Systemic Lupus Erythematosus with Organic Brain Syndrome: serial electroencephalograms accurately evaluate therapeutic efficacy

Takashi Kato¹, Kyoji Shiratori¹, Tsuyoshi Kobashigawa² and Yuji Hidaka¹

Abstract

A 48-year-old man with systemic lupus erythematosus developed organic brain syndrome. High-dose prednisolone was ineffective, and somnolence without focal signs rapidly developed. Electroencephalogram (EEG) demonstrated a slow basic rhythm (3 Hz), but brain magnetic resonance imaging was normal. Somnolence resolved soon after performing plasma exchange (two sessions). However, memory dysfunction persisted, with EEG demonstrating mild abnormalities (7-8 Hz basic rhythm). Double-filtration plasmapheresis (three sessions) was done, followed by intravenous cyclophosphamide. Immediately after the first plasmapheresis session, memory dysfunction began to improve. After the second dose of cyclophosphamide, intellectual function resolved completely and EEG findings also normalized (basic rhythm of 10 Hz waves). Serial EEG findings precisely reflected the neurological condition and therapeutic efficacy in this patient. In contrast, protein levels in cerebrospinal fluid remained high and did not seem to appropriately reflect the neurological condition in this patient.

Key words: double-filtration plasmapheresis (DFPP), electroencephalogram (EEG), intravenous cyclophosphamide, neuropsychiatric manifestations of systemic lupus erythematosus (NP-SLE), organic brain syndrome (OBS), plasma exchange

(Introduction)

Neuropsychiatric manifestations of systemic lupus erythematosus (NP-SLE) include organic brain syndrome (OBS), stroke syndrome, seizures, polyneuropathy or mononeuropathy, cranial neuropathy, psychiatric disorders, transverse myelitis, and intractable headache (1). OBS is defined by altered mental function with impaired orientation, memory, or other intellectual function (2). Delirium is a form of OBS and it is often observed in NP-SLE (3). NP-SLE is sometimes a critical condition, and both NP-SLE and its treatment carry a considerable (7% to 19%) mortality rate (4).

In this report, we describe a patient with OBS as a manifestation of NP-SLE who was successfully treated with high-dose corticosteroids, plasma exchange, double-filtration plasmapheresis (DFPP), and intravenous cyclophosphamide. In addition, concomitant lupus nephritis, myositis, and pericarditis resolved during treatment. With this patient, serial electroencephalograms (EEGs) precisely demonstrated the neurological condition and therapeutic efficacy, in contrast with serial assessment of protein levels in cerebrospinal fluid which did not appear to parallel changes in the neurological condition.

Case Report

A 48-year-old Japanese man was admitted to our hospital in September 2004 with a one-month history of low-grade fever, general malaise, and weakness of the lower extremities. He had been diagnosed with discoid lupus erythematosus in 2001 and treated with topical corticosteroids. He had noticed photosensitivity and Raynaud’s phenomenon prior to the current admission.

¹Department of Rheumatology, Kameda Medical Center, Kanagawa and ²Institute of Rheumatology, Tokyo Women’s Medical University, Tokyo
Received for publication March 28, 2005; Accepted for publication October 10, 2005
Reprint requests should be addressed to Takashi Kato, Division of Internal Medicine, Murayama Medical Center, 2-37-1 Gakuen, Musashimurayama City 208-0011
On admission, the patient was febrile (38.0°C) and normotensive (106/56 mmHg) with a regular heart rate of 96 beats per minute. His height was 171.2 cm and he weighed 69.8 kg. His consciousness was clear, and meningeal signs were absent. Examination of cranial nerves was normal and sensory function appeared unremarkable. Mild muscle weakness was evident in the proximal lower extremities, although myalgia was absent. Swollen or tender joints were not observed. Facial erythema including malar rash and alopecia were apparent. Palmar and plantar erythema and discoid lesions on the neck were also observed. Sclerodactyly or nail fold infarction was not observed. There was no edema of the lower extremities. Examination of the oral cavity, lymphoreticular system, chest, and abdomen was unremarkable.

