Clinical commentary

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Electroclinical and radiological observation of dysfunctional zones in a patient with neurosyphilis

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ABSTRACT – We report a 33-year-old Japanese man who suffered from repetitive generalized tonic-clonic seizures which were medically intractable. Neurosyphilis was serologically diagnosed in blood and cerebrospinal fluid, and penicillin G (PcG) was consequently effective. The EEG during PcG pre-treatment showed frequent right occipital spikes and right frontocentral slow waves, which disappeared after treatment. During pre-treatment, positron emission tomography with 18-fluorodeoxyglucose and Tc-99m ethyl cysteinate dimer single-photon emission computed tomography revealed occipital hypermetabolism and hyperperfusion ("hot" area) and fronto-temporo-parietal hypometabolism and hypoperfusion ("cool" area) over the right hemisphere. The spike sources of magnetoencephalography during pre-treatment were localized to "hot" areas, and the slow activities were distributed to the fronto-temporo-parietal region, corresponding to "cool" areas. The inflammatory seizure focus and reversible dysfunctional zone associated with neurosyphilis were clearly delineated using these techniques.

Key words: neurosyphilis, epilepsy, PET, SPECT, electroencephalography, magnetoencephalography

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The usefulness of positron emission tomography with 18-fluorodeoxyglucose (FDG-PET) in patients with focal epilepsy is well established, and numerous studies support the association between FDG-PET and epileptogenic focus, *i.e.* an irritative area in the epileptic brain that demonstrates interictal hypoactive glucose metabolism and ictal hypermetabolism. However, the relationship between slow waves in EEG and FDG-PET is rarely reported. Here, we describe and discuss a patient with neurosyphilis, who demonstrated unique findings on EEG/MEG and PET/SPECT.

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Case study

A 33-year-old Japanese man with no prior history of epilepsy or other neurological diseases presented with generalized tonic-clonic (GTC) convulsions and was admitted to hospital. Brain MRI was normal, and interictal EEG showed no paroxysmal abnormalities. One month later, the patient was discharged without medication because this was his first unprovoked seizure. However, a GTC recurred after two months and the patient was readmitted to the same hospital. The seizures continued for more than 30 minutes, but resolved following treatment with intravenous diazepam followed by phenytoin. Although oral levetiracetam (LEV) was then started, the GTCs continued to occur once every day or two.

Two weeks after the second episode, the patient was transferred to our hospital for further evaluation and treatment. The seizures started as tonic convulsions of the left limbs, immediately followed by GTC movements. Neither visual symptoms nor auras were reported ictally or interictally. Neurologically, anisocoria (7 mm/4 mm) and cognitive impairment (Mini-Mental State Examination [MMSE] score of 18) were demonstrated. Other deficits were not detected. No skin lesions, such as ulcers or rash, were found. Laboratory examination showed no specific abnormalities, including autoantibodies or anti-HIV antibody. Syphilis serology was positive in blood and cerebrospinal fluid (CSF) using the rapid plasma reagin (RPR) test and *Treponema pallidum* haemagglutination assay (TPHA). Mild pleocytosis (48 cells/μl) with predominant lymphocytes (96%) and increased protein (81 mg/dl) were found in the CSF. IgG index was 2.22. EEG revealed focal quasi-rhythmic slow waves (3-Hz) in the right frontocentral region, and focal frequent spikes in the right occipital area (*figure 1A*). Brain MRI showed thickening and diffuse enhancement of the dura mater, and T2-weighted images demonstrated white matter hyperintensity of the right frontal and temporal lobes (*figure 1B*). Tc-99m ethyl cysteinate dimer single-photon emission computed tomography (Tc-99m ECD-SPECT; Discovery NM/CT670, GE, USA) revealed a widespread decrease in blood flow from the right frontal to temporal lobes, as well as an increase in focal blood flow in the right medial occipital lobe (*figure 1C*). Interictal FDG-PET (Biograph PET/CT, Siemens, Germany) demonstrated glucose hypometabolism in the right hemisphere, but with increased uptake in the right occipital lobe (*figure 1D*), consistent with the perfusion abnormality observed on ECD-SPECT.

