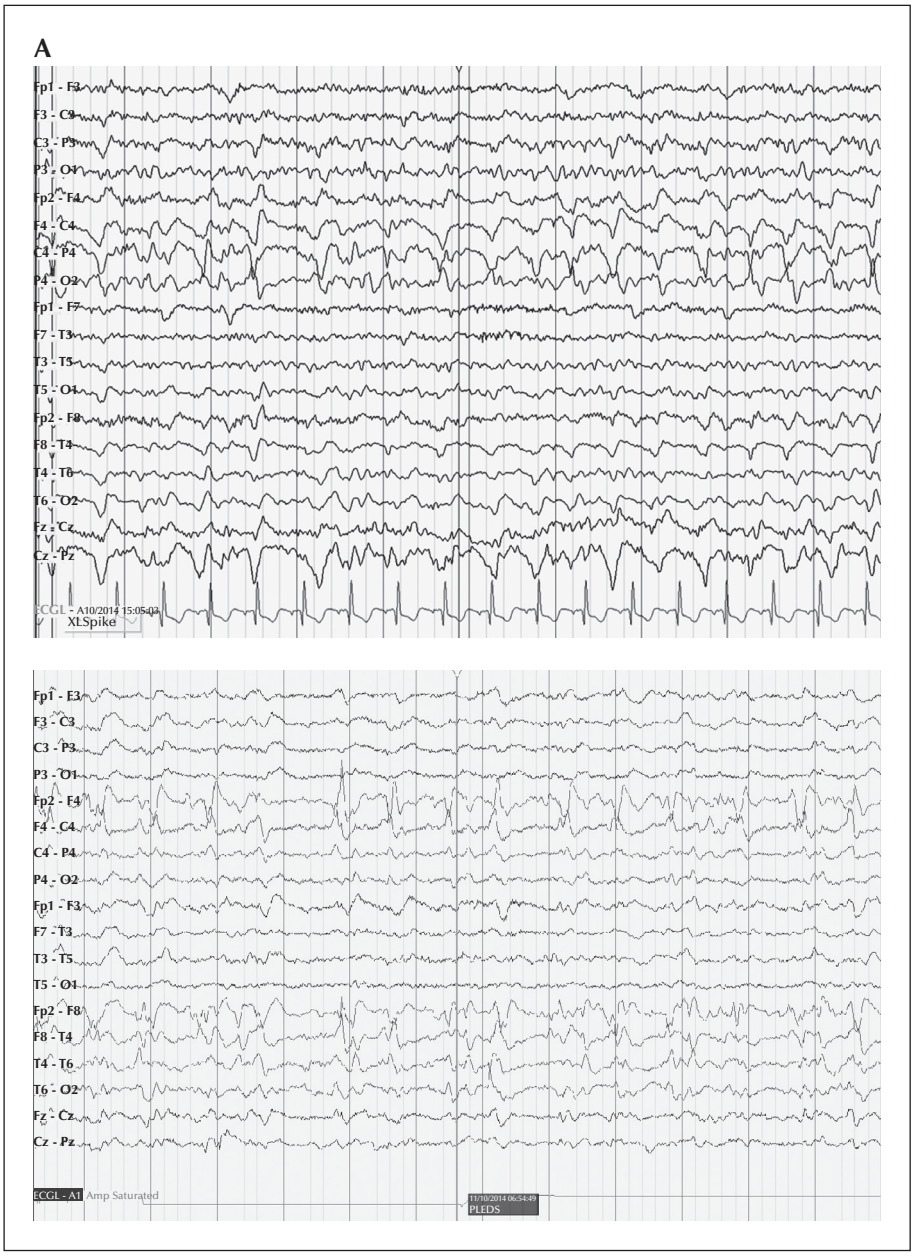

Figure 1A. Representative EEG samples of two of the patients in the study; one with right parietal (top panel) and one with right frontotemporal PLEDs (bottom panel).

