

CASE REPORT

Periodic lateralized epileptiform discharges (PLEDs) in cerebral lupus correlated with white-matter lesions in brain MRI and reduced cerebral blood flow in SPECT

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This is a case report on an uncommon correlation between periodic lateralized epileptiform discharges (PLEDs) and white-matter lesions in cerebral lupus, and with a reduced cerebral blood flow (CBF) in single-photon emission computed tomography (SPECT). A 47-year-old woman with a long-term history of systemic lupus erythematosus (SLE) presented with a seizure followed by frontal lobe dysfunction clinically. An electroencephalogram (EEG) showed bilateral independent PLEDs in the frontal region. A magnetic resonance image of the brain showed white-matter changes in the frontal periventricular region. Cerebral angiogram did not reveal any evidence of vasculitis. A cerebral SPECT with tracer injected during the EEG showing PLEDs showed a reduction in CBF in the frontal regions. Clinical recovery was observed with intravenous immunoglobulin. This case shows that PLEDs can be seen with white-matter changes in SLE. *Lupus* (2013) **22**, 510–514.

Key words: PLEDs; SPECT; cerebral lupus; white matter

Introduction

Periodic lateralized epileptiform discharges (PLEDs), first reported by Chatrian et al., are electroencephalogram (EEG) patterns that are defined as periodic, focal or hemispheric epileptiform discharges (spikes, spike and waves, polyspikes, or sharp waves) usually recurring every one to two seconds.¹

PLEDs are usually indicative of an acute unilateral structural brain lesion, usually destructive. They have been described mainly in the presence of stroke, fast-growing brain tumors (as glioblastoma multiforme), brain abscesses, viral encephalitis (especially related to the *Herpes Simplex* virus), Creutzfeldt-Jakob disease (CJD), and hematomas.^{2,3} PLEDs have been associated with cerebritis in a case with systemic lupus erythematosus (SLE).⁴

Neuroimaging abnormalities are seen in 90% to 100% of patients with PLEDs, most commonly in those acute structural lesions involving cortical gray matter with adjacent subcortical white matter.^{2,5,6} Only a few cases of PLEDs associated with white-matter changes have been reported. In a study on structural lesions in PLEDs, 4.2% of 71 adults with PLEDs were found to have only subcortical white-matter lesions.⁶ A larger series by Fitzpatrick and Lowry reported 96 patients² and showed that 5.2% of the patients with PLEDs were related to white-matter disorders; i.e. two cases each with multiple sclerosis and posterior reversible encephalopathy syndrome (PRES), and one with osmotic demyelination. There were also a few case reports of PLEDs with white-matter disorders such as PRES.^{7,8}

The origin of PLEDs is a matter of controversy. While most authors propose a cortical origin, others believe that PLEDs occur because of isolation of portions of the cerebral cortex due to subcortical inhibition. Although there were only a few case reports relating PLEDs and white-matter changes,^{2,6–9} in these cases the location of PLEDs corresponded to the region of white-matter

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changes. In addition, in those with PLEDs secondary to a cortical lesion, involvement of the adjacent subcortical white matter was commonly reported.⁶ In a postmortem study with nine patients with periodic EEG patterns, eight were found to have both cortical and subcortical lesions secondary to subacute sclerosing panencephalitis and Heidenhain variant of Creutzfeldt-Jakob disease.¹⁰ These studies support that white-matter abnormality might play a role in the generation of PLEDs.

Functional impairment in cerebral diseases can precede structural changes, and cerebral perfusion single-photon emission computed tomography (SPECT) is a useful tool for detecting functional impairment, especially when magnetic resonance imaging (MRI) of the brain does not reveal any structural changes.¹¹ Studies showed that PLEDs can be associated with increased regional cerebral blood flow (CBF) in SPECT, if it is an ictal phenomenon.¹² In contrast, reduction in regional CBF in SPECT will indicate a functional impairment.¹¹

To our knowledge, this is the first case of PLEDs in cerebral lupus correlated anatomically with reduced CBF in SPECT and white-matter lesions in MRI brain reported in the literature.

Case report

A 47-year-old Malay woman with SLE presented with autoimmune hemolytic anemia and thrombocytopenia with positive antinuclear antibody (ANA) since the age of 34 in 1999. She subsequently developed class IV lupus nephritis five years later, with biopsy showing diffuse proliferative glomerulonephritis, which was treated with intravenous methylprednisolone and 10 cycles of cyclophosphamide. She had recurrent nephritis for which azathioprine was added one year later, mycophenolate mofetil in 2009 and another five cycles of cyclophosphamide in 2010.

