Epileptic Disord 2014; 16 (2): 218-22

Chronic periodic lateralised epileptic discharges and anti-N-methyl-D-aspartate receptor antibodies

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Received November 12, 2013; Accepted March 18, 2014

ABSTRACT – Periodic lateralised epileptiform discharges (PLEDs) are uncommon transient electroencephalographic findings accompanied by acute brain lesions. A small proportion of PLEDs persist for more than three months and are called "chronic" PLEDs, the pathophysiology of which is still debated. Herein, we report a man with right hemispheric PLEDs which lasted for more than 14 months and mild left hemispatial neglect after he experienced status epilepticus. Although MRI was normal, positron emission tomography revealed right temporo-parieto-occipital hypometabolism, which coincided with the source area of PLEDs estimated by magnetoencephalography. In addition, levels of anti-*N*-methyl-D-aspartate (NMDA) receptor antibodies and granzyme B were found to be high in the cerebrospinal fluid. Following two courses of steroid pulse therapy, the patient's left spatial neglect improved and the PLEDs were partially resolved. These findings suggest that the chronic PLEDs present in this case were an interictal phenomenon and that their pathophysiology involved autoimmune processes.

Key words: status epilepticus, magnetoencephalography, steroid pulse therapy, left hemispatial neglect

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Periodic lateralised epileptiform discharges (PLEDs) are uncommon electroencephalographic findings characterised by repetitive focal complexes that contain one or more sharp-wave components of approximately 0.5-3 Hz in frequency (Chatrian *et al*., 1964).

Most PLEDs are relatively transient, appearing within 24 to 72 hours after the onset of acute brain lesions and resolving in a few days or weeks (Chatrian *et al*., 1964; García-Morales *et al*., 2002). However, a small portion of PLEDs persist for more than three months and are differentially termed "chronic" PLEDs, the underlying cause of which appears to differ (Westmoreland *et al*., 1986; Fitzpatrick and Lowry, 2007). Although more than 80% of patients with PLEDs experience clinical

doi:10.1684/epd.2014.0655

seizures or status epilepticus, the pathophysiology of PLEDs is still a subject of debate and it remains unclear whether they can be characterised as ictal phenomena (Fitzpatrick and Lowry, 2007). Here, we report a man with chronic right hemispheric PLEDs for more than 14 months with elevated levels of anti-*N*-methyl-d-aspartate (NMDA) receptor antibodies and granzyme B in his cerebrospinal fluid (CSF). We administered two courses of steroid pulse therapy, which partially resolved the PLEDs and improved subtle neurocognitive deficits. In the light of these findings, the pathophysiology of chronic PLEDs is briefly discussed.

Case study

The patient, a 54-year-old man, experienced monthly seizures with loss of consciousness from the age of 10. Phenytoin reduced the patient's seizure frequency to one a year. The patient graduated from a university, lived alone, and was employed as an office worker. An EEG recorded when the patient was 43 revealed no epileptic discharge, but registered sporadic, diffuse theta waves (4-7 Hz) and high-voltage slow waves (3 Hz) with right fronto-centro-parietal dominancy. After being seizure-free for a number of years, the patient discontinued his medication.

When the patient was 52 years old, a cluster of seizures culminating into status epilepticus occurred and he was brought to a hospital. Left hemiparesis was observed between ictus and he was intubated and sedated for four days. Seizures recurred after extubation and a 1,000 mg of valproate was started. MRI, 12 days after admission, revealed cortical thickening and hyperintensity on fluid-attenuated inversion recovery (FLAIR) in the right temporal, parietal, and occipital lobes (*figure 1A*). Seizures were controlled by administering 200 mg of carbamazepine and 3,000 mg of levetiracetam. During the follow-up period, right hemispheric PLEDs emerged on an EEG taken five months after the status.