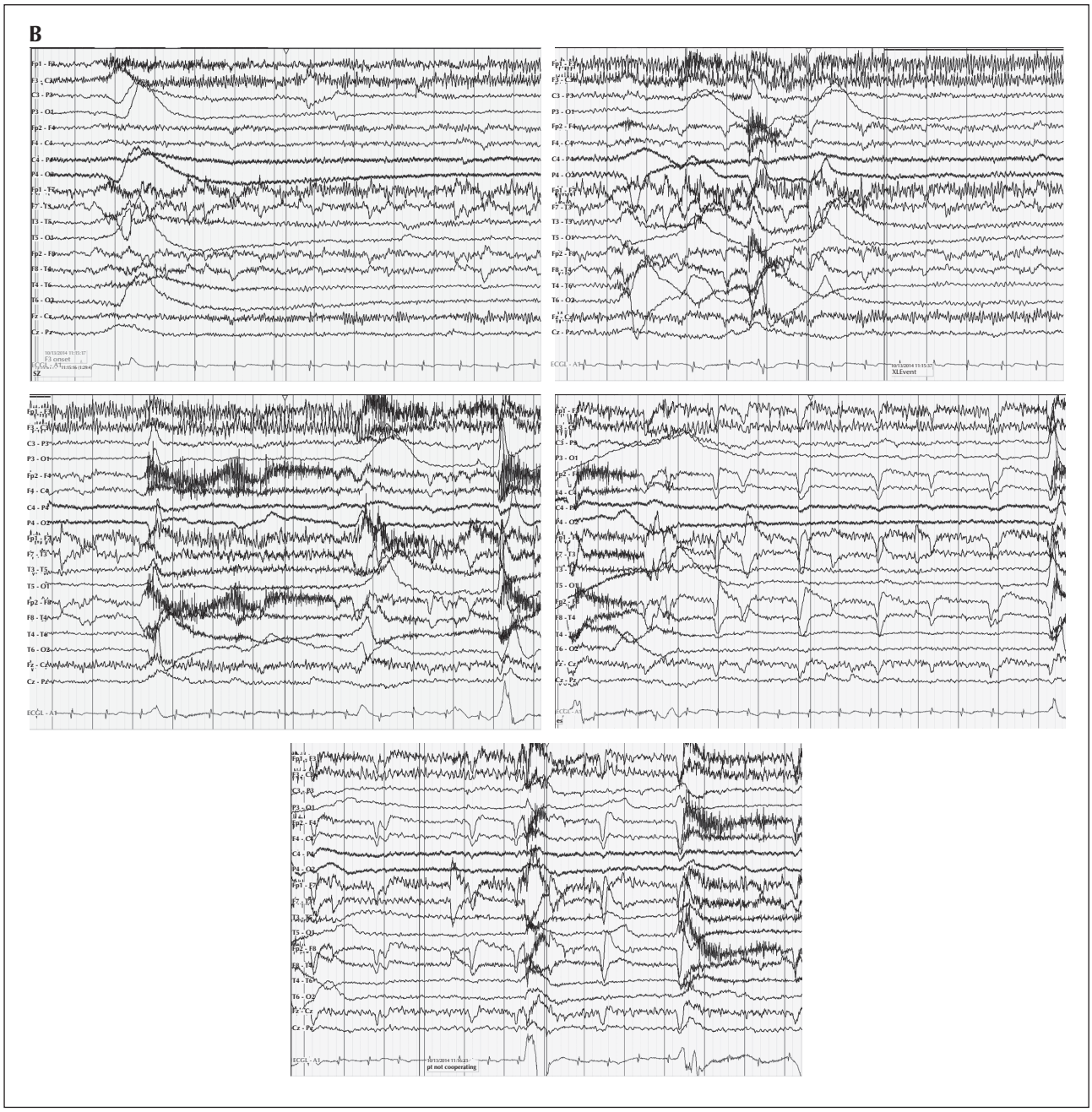

Figure 1B. Representative EEG samples of one of the patients showing an evolving left frontal seizure.

