J Neurol (2014) 261:2150–2158
DOI 10.1007/s00415-014-7472-y

ORIGINAL COMMUNICATION

New-onset psychiatric disorders after corticosteroid therapy in systemic lupus erythematosus: an observational case-series study

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Received: 20 June 2014 / Revised: 7 August 2014 / Accepted: 11 August 2014 / Published online: 21 August 2014

Abstract The objective of this study was to clarify the incidence, clinical characteristics, and courses of new-onset psychiatric manifestations after corticosteroid therapy in patients with systemic lupus erythematosus (SLE), including possible ways of differentiating between corticosteroid-induced psychiatric disorders (CIPDs) and central nervous system manifestations of SLE (CNS-SLE). We prospectively followed for 8 weeks 139 consecutive episodes in 135 in-patients who had a non–CNS-SLE flare treated with corticosteroids. Psychiatric events were evaluated once a week using DSM-IV criteria. We then conducted a post hoc etiological analysis of any newly developed psychiatric events during this follow-up period. In the 8 weeks of corticosteroid administration, new psychiatric events occurred in 20 (14.4 %) of the 139 episodes. The mean dosage of corticosteroids administered was prednisolone at 0.98 (range 0.24–1.39) mg/kg/day. Of the 20 psychiatric events, 14 (10.1 %) were suitable for the strict definition of CIPDs, accompanied by mood disorders in 13 (depressive in 2, manic in 9, and mixed in 2) and psychotic disorder in one. Two (1.4 %), both presenting delirium, were diagnosed as CNS-SLE on the basis of evidence of abnormal CNS findings even before psychiatric manifestations, all of which improved in parallel with these patients' recoveries through augmentation of immunosuppressive therapy. The other four events (2.9 %) could not be etiologically identified. This study suggests that corticosteroid therapy triggers CIPDs and CNS-SLE in patients with SLE. Delirium may be suggestive of CNS-SLE, while mood disorders may be more suggestive of CIPDs. Electroencephalographic abnormalities may possibly be predictive of CNS-SLE.

Keywords Corticosteroid therapy · Corticosteroid-induced psychiatric disorders · Neuropsychiatric lupus · Systemic lupus erythematosus

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Introduction

Systemic lupus erythematosus (SLE) is associated with a high incidence of psychiatric manifestations [1–4]. It is unknown whether this association is a direct consequence of systemic autoimmunity and inflammation [e.g., entry of immune cells and molecules into the central nervous system (CNS)], an indirect effect (e.g., an epiphenomenon associated with accumulation of toxic metabolites), or a consequence of immunosuppressive therapy with corticosteroids [5–7]. Psychopathology may be similar or identical in all three [8, 9] and no diagnostic gold standard for CNS manifestations of SLE (CNS-SLE) exists [8, 10, 11].

In practice, it is often difficult to distinguish corticosteroid-induced psychiatric disorders (CIPDs) from CNS-SLE [10, 12]. When SLE patients on corticosteroids

present new psychiatric symptoms, clinicians confront the emerging dilemma of whether the dosage of corticosteroids should be decreased or increased. Despite the clinical importance, no surveys have examined the incidence, clinical characteristics, and courses of new-onset psychiatric symptoms after corticosteroid therapy in patients with SLE from the viewpoint of possible ways to differentiate between CIPDs and CNS-SLE. To detect this difference, we first prospectively followed unselected, consecutive psychiatric episodes in SLE patients who had a non-CNS-SLE flare treated with corticosteroids. Second, we conducted a post hoc and retrospective analysis of the etiologies of the newly developed psychiatric events during follow-up of the case-series.

Patients and methods

This case-series was extracted from a prospective cohort of SLE patients treated with corticosteroids, which had been previously reported with a focus on CIPDs [13]. To analyze more fully all the newly developed psychiatric diagnoses in this cohort, we also included here the cases that had not met the definition of CIPDs previously and that had been excluded from the previous study. The population in this study included 135 SLE inpatients (130 women, 5 men) with non-CNS-SLE flares treated with corticosteroids in our rheumatologic unit from August 1999 to December 2004. During the study period, we noted 139 consecutive episodes, including four patients who required a second hospitalization and course of therapy because of another manifestation of SLE. Of the 139 episodes, 69 (49 %) were treated with corticosteroids for the first time and the others were treated with an augmented dose of the drug. The mean dosage of corticosteroids administrated was 46.5 mg/day [standard deviation (SD) 14.7, range 15–100) or 0.95 mg/kg/day (SD 0.20, range 0.27–1.95) as prednisolone. Additionally, intravenous methylprednisolone pulse therapies were initially conducted in 39 (28 %) of 139 episodes: 0.5 g/day for 3 days in 17 episodes and 1 g/day for 3 days in 22 episodes. All patients in this study were Japanese and fulfilled the 1982 revised criteria of the American College of Rheumatology for SLE [14].

The 139 episodes were prospectively followed for 8 weeks after corticosteroid therapy to assess for newly developed psychiatric symptoms. Psychiatric events in our rheumatologic unit were evaluated at regular intervals (once a week) by experienced psychiatrists (K.N. and M.O.) using subcategories of substance-induced disorders/mental disorders owing to a general medical condition in the *Diagnostic and Statistical Manual of Mental Disorders, 4th edition* (DSM-IV) [15]. Among these subcategories, sexual dysfunction and sleep disorder were excluded. According to the DSM-IV, the disturbances must be severe enough to cause clinically significant distress or impairment in social functioning.