The patient was referred to our hospital 19 months after the status with major complaints of sleepiness and loss of appetite. Upon admission, the man appeared untidy, and put all of his valuables and what appeared to be useless rubbish into a dirty sack. He also presented with mild left hemispatial neglect. Laboratory tests were normal. Cessation of valproate improved the patient's sleep patterns and appetite. An EEG showed intermittent PLEDs prevailing for more than 50% of the total EEG recording (*figure 2A*). In addition, a hypermotor seizure occurred during the EEG, at which time PLEDs disappeared several seconds before the onset of a clinical seizure (*figure 2C*). FLAIR and diffusion-weighted MRI sequences revealed no significant abnormalities. However, fluorodeoxyglucose positron emission tomography (FDG-PET) showed right temporo-parieto-occipital hypometabolism, which was consistent with the source area of the PLEDs, as estimated by magnetoencephalography (MEG) (*figure 1B, 1C, and 1D*). No signs of inflammation were found in the CSF test and a systemic workup aimed at tumour identification, including whole-body FDG-PET and serological tumour markers, was negative. In addition, autoantibodies associated with systemic lupus erythematosus and thyroiditis tested negative. Upon further examination, we found that anti-NMDA receptor (anti-GluR2B and anti-GluR1) antibodies, as well as granzyme B, were strongly elevated in the CSF, compared with disease controls (Takahashi *et al*., 2009).

Based on these findings, two courses of steroid pulse therapy (1,000 mg/day of methylprednisolone for three days) were performed, which improved the patient's left hemispatial neglect (*figure 3*) and caused the patient's PLEDs to dissolve into periodic delta activity (*figure 2C*).

Written informed consent was obtained from the patient for this case report.

Discussion

Chronic PLEDs are usually found in patients with prolonged partial seizure disorders, and are associated with sustained structural brain abnormalities (Westmoreland *et al*., 1986). In agreement with previous reports, the patient in this case presented with chronic epilepsy, however, the patient demonstrated no structural brain abnormalities.

As previously mentioned, it is still unclear whether PLEDs represent ictal activity (Fitzpatrick and Lowry, 2007). Based on the finding that the onset of PLEDs is accompanied by ipsilateral hypermetabolism in PET studies, some have argued that these discharges represent ictal activity, comparable to that of partial status epilepticus (Handforth *et al*., 1994). Others, however, consider that PLEDs reflect acute cerebral damage and are not necessarily related to seizures (García-Morales *et al*., 2002). It has been proposed that ictal/interictal differences should be considered as a continuum rather than a discrete dichotomy, with PLEDs stretching across the entire ictal-interictal continuum (Chong and Hirsch, 2005). Because PLEDs accompanied by rhythmic discharges (PLEDs plus) are more frequently followed by seizures than those without rhythmic discharges (PLEDs proper), the former are placed towards the ictal end and the latter towards the interictal end of the spectrum (Reiher *et al*., 1991).

A couple of points should be discussed regarding the nature of PLEDs observed in the present case. First, the