When PLEDs were seen during an EEG study, the patient was placed on continuous EEG monitoring for 24 hours to examine seizures. We prospectively followed 10 such patients and found that five of them had electrographic seizures on continuous EEG monitoring (*table 1*). Brain MRI was also provided for the patients. In our study, all the patients with seizures on EEG showed a restricted diffusion pattern on brain MRI. Conversely, all the patients who did not have seizures on EEG did not have a restricted diffusion pattern on brain MRI.

Diffusion restriction patterns on MRI of patients in the peri-ictal state and during seizures and status epilepticus have been reported before (Wieshmann *et al*., 1997; Diehl *et al*., 1999; Kim *et al*., 2001; Cianfoni *et al*., 2013), however, these are somewhat reversible changes (Handforth *et al*., 1994; Pohlmann-Eden *et al*., 1996; Kim *et al*., 2001; Cianfoni *et al*., 2013). It has

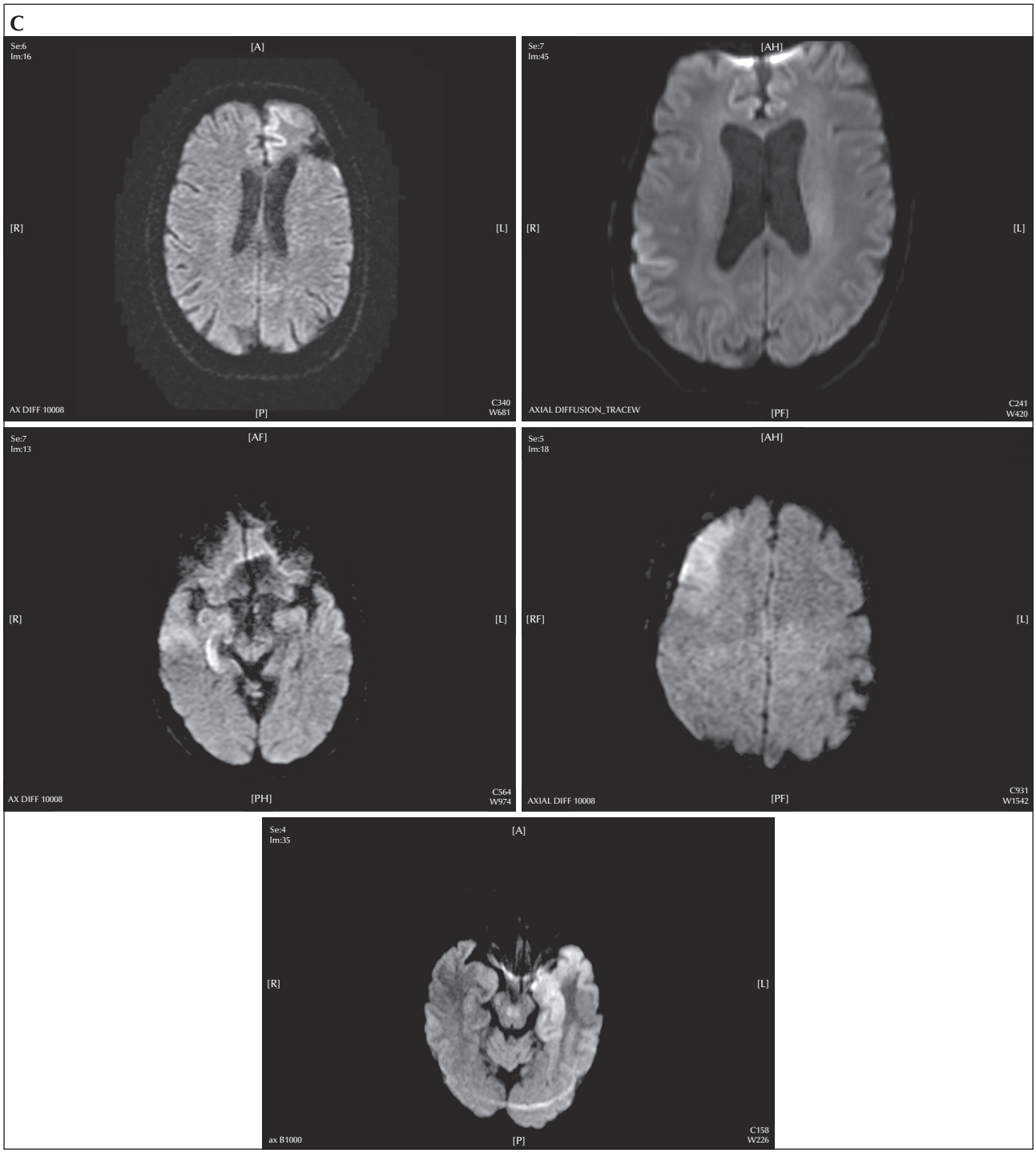

Figure 1C. Brain MRI images showing restricted diffusion pattern in the region of the PLEDs in the five patients who had PLEDs and electrographic seizure patterns on their EEGs (Patients 6-10).

been suggested that the ADC changes in epilepsy are related to cell damage caused by seizure (Helpern and Huang, 1995). To our knowledge, no prospective studies have addressed a possible correlation between restricted diffusion pattern and the presence of seizures in patients with PLEDS. We understand that the restricted diffusion pattern is probably a function of the seizures rather than a function of the PLEDs on EEG. This is furthermore supported by our study, although very preliminary, on the basis that a restricted

Table 1. Observational data from ten patients with PLEDs, with or without associated seizures.

	Age (years)	Location of PLEDs	Presence of Seizures	Structural lesion	Restricted Diffusion on brain MRI
Patient 1	59	Left temporal	No	No	No
Patient 2	52	Independent bilateral temporal	No	Nodular heterotopia (left more than right), left mesial temporal sclerosis	No
Patient 3	71	Left temporal	No	Left temporal oedema, left cavernous meningioma	No
Patient 4	44	Left frontal	No	Left frontal oedema through craniectomy, left parietal epidural haematoma	No
Patient 5	78	Right anterior	No	Right intra-parenchymal haemorrhage	No