There was no history of cerebral lupus until the end of 2011, when she developed the first episode of seizure, which was described as loss of consciousness associated with up-rolling of the eye balls and fecal incontinence without tonic or clonic movement, lasting two minutes. She had weakness of both legs after the seizure and was unable to walk for about three days, which later improved gradually. Twelve days later, she presented to another hospital with a change in personality consisting of mental obtundation, social inhibition, and memory loss, especially forgetting how to recite a Muslim prayer that she had been practicing daily since she

was young. The patient had not had vaccinations, recent infections, drug abuse or a change in her medication regimen prior to the presentation. Prior to admission, she was on a stable dose of oral prednisolone 10 mg daily and mycophenolate mofetil 1 g twice daily (b.d.). On examination, she was disorientated, inhibited, and answered only simple questions. There was no neck stiffness but presence of tetraparesis with power of 3/5, brisk reflexes, ankle clonus and equivocal plantar response.

Investigations revealed a normal cerebrospinal fluid (CSF) study. Full blood count was within normal limits. Blood urea was 16.3 mmol/l and creatinine was 189 µmol/l. There was no evidence of increased lupus activity with non-reactive ANA, normal anti-double-stranded (anti-ds)DNA level (11 IU/ml), and C3 and C4 levels were within normal limits. Anti-smith, anti-RNP, and anti-Scl-70 antibodies were negative. Anti-cardiolipin IgG was within normal ranges, i.e. one unit and lupus anticoagulant was not tested. An EEG showed persistent bilateral independent PLEDs over the frontal regions (Figure 1(a)), not responsive to intravenous midazolam, phenytoin, sodium valproate and levetiracetam. An MRI of the brain showed T2 hyperintensity in the thalamus, basal ganglia and frontal subcortical region (Figure 2(a)). Diffusion-weighted imaging (DWI) did not show any lesion with restricted diffusion to suggest acute infarcts. A cerebral angiogram did not reveal any evidences of vasculitis. A cerebral SPECT, with hexamethylpropyleneamine oxime (HMPAO) tracer injected during EEG showing periodic epileptiform discharges, showed reduced CBF in both frontal lobes (Figure 3). It was concluded that the patient had active cerebral lupus despite the absence of evidence of increased lupus activity. She received intravenous methylprednisolone without any clinical or electrophysiological improvement. A decision for a trial of intravenous immunoglobulin (ivIG) was made because of a previous successful case report.⁴ In retrospect, cyclophosphamide could have been given if access to ivIG is delayed.

However, because ivIG was unaffordable and not officially approved to be used in cerebral lupus, hospital approval to fund ivIG was obtained only three months later. On review, prior to ivIG, there was no improvement in her clinical state in which functionally she had difficulty parking a car and cooking a meal. No recurrence of seizure was reported. Neurological examination showed evidence of frontal lobe dysfunction with perseveration in alternative sequence testing and loss of