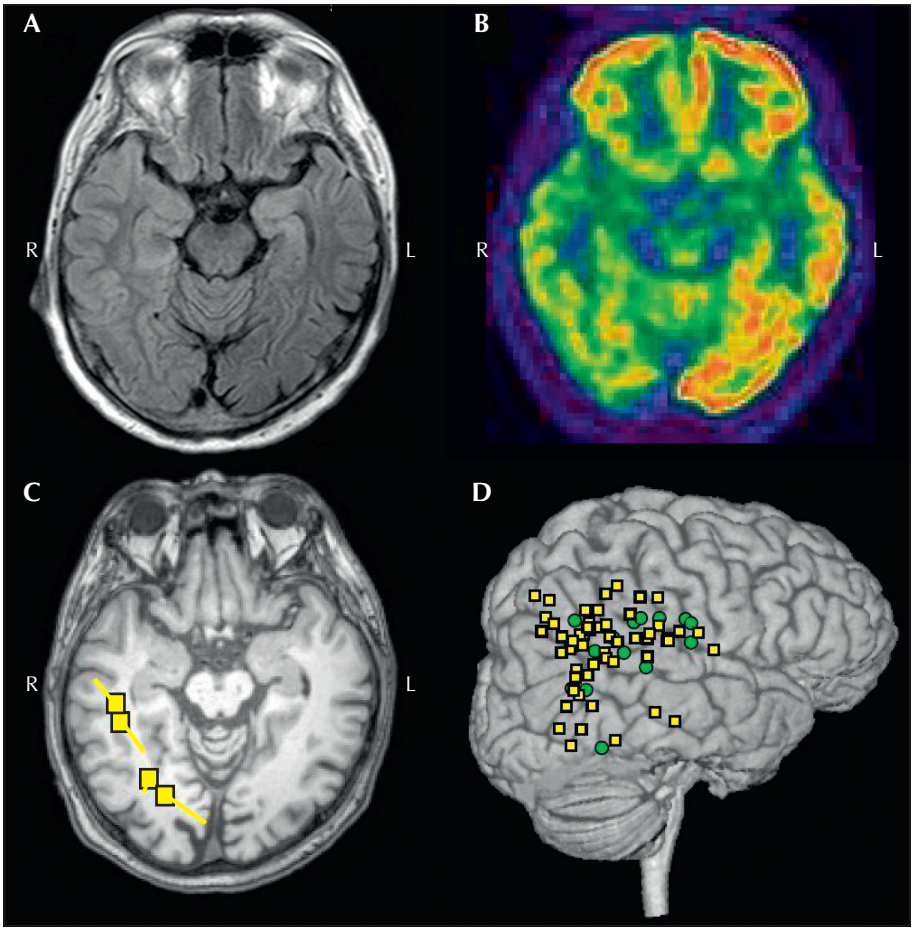

Figure 1. (A) Axial fluid-attenuated inversion recovery MRI of the brain, acquired 12 days after the onset of status epilepticus. Thickening and hyperintensity were observed in the right temporo-parieto-occipital cortex. (B) Fluorodeoxyglucose positron emission tomography and spike dipoles of periodic lateralised epileptiform discharges (PLEDs) estimated by magnetoencephalography, superimposed on T1-weighted MR images obtained upon referral to our hospital (C, D).
Yellow squares represent dipoles with a goodness of fit of more than 90%. Green circles represent dipoles with a goodness of fit of more than 80%. The source area of PLEDs roughly coincided with the hypometabolic region.

patient presented with mild left hemispatial neglect. Meador and Moser (2000) described left hemispatial neglect to be a possible sign of negative seizures and reported a patient with PLEDs in the left parietal region who experienced negative symptoms including right hemiparesis, aphasia, apraxia, and severely depressed mood, which were improved with phenobarbital. Because the negative symptom in the present case was far milder than the aforementioned case, it might be better interpreted as a functional impairment caused by neuropathology underlying chronic epileptiform discharges.

The present case exhibited clinical seizures. However, observed PLEDs were unaccompanied by rhythmic discharges. Moreover, PLEDs disappeared several seconds before the onset of a clinical seizure. This pattern is different from the reported progression of PLEDs proper to PLEDs plus to seizures, and supports the hypothesis that the recorded PLEDs were interictal discharges (Reiher *et al*., 1991).

In the present case, PET studies disclosed hypometabolism rather than hypermetabolism in the right temporo-parieto-occipital region, which roughly coincided with the localisation of the source dipole of the PLEDs estimated by MEG. This finding is similar to a previous study of a patient who experienced recurrent PLEDs due to a metastatic brain tumour and was investigated using MEG and PET (Hisada *et al*., 2000). Hypometabolism is indicative of an interictal brain state during PET. However, lack of concurrent EEG recordings restrict the significance of the PET findings as conclusive evidence that observed PLEDs were interictal phenomenon, since PLEDs might have resolved during a PET scan.