After the diagnosis of neurosyphilis was confirmed based on CSF and serological findings, intravenous penicillin G (PcG) was administered (24,000,000 units/day for 14 days). One month after the start of treatment, cognitive function improved (MMSE score: 25) and serum and CSF RPR was negative. The IgG index also decreased to 1.28. EEG revealed restoration of posterior dominant rhythm in the right hemisphere. The spikes in the right occipital area had disappeared, and slow activity in the frontocentral region had decreased (*figure 1F*). The hyperintensity of the right frontal and temporal lobes on MRI had disappeared (*figure 1G*). Right frontal hypoperfusion was restored, however, right mesial occipital flow was diminished on ECD-SPECT (*figure 1H*). Upon careful examination of the MRI, structural abnormality was identified in the right mesial occipital lobe (*figure 1G; yellow arrow*).

MEG recording, analysis, and findings

MEG was measured on the next day of EEG recording both pre- and post-treatment with PcG. The MEG signals were collected using a whole-head neuromagnetometer with 204 planar gradiometers and 102 magnetometers (Neuromag MEG system; Elekta Neuromag Oy, Helsinki, Finland). In both recordings, raw data were collected for four minutes as a single session, and six sessions were recorded. Sampling frequency was 1,020 Hz, and low- and high-pass filters were set to 120 and 0.1 Hz, respectively. All data were preprocessed using Maxfilter (software by Neuromag), using the temporal extension of the signal space separation (Taulu *et al*., 2004) method with buffer length of 10 seconds and correlation limit of 0.9.

MEG spikes were visually determined, and equivalent current dipole was fitted at the spike peak using Neuromag data analysis software. The criteria for equivalent current dipole were >90% local goodness-of-fit and <500 mm^3 confidence volume. Slow wave analysis was conducted using an in-house script running on MATLAB (MathWorks, Inc., Natick, MA, USA). Continuous raw data corresponding to approximately four minutes from two different sessions of both pre- and post-treatment were used for MEG amplitude spectra calculation. Fast Fourier transform with a one-second time window (equal to 1-Hz frequency resolution) was applied for whole data length with half-window overlapping. Results from two different sessions were superimposed to confirm reproducibility. After confirming a 3-Hz peak in the left central area based on the pre-treatment data (*supplementary figure 1D, E*), the source of the 3 Hz was estimated by using spatial filter (sLORETA; Pascual-Marqui, 2002). The colour scale was adjusted to the difference of 3-Hz power between pre- and post-treatment (*supplementary figure 1F*).

During pre-treatment, current sources of MEG spikes were clustered in the right occipital lobe, corresponding to the hypermetabolic focus on FDG-PET (*figure 1E,*