Patient 6	71	Right fronto-temporal	Yes	No	Right fronto-temporal restricted diffusion
Patient 7	49	Right temporal	Yes	No	Right temporal restricted diffusion
Patient 8	72	Left fronto-temporal	Yes	Left frontal encephalomalacia	Left fronto-temporal restricted diffusion
Patient 9	60	Right parietal	Yes	No	Right parietal restricted diffusion
Patient 10	70	Left temporal	Yes	No	Left temporo-insular region

diffusion pattern on brain MRI was not detected in patients with PLEDs and no seizures, but was present in patients with seizures, hence suggesting that PLEDs by themselves, with no associated seizures, do not cause restricted diffusion pattern on MRI. Our hypothesis-driven observation is that, since continuous attended EEG monitoring may not always be logistically possible, if spot EEG shows PLEDs in patients with no overt clinical seizures, those without restricted diffusion pattern on MRI may not need to be treated aggressively for seizures.

In conclusion, although our sample size was very small and the findings very preliminary, our study suggests that PLEDs on EEG, without coexisting seizures, are not associated with restricted diffusion pattern on MRI, but in the presence of coexisting seizures, the MRI tends to show a restricted diffusion pattern. It may therefore be possible to use the absence of restricted diffusion pattern on MRI as a marker to identify patients with PLEDs on EEG who are unlikely to have coexisting seizures, and hence may not need aggressive anti-seizure treatment. We will continue to prospectively assess DWI findings in this group of patients and encourage other centres to also review similar data. If our observation is replicated, this would indicate that restricted diffusion on brain MRI may be a useful marker to identify patients with PLEDs on their EEG who are likely to have associated seizures. □

Supplementary data.
Summary didactic slides are available on the www.epilepticdisorders.com website.

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None of the authors have any conflict of interest to declare.

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TEST YOURSELF

(1) What is the exact clinical significance of finding PLEDs on the EEG of patients?

(2) Can diffusion restriction patterns be seen on brain MRI of patients with seizures?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".