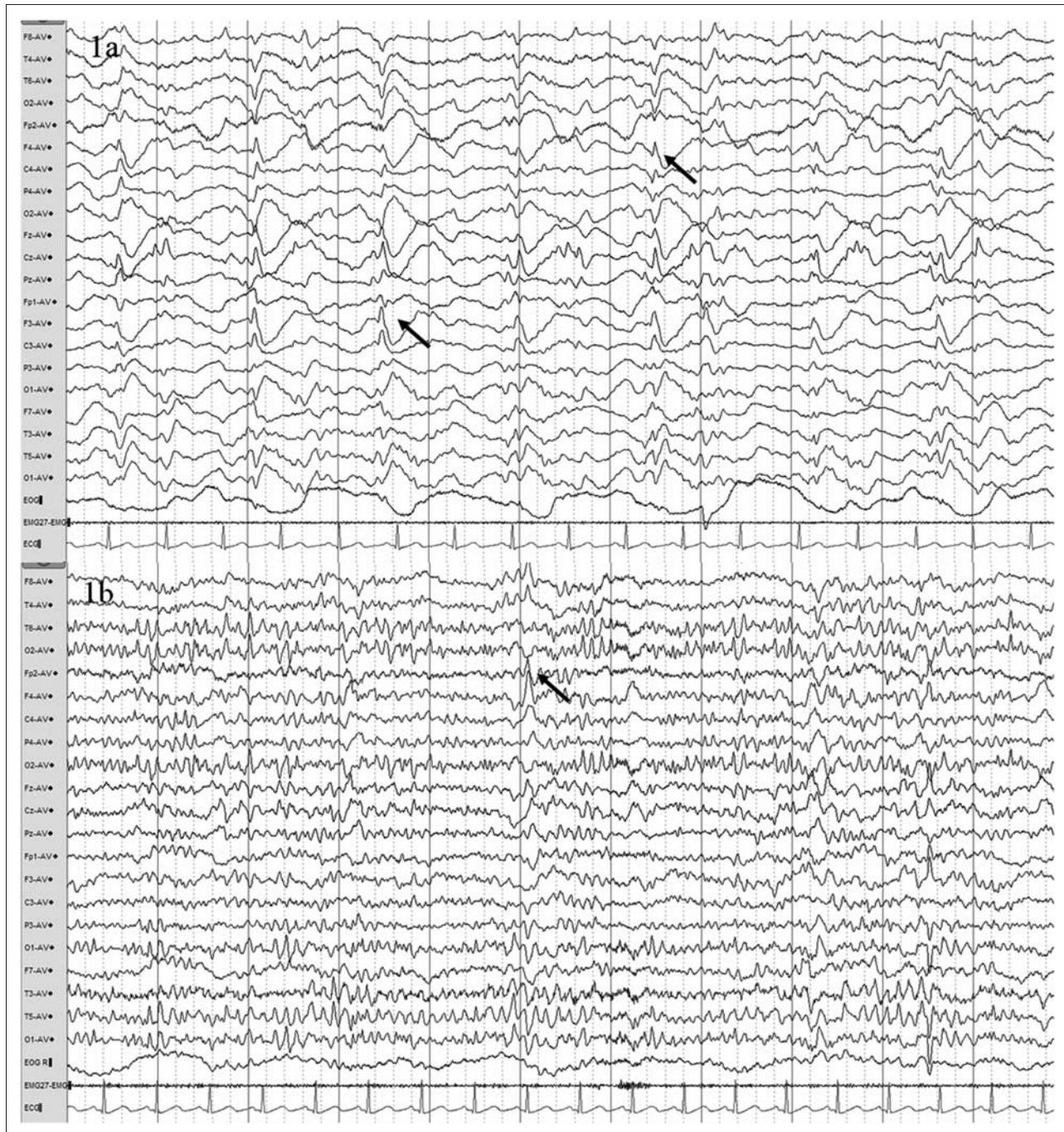


Figure 1 Electroencephalogram (EEG) showed (a) bilateral independent periodic lateralized epileptiform discharges (PLEDs) (black arrows) over the frontal regions; and (b) less frequent bilateral independent frontal epileptiform discharges (black arrow) three months later.

ability to interpret common Malay proverbs. Repeated EEG showed infrequent bilateral independent frontal epileptiform discharges, significantly less than the previous EEG (Figure 1(b)). Two weeks after completion of ivIG (0.4g/kg for five days), she became more alert, was not inhibited and was able to respond to questions fluently and

express herself in full sentences. She was able to elaborate a cooking recipe in detail with appropriate facial expression, and showed complete resolution of the frontal lobe signs. A repeat MRI scan one week after completion of ivIG showed progression of the deep white matter, basal ganglia, and thalamic lesions (Figure 2(b)), despite clinical

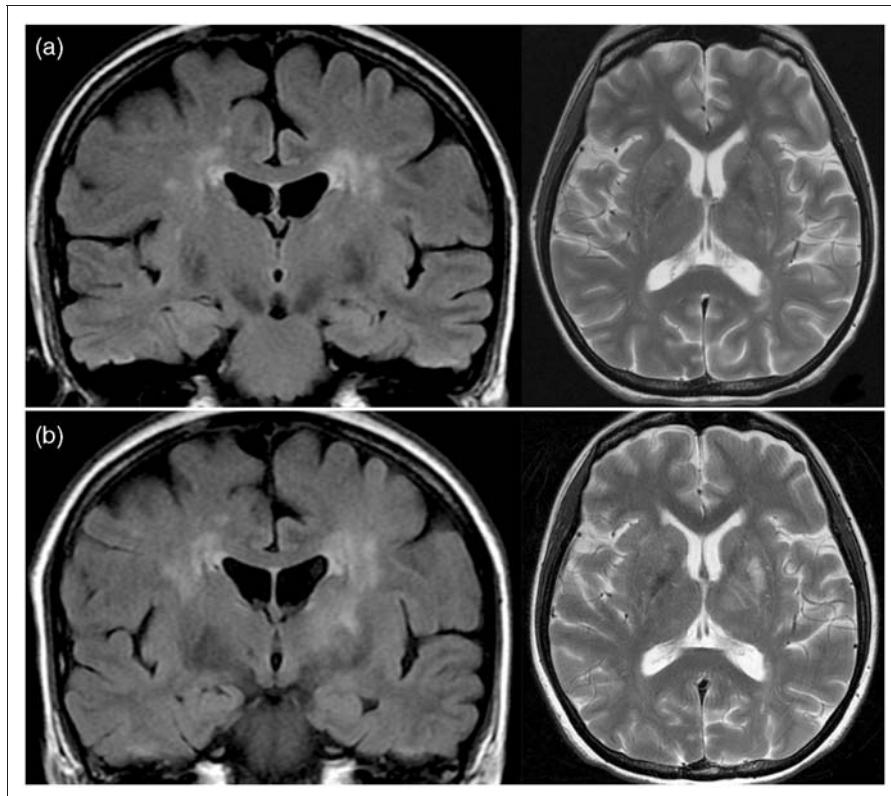


Figure 2 Magnetic resonance imaging (MRI) of the brain showed (a) T2 hyperintensity in the periventricular white matter and posterior limb of the internal capsule; and (b) further progression of the lesions after intravenous immunoglobulin into both basal ganglia and thalamus.