By combining clinical, EEG, and PET findings together, the chronic PLEDs recorded in this case apparently

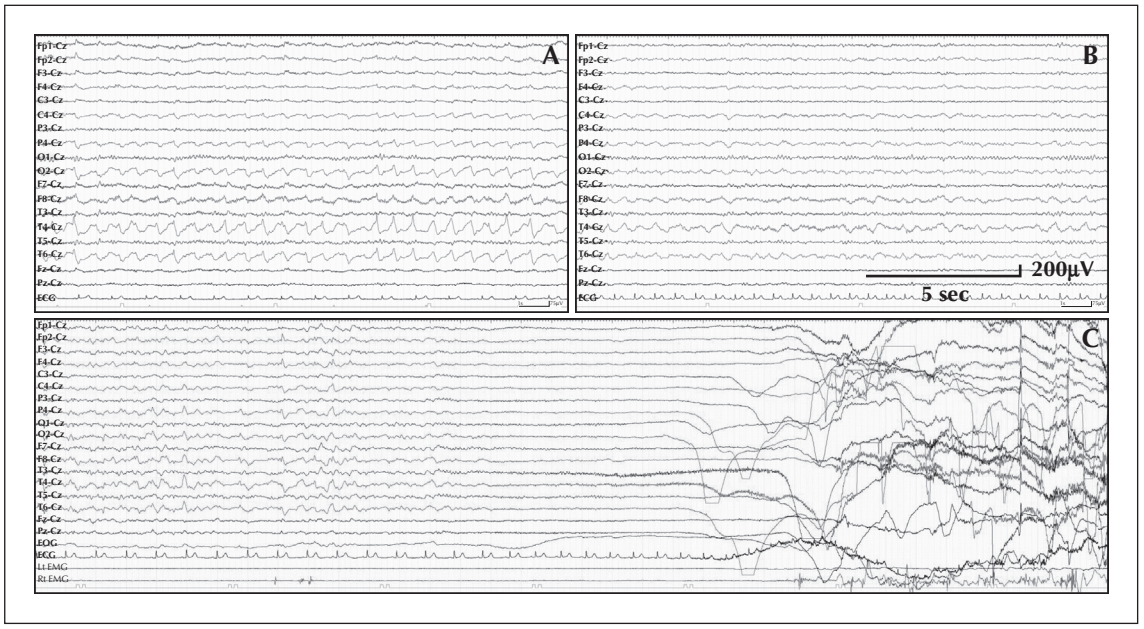

Figure 2. (A) EEG tracing 19 months after the status epilepticus. Right hemispheric periodic complexes (1.0-1.5 Hz) were observed with the highest voltage of the sharp-wave components recorded at T4 and T6 using the international 10-20 EEG system. Because the A2 reference was contaminated by periodic lateralised epileptiform discharges (PLEDs), the midline (Cz) reference was used. (B) EEG after two courses of steroid pulse therapy; sharp-wave components of the PLEDs disappeared and only right hemispheric periodic delta waves could be observed. (C) Seizure onset; the interval between PLEDs became longer and finally disappeared about 10 seconds before the onset of the clinical seizure.