Laboratory findings were as follows: erythrocyte sedimentation rate 122 mm/hr, white blood cell count 4900/μL (lymphocyte 343/μL), hemoglobin 8.3 g/dL, platelet count 19.7×10^10/μL, total protein 7.1 g/dL, albumin 2.7 g/dL, total bilirubin 0.4 mg/dL, aspartate aminotransferase 91 U/L, alanine aminotransferase 98 U/L, lactic dehydrogenase 838 U/L, creatine phosphokinase (CPK) 702 U/L (normal range <150), blood urea nitrogen 40 mg/dL (normal range <23), creatinine 1.2 mg/dL (normal range <1.2), uric acid 5.0 mg/dL, and ferritin 4310.0 ng/mL (normal range <260). Serum electrolytes and fasting blood sugar were normal. Serological findings were as follows: C-reactive protein 0.85 mg/dL (normal range <0.4), immunoglobulin G (IgG) 2801 mg/dL, IgA 357.3 mg/dL, IgM 151.6 mg/dL, complement factor 3 (C3) <30 mg/dL (normal range 45-102), C4 <6.0 mg/L (normal range 10-40), CH50 <12.0 IU/mL (normal range 30-45), anti-nuclear antibody (ANA) 1:2560 (speckled pattern), anti-double stranded DNA (anti-ds DNA) >400 U/mL (normal range <10), anti-Sm 32 U/mL (normal range <10), anti-RNP 16 U/mL (normal range <10), anti-Ro, anti-La, anti-Jo 1, and anti-beta 2 glycoprotein I-cardiolipin complex were all negative. The prothrombin time and activated partial thromboplastin time were normal, and lupus anticoagulant was negative. Proteinuria (3+), hematuria (2+), pyuria without evidence of bacterial infection, and cellular casts were detected in urinalysis. Chest X-ray and electrocardiogram were normal.