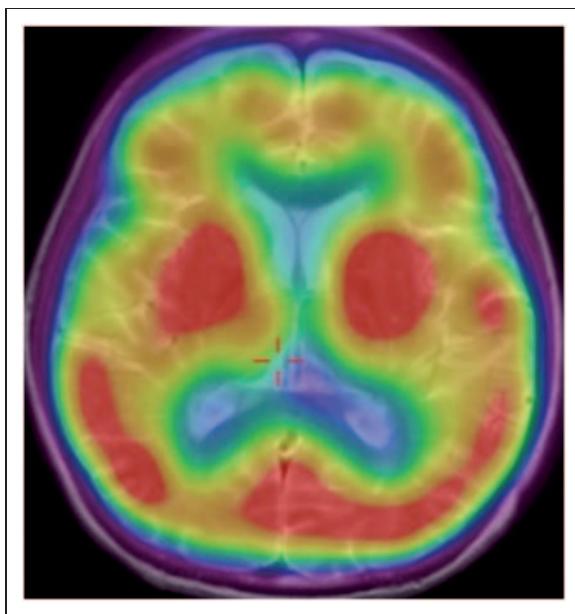


Figure 3 Cerebral single-photon emission computed tomography (SPECT) showed reduced regional cerebral blood flow in both frontal lobes.

improvement. Her improvement maintained at follow-up six months after completion of ivIG.

Discussion

This case report demonstrates the usefulness of PLEDs as a marker of functional impairment in cerebral lupus, correlating with clinical frontal lobe dysfunction, such as inhibited personality, apraxia in cooking, and car parking, inability to interpret proverbs, perseveration in alternative sequence testing, and presence of bilateral pyramidal signs.

This is also the first reported case with cerebral lupus correlating a reduced CBF in SPECT and PLEDs in EEG. SPECT is a useful tool for detecting functional impairment especially and other newer functional techniques such as magnetic resonance spectroscopy, diffusion and perfusion-weighted imaging, and magnetization transfer imaging can be considered when the MRI of the brain

has not revealed any structural changes.^{11,13} A reduction in CBF in our patient further supports the correlation of PLEDs and functional impairment. Most PLEDs developed within the first 72 hours of the illness and were replaced by sporadic spikes or focal slowing after eight to 10 days of evolution,³ which suggests that PLEDs were an acute and transient manifestation of functional denervation.

Differential diagnosis of central nervous system (CNS) infection, vascular disorders, e.g. stroke and cerebral venous thrombosis, and causes of multifocal leukoencephalopathy were considered. However, in view of (1) lack of clinical, biochemical, and radiological supportive evidence of the above and (2) the presence of recurrent flares as evidenced by history of recurrent nephritis, cerebral lupus was judged to be the provisional diagnosis despite the absence of systemic evidence of active lupus other than nephritis.

PLEDs in this patient are not an ictal phenomenon although the patient first presented with a seizure. There were no EEG patterns supportive of an ictal phenomenon such as evolution in frequency and amplitude of the discharges, incrementing onset or decrementing offset, resolution with intravenous antiepileptic medications, and presence of PLEDs-plus.² In addition, the cerebral SPECT of this patient did not reveal an increase in regional CBF supportive of ictal phenomenon.¹²

In our patient, MRI of the brain showed only white-matter changes in the frontal lobe without any cortical gray matter involvement. However, the location of PLEDs corresponded to the region of white-matter changes. Though rare, association between PLEDs and white matter changes has been reported,^{2,6-9} and it is postulated to occur because of isolation of portions of the cerebral cortex due to subcortical inhibition.

An alternative explanation for the correlation between PLEDs and white-matter changes is that PLEDs in cerebral lupus can be a result of underlying inflammation in the gray matter, which was not apparent in the brain MRI of this patient. We have previously reported a case of cerebral lupus with PLEDs associated with cerebritis⁴ supporting this alternative explanation. However, there was no evidence of vasculitis in cerebral angiogram, absence of cortical involvement on repeated brain MRI, and absence of abnormal serological markers of lupus activity such as ANA, anti-dsDNA antibody, and C3 and C4 levels in this patient during the acute phase of cerebral lupus.

Conclusion

PLEDs can be a reliable indicator of functional impairment in cerebral lupus. If PLEDs are present in a patient with SLE, clinical assessment of corresponding cortical function and functional neuroimaging such as SPECT are recommended.

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Conflict of interest

The authors have no conflicts of interest to declare.

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