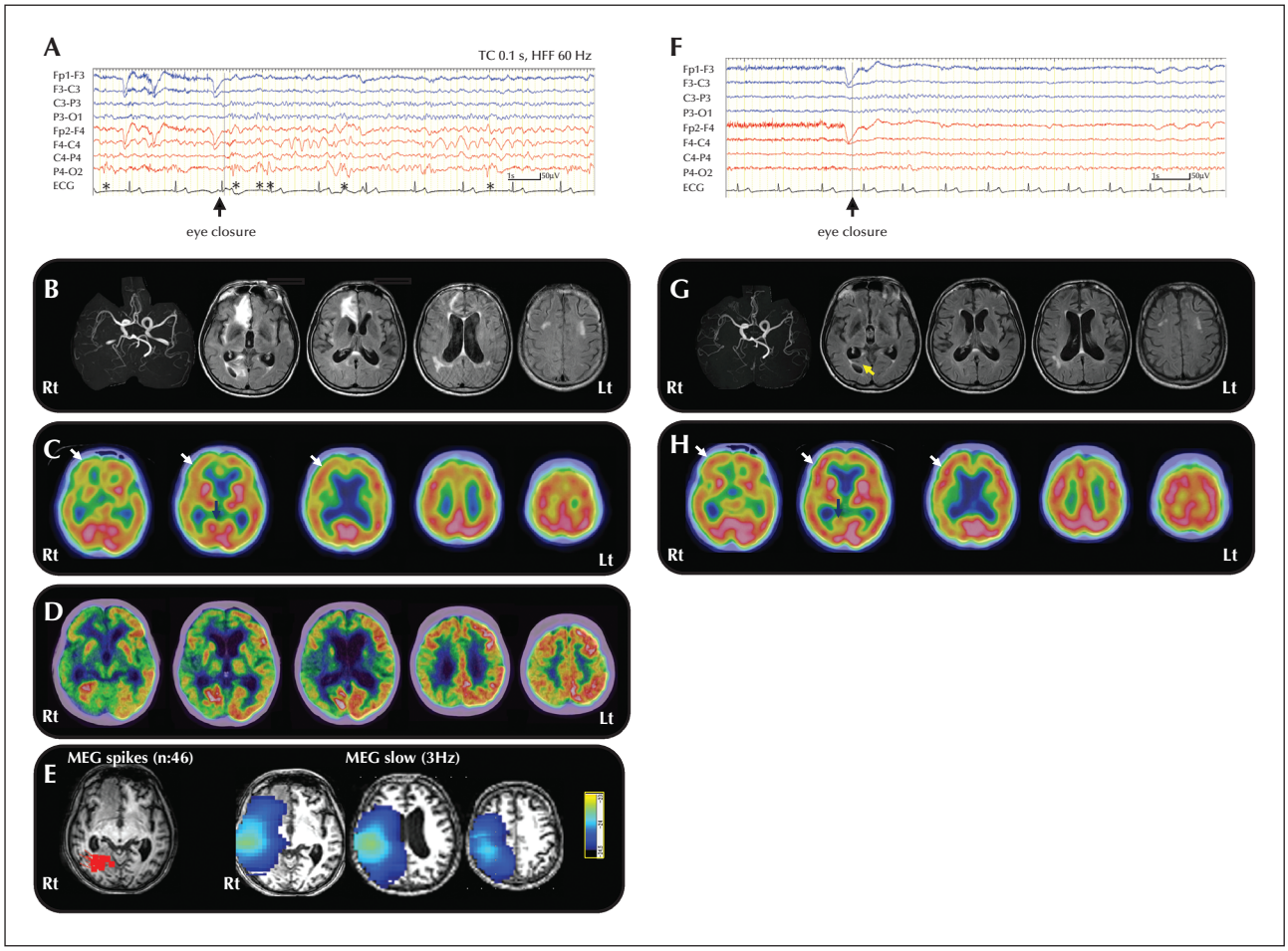

Figure 1. Neurophysiological and neuroradiological studies of pre- (A-E) and post- (F-H) PcG treatment.
During pre-treatment, EEG showed regional intermittent quasi-rhythmic slow waves (3-Hz) over the right frontocentral area, and frequent spikes (*) at O2 during pre-PcG treatment. Vasogenic oedema in the right frontal and occipital lobes and meningeal enhancement were identified on MRI (B). Decreases in blood flow and metabolism were observed widely over the right hemisphere ("cool" area) on 99mTc ECD-SPECT (C) and FDG-PET (D). In contrast, focal increases in both blood flow and metabolism were noticed in the right medial occipital lobe ("hot" area). MEG data were collected on the day after EEG (A). All MEG spikes were clustered in this "hot" occipital lobe, and distribution of MEG 3-Hz slow wave activity corresponded to the "cool" fronto-parieto-temporal lobes (E). One month after the PcG treatment, abnormal slow activity and spikes disappeared on EEG (F), and MEG, MRI, and blood flow abnormalities almost resolved (G, H). There was no difference between the MR angiography. White and black arrows for SPECT indicate increased and decreased blood flow according to treatment, respectively.

supplementary figure 1A-C). Furthermore, in order to visualize the 3-Hz slow distribution, power spectra were calculated from MEG raw data obtained between pre- and post-treatment. MEG power at 0-60 Hz was greater during pre-treatment than during post-treatment, and this discrepancy was especially pronounced for the slow waves. The power differences were observed over the right frontocentral area. The 3-Hz distribution corresponded to a "cool" area as the hypometabolic site on FDG-PET and the site of decreased blood flow on SPECT (*figure 1E, supplementary figure 1D-F*). EEG, MRI, SPECT, and CSF findings demonstrated an improvement with the initial antiepileptic drug (AED) regimen, and seizures did not recur after PcG treatment.