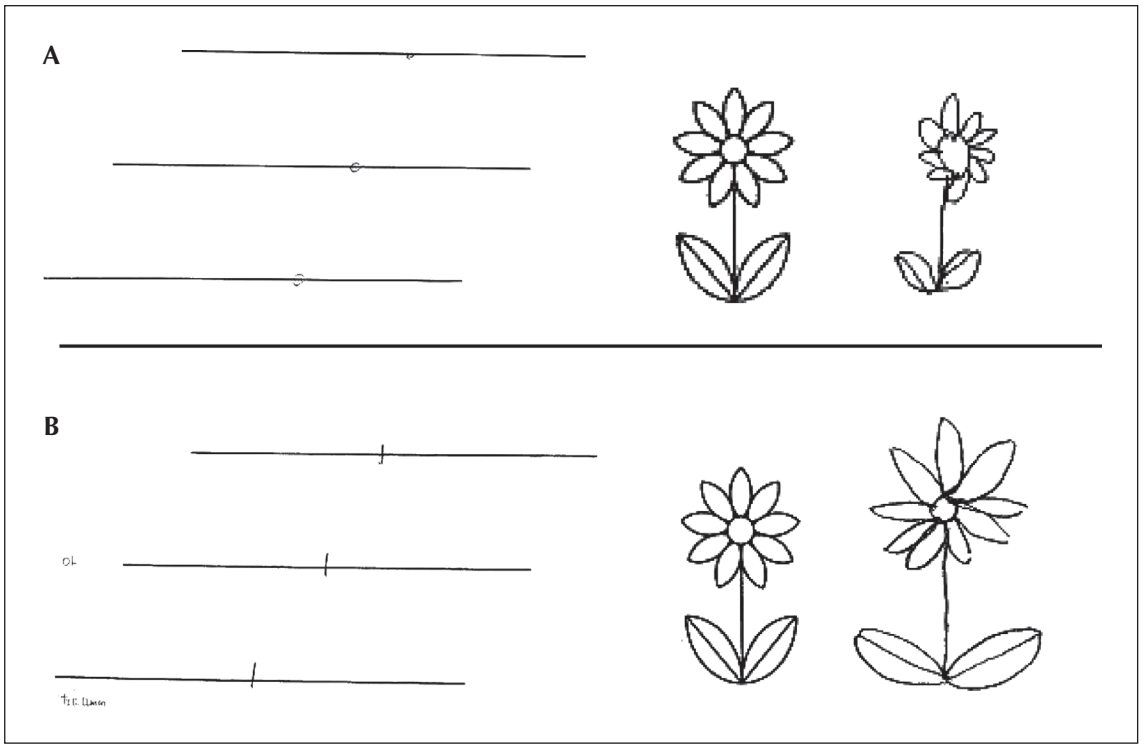

Figure 3. Improvement of left hemispatial neglect after steroid pulse therapy. The patient was asked to mark the centre of three horizontal lines (left) and to copy a picture of a flower (right).
(A) Test result before the two courses of steroid pulse therapy. (B) Test result after the steroid pulse therapy.

correspond to the interictal end of the ictal-interictal continuum.

What is notable in this case was the positive finding of anti-NMDA receptor antibodies in the CSF. Anti-NMDA receptor antibodies have received attention lately because of the recent establishment of anti-NMDA receptor encephalitis as a clinical entity associated with ovarian teratoma (Dalmau *et al*., 2011). Rasmussen's encephalitis is also accompanied by anti-NMDA receptor (anti-GluR2B) antibodies (Takahashi *et al*., 2009). Moreover, although rare, PLEDs can be accompanied by the presence of anti-NMDA receptor antibodies (Labate *et al*., 2009) and Rasmussen's encephalitis (Fitzpatrick and Lowry, 2007).

The causative role of anti-NMDA receptor autoantibodies in the induction of status in the present case is equivocal; although epileptic status and cortical thickening are common in patients with encephalitis, the clinical course in the current case was dissimilar to that of patients with anti-NMDA receptor or Rasmussen's encephalitis. In addition, since the patient had been affected by epilepsy for a long period of time, the withdrawal of antiepileptic medication may have caused the status.

Granzyme B is a serine protease secreted chiefly from cytotoxic T lymphocytes, which induces DNA fragmentation and apoptosis in target cells. Granzyme B in the CSF of patients with Rasmussen's encephalitis is reported to be elevated, and is considered to be involved in the autoimmune pathophysiology of the disease (Takahashi *et al*., 2009). The existence of anti-NMDA autoantibodies and granzyme B in the CSF may be a sign of cytotoxic T-cell-mediated neuronal injury and fragmentation of neuronal molecules including glutamine receptors, which could cause the production of autoantibodies against them (Takahashi *et al*., 2009). In the present case, the effectiveness of steroid pulse therapy indicates that reversible autoimmune processes were involved in the pathology that caused both chronic epileptiform discharges and the subtle neurocognitive deficit. □

Acknowledgements and disclosures.

We acknowledge Grants-in-aid for Scientific Research I Nos. 21591342, 23591238 and 24591537; Comprehensive Research on Disability Health and Welfare; Research on Rare and Intractable Diseases; Intramural Research Grant (22-3) for Neurological and Psychiatric Disorders of NCNP; and grants from The Japan Epilepsy Research Foundation.

The authors have no conflicts of interests to disclose.

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