Based on the findings of malar rash, discoid rash, photosensitivity, renal disorder, hematologic disorder, positive status for anti-ds DNA, anti-Sm and ANA, a diagnosis of SLE was made (5, 6). Because the presence of lupus nephritis and myositis was under consideration, further investigations were planned. The putative systemic lupus erythematous disease activity index (SLEDAI) was 28 points (2). High fever spikes continued and progressive muscle weakness developed that resulted in the patient becoming unable to walk without assistance (manual muscle test of the bilateral iliopsoas had decreased from 4+ to 3+). In addition, the laboratory findings such as an extremely high level of anti-ds DNA and severely decreased complement levels, as well as the long duration between onset and admission (at least one month), suggested the necessity of immediately starting treatment with high-dose corticosteroids. On day 3 of the admission, 65 mg/day oral prednisolone was started without performing baseline renal or muscle biopsy. On day 5, high fever spikes were partially ameliorated and progression of muscle weakness slowed. On day 6, severe chest pain developed temporally and a diagnosis of acute pericarditis was made. Later the same day, a disturbance of consciousness (somnolence) without focal signs developed. Hypertension did not develop. Head computed tomographic scanning did not demonstrate intracranial bleeding. Lumbar puncture revealed a protein level in cerebrospinal fluid (CSF) of 86 mg/dL (normal range <40) without pleocytosis and with normal lumbar CSF pressure (Fig. 1). Blood tests did not reveal any causes for the change in consciousness such as hypoglycemia, hypoxia, hypercapnia, or electrolyte abnormalities. A diagnosis of organic brain syndrome (OBS) as a sign of neuropsychiatric manifestations of SLE (NP-SLE) was strongly suggested. On day 9, the disturbance of consciousness continued, and an electroencephalogram (EEG) revealed a slow basic rhythm (around 3 Hz) without paroxysmal activity (Fig. 2A). Plasma exchange (3.2 L, replaced by fresh frozen plasma) was performed on the same day, and the somnolent state began to improve during treatment (Fig. 1). Furthermore, the malar rash also appeared to improve during plasma exchange. On day 10, intravenous methyl-prednisolone pulse treatment (1 g/day, for 3 consecutive days) followed by 65 mg oral prednisolone daily was begun. On day 11, head magnetic resonance imaging (MRI) did not demonstrate any abnormal signals in the brain. On day 12, a second plasma exchange was performed; the orientation disorder resolved immediately (Fig. 1). On day 13, EEG findings were slightly improved, and 5 Hz waves appeared (Fig. 2B). Also on day 13, results from the CSF sample obtained on day 6 were received: normal cytology, no growth in culture (including investigation of tuberculosis), and negative status for cryptococcal antigens. In addition, beta-D glucan, cytomegalovirus antigens, and haptoglobin level in a blood sample obtained on day 6 did not demonstrate any abnormalities. Based on these findings, a diagnosis of OBS as a manifestation of NP-SLE was confirmed by exclusion. On day 24, although EEG findings had improved further (Fig. 2C), CSF protein level was increasingly elevated, from 86 mg/dL to 116 mg/dL, still without pleocytosis (Fig. 1). Prednisolone dosage was tapered gradually after day 27. Somnolence did not recur; however, disturbance of recent memory was apparent. Methyl-prednisolone pulse treatment was repeated for days 33 to 35, but the memory disturbance did not improve. On day 37, EEG findings were slightly improved (basic rhythm of 7-8 Hz waves) but had not yet normalized (Fig. 2D). Therefore, double-filtration plasmapheresis (DFPP) (3 L, replacement with 5% albumin) was performed on days 38, 41, and 45 (Fig. 1). In addition, intravenous cyclophosphamide (700 mg, 400 mg/m²) was given on day 39. Soon after the first DFPP treatment, memory dysfunction improved markedly (Fig. 1). On day 51,
EEG findings revealed an almost normal basic rhythm (9 Hz waves) (Fig. 2E); however, CSF protein level on day 59 remained high (105 mg/dL), without pleocytosis. CPK level decreased to the normal range on day 17, and renal disorders including urinalysis abnormalities disappeared by day 43. On day 65, anti-ds DNA level had risen from 17 U/mL to 52 U/mL again, and intravenous cyclophosphamide (500 mg) was given on day 74 (Fig. 1). On day 82, a mild *Pneumocystis carinii* pneumonia developed and the beta-D glucan level increased to 113 pg/mL (normal range <20). Treatment with sulfamethoxazole-trimethoprim improved the pneumonia by day 90. The patient’s intellectual function recovered gradually, and EEG examination was normal on day 97 (Fig. 2F). Furthermore, he could solve crossword puzzles and operate a personal computer by day 110. On day 116, the CSF protein level had decreased to 66 mg/dL, without pleocytosis. In all four CSF studies performed in this case, findings suggestive of infection of the central nervous system were absent. On day 126, 50 mg azathioprine daily was added as a maintenance treatment. Prednisolone was successfully tapered to 20 mg on day 154 (Fig. 1).

**Discussion**

A diagnosis of NP-SLE is made not only by the presence of SLE with concomitant neurological disorders but also by exclusion of other possible etiologies such as infection, malignancy, hypertension, and metabolic disorders (7). Therefore, intensive investigations including CSF analysis, brain imaging, and serological study are mandatory for diagnosis (7). However, one review found that a series of CSF analysis was normal in 13 of 28 patients with NP-SLE (1); therefore, normal CSF findings cannot exclude the presence of the illness. In the present case, although elevated CSF protein levels supported a diagnosis of NP-SLE, the levels remained high even after neurological improvement became clinically evident. However, the EEG findings recorded serially with our patient reflected neurological improvement precisely, in marked contrast with serial CSF protein levels. Regarding EEG findings in the setting of NP-SLE, abnormalities closely relate to the clinical evidence of cerebral involvement with SLE (8). EEG findings can also indicate the response to treatment with corticosteroids (8). In addition, EEG findings may help to distinguish psychosis as a manifestation of NP-SLE from steroid psychosis (8). However, Colamussi et al reported only 60% of SLE patients with central nervous system (CNS) manifestations such as stroke, seizures, personality disorders, psychosis, cerebellar ataxia, and dementia, demonstrated abnormal EEG findings (9). Therefore, normal EEG findings may not exclude the presence of CNS lesions due to SLE. Recently, brain single photon emission computerized tomography (SPECT) has been introduced as a sensitive tool to detect brain abnormalities in patients with SLE (9, 10). However, EEG is more convenient compared with other tools such as MRI and SPECT, and EEGs should be performed for the primary investigation of OBS as a manifestation of NP-SLE.