Discussion

Syphilis, which is caused by the spirochete *Treponema pallidum*, has re-emerged as a significant cause of neurological disease (neurosyphilis). It can infiltrate any part of the nervous system at any stage of infection and causes a non-specific variety of neurological symptoms, which makes clinical diagnosis difficult (Bhai and Lyons, 2015). Currently, classic staging of syphilis is

difficult in such atypical cases (Bhai and Lyons, 2015). The negative RPR both in serum and CSF post-treatment, as well as the reduction of IgG index, reflects the therapeutic effect (Jones *et al*., 1990). The patient in this report was diagnosed with the meningovascular subtype of neurosyphilis, and IV PcG was effective. Although the incidence of symptomatic seizures in neurosyphilis has been reported to range from 14% to 60%, patients rarely develop status epilepticus (Ances *et al*., 2004; Li *et al*., 2006; Kumari *et al*., 2015). Seizures most commonly occur with the meningovascular form of neurosyphilis and can appear at any stage of infection (Sinha *et al*., 2008), as in our patient. PcG treatment is essential, however, accurate diagnosis and treatment initiation will be delayed if other diseases, such as new-onset refractory status epilepticus, are suspected (Kumari *et al*., 2015).

Interestingly, MEG/EEG and PET/SPECT findings in neurosyphilis show coupling of inflammatory and functional abnormality in the brain. Here, we defined the "cool" area as the location with regional hypoperfusion and hypometabolism, in contrast to the "hot" area. In our patient, current sources of spikes were clustered focally in the hot area. This location became a structural focal lesion on MRI (*figure 1G; arrow*), which was suggestive of invasive inflammation and the epileptic focus. Although there have been no reports of patients with neurosyphilis, FDG-PET is recommended for the diagnosis of autoimmune encephalitis in order to delineate inflammatory foci if MRI is normal (Morbelli *et al*., 2016). On the other hand, slow wave distribution on EEG/MEG in this patient coincided with the cool area. These findings, MMSE, and even the MRI abnormality in the cool area were reduced by PcG treatment without the need for AED adjustment. Regional MEG slow activity associated with cerebral ischaemia was reported to be reversible by surgical vascular reconstruction (Sakamoto *et al*., 2008). However, MR angiography in the presented patient did not change pre- and post-treatment, in contrast to the case of Sakamoto *et al*. (2008). Hypoperfusion in the presented patient was unlikely to be due to ischaemia. The MEG/EEG slow activity in this patient appears to indicate functional impairment of the mildly affected syphilitic brain.

Semiologically, no visual symptoms were reported by this patient ictally or interictally. There are various symptoms of occipital lobe epilepsy (OLE), and ictal activity in OLE can rapidly spread anywhere in the brain, including the frontal lobe (Williamson *et al*., 1992). It is therefore possible that the seizures in our patient arose from the occipital lobe.

In conclusion, neurosyphilis is a classic condition which is re-emerging today, and the meningovascular subtype causes global invasion to the brain. The multi-modal neurophysiological approach used in this case demonstrates the various pathophysiological processes of the disease, as well as the active inflammation and reversible dysfunction of the cortex caused by syphilitic infection. As for treatment, PcG was effective. □

Supplementary data.
Supplementary figure is available on the www.epilepticdisorders.com website.

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

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TEST YOURSELF

(1) What is the first treatment option for neurosyphilis?

(2) How frequent do seizures occur in neurosyphilitic patients, and do these commonly progress to status epilepticus?

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".