When we consider the pathogenesis of NP-SLE, vasculitis
and thrombosis are known to be responsible for catastrophic focal brain injury in patients with NP-SLE (11). Recently, neuronal apoptosis directly caused by a kind of anti-ds DNA in CSF was demonstrated as a new pathogenic agent of NP-SLE manifested by cognitive dysfunction (11). In lupus patients with CNS lesions, levels of CSF proinflammatory cytokines such as interleukin-1 (IL-1), IL-6, and IL-8 are significantly elevated and levels tend to reflect disease activity (12, 13). In addition, intrathecal treatment with methotrexate and dexamethasone is considered to be effective in some patients with refractory NP-SLE (7, 14). These findings suggest that intrathecal immunological inflammation plays an important role in the pathogenesis of NP-SLE. However, treatment with plasma exchange, which quickly removes systemically circulating pathogenic factors including anti-ds DNA, immune complexes, and proinflammatory cytokines from plasma (15), resulted in immediate improvement of manifestations of OBS with our patient. Therefore, not only intrathecal events but also systemically circulating pathogenic factors, such as anti-ds DNA, immune complexes and proinflammatory cytokines, may contribute to the pathogenesis of OBS as a manifestation of NP-SLE. In this consideration, impairment of the blood-brain barrier may be partially related to the pathogenesis of the CNS involvement related to lupus (16).

The efficacy of plasmapheresis for NP-SLE is anecdotal, and no controlled trial to confirm efficacy has been done to date (7). However, Neuwelt et al (1) reported that 6 of 8 patients with intravenous cyclophosphamide-resistant NP-SLE improved with plasma exchange, and plasmapheresis tends to be performed for patients with refractory NP-SLE. In severe lupus nephritis (World Health Organization (WHO) III-V), plasma exchange plus conventional treatment (high-dose prednisolone and oral cyclophosphamide) does not improve clinical outcomes in comparison with conventional treatment alone (17). However, patients treated with plasma exchange have a significantly more rapid reduction of serum anti-ds DNA levels (17). In patients with OBS as a manifestation of NP-SLE (such as our patient), cerebral function can deteriorate rapidly and can result in decerebrate rigidity that is a highly critical condition if effective treatment is not initiated (18). Therefore, the speed of therapeutic effectiveness may be important in NP-SLE, and plasmapheresis may improve the clinical outcome as reported in an uncontrolled study. In the setting of Guillain-Barre syndrome (GBS), an autoimmune polyneuropathy caused by anti-ganglioside autoantibodies, the clinical improvement appears more quickly with plasma exchange than with DFPP (19). In addition, the ability of plasma exchange to remove both IgG and anti-ganglioside IgG antibodies is significantly superior to that of DFPP (20). According to these findings, plasma exchange may also remove pathogenic IgG species such as anti-ds DNA more quickly and more effectively than DFPP for patients with SLE.

Finally, the findings demonstrated in the present case suggest that EEG findings are useful for making a diagnosis of

![Figure 2. Electroencephalographic (EEG) findings over the course of hospitalization. EEGs were recorded with referential derivation. Panel A was recorded on day 9. Slow basic rhythm (around 3 Hz) without paroxysmal activity is apparent. Panel B was recorded on day 13, with a basic rhythm of around 5 Hz. Panel C was recorded on day 24, with a basic rhythm of around 6-8 Hz. Panel D was recorded on day 37, with a basic rhythm of around 7-8 Hz. Panel E was recorded on day 51, with a basic rhythm of 9 Hz. Panel F was recorded on day 97. The basic rhythm was 10 Hz, and the frequency of the basic rhythm appears to be increased compared with Panel E.](image-url)
NP-SLE and for evaluating the therapeutic efficacy for the illness, while IgG and proinflammatory cytokines levels in CSF have been recognized to be clinically informative in patients with NP-SLE.

References