Based on previous reports [12, 13, 16, 17], CIPDs were defined as new-onset psychiatric symptoms that developed within 8 weeks of corticosteroid administration and that resolved completely through a reduction in corticosteroid dosage and without additional immunosuppressive agents. This definition was employed because of the dose dependency of CIPDs [18] and because increasing the dosage of corticosteroids and/or administering additional immunosuppressive agents in a patient who subsequently improves implicates active CNS-SLE. If the psychiatric symptoms resolved with the use of psychotropic agents, this was not recognized as recovery from the psychiatric event until the symptoms did not relapse after discontinuation of the agents.

Laboratory and neurologic tests were mostly performed within a week before administration of corticosteroids. Neurologic tests, including brain magnetic resonance imaging (MRI), electroencephalography (EEG), and cerebrospinal fluid (CSF) analysis, were performed, if patients gave standard clinical informed consent for these examinations as part of a systematic evaluation of the disease, because there could have been CNS involvement even in the absence of current overt neuropsychiatric symptoms or in the absence of an abnormal EEG or MRI lesions [10, 19]. Biochemical analysis of CSF samples included determinations of immunoglobulin G (IgG) index and Q-albumin (CSF/serum albumin ratio; an indicator of blood–brain barrier damage) as well as analysis of interleukin (IL)-6 and interferon (IFN)-α, which have been reported to be associated with active CNS-SLE [11, 20–23]. To address the possibility of development of CNS-SLE or of other secondary causes such as infection or metabolic derangement, we conducted laboratory and the above-mentioned neurologic tests as soon as psychiatric events occurred.

For statistical analyses, the non-parametric Mann–Whitney *U* test was used to identify differences between groups for continuous variables, and categorical variables were compared by the Fisher exact test. To identify independent risk factors for new-onset psychiatric disorders, we performed a multiple logistic regression analysis by forward stepwise variable selection methods using data sets that were significantly ($p < 0.05$) or almost significantly ($p < 0.25$) associated with the new-onset psychiatric disorders in the univariate analysis. Regression coefficients were used to calculate the odds ratios (ORs) and 95 % confidence intervals (CI) of the ORs. In all statistical analyses, $p < 0.05$ was taken to indicate statistical significance. We performed all analyses using the SPSS® Statistics 17.0 (SPSS Inc., Chicago, IL, USA).

Table 1 Univariate analysis of risk factors for new-onset psychiatric disorders after corticosteroid therapy in patients with systemic lupus erythematosus

Variable	New-onset psychiatric disorders $N = 20$	No psychiatric events $N = 119$	p value
Disease duration after diagnosis, months	2.5 (0–28.3)	0.5 (0–72)	0.775
Cumulative clinical manifestations			
Nephritis	11/20 (55 %)	85/119 (71 %)	0.141
Hematological disorder	13/20 (65 %)	57/119 (48 %)	0.159
Arthritis	10/20 (50 %)	49/119 (41 %)	0.460
Mucocutaneous disorder	10/20 (50 %)	58/119 (49 %)	0.917
Serositis	3/20 (15 %)	14/119 (12 %)	0.683
Corticosteroid therapy			
First-time corticosteroid therapy	12/20 (60 %)	60/119 (50.4 %)	0.428
Duration of corticosteroid therapy at admission, months	0 (0–51.8)	2.5 (0–76.8)	0.334
Baseline dose/body weight, mg/kg/day	0 (0–0.16)	0 (0–0.23)	0.345
Initiation/augmentation dose/body weight, mg/kg/day	1.05 (0.91–1.28)	0.83 (0.67–1.08)	0.002[a]
Methylprednisolone pulse therapy	7/20 (35 %)	28/119 (24 %)	0.274
Laboratory tests			
White blood cell count (cells/mm^3)	4,200 (2,925–6,675)	5,100 (3,500–6,900)	0.215
Red blood cell count ($\times 10^6$/mm^3)	3.83 (3.53–4.23)	3.98 (3.58–42.1)	0.496
Hemoglobin (g/dl)	11.4 (10.0–12.6)	11.5 (10.1–12.4)	0.813
Platelet count ($\times 10^4$/mm^3)	20.4 (15.4–24.6)	21.2 (15.7–26.5)	0.525
Serum albumin (g/dl)	3.2 (2.7–3.8)	3.4 (2.9–3.7)	0.394
Serum creatinine, mg/dl	0.6 (0.5–0.9)	0.7 (0.6–0.8)	0.366
CH50 level (U/ml)[b]	13 (10–21)	24 (14–34)	0.009[a]
C3 level (mg/dl)	42 (32–60)	63 (46–80)	0.001[a]
C4 level (mg/dl)	5 (2–11)	11 (5–17)	0.005[a]
Antinuclear antibody[c]	6 (5–8)	5 (4–7)	0.027[a]
Anti-DNA antibody (U/ml) (RIA)	49.5 (15–152)	38 (8–129)	0.455
Anti-ds-DNA IgG antibody (U/ml) (ELISA)	31 (11–142)	18 (5–83)	0.371
Positive anti-Sm antibody (ELISA)	5/20 (25 %)	20/113 (18 %)	0.310
Positive antiphospholipid antibodies[d]	2/18 (11 %)	20/105 (19 %)	0.525
Neurologic tests			
Magnetic resonance images of the brain, abnormal[e]	5/18 (28 %)	23/84 (27 %)	0.590
Electroencephalogram, abnormal	4[f]/20 (20 %)	11[g]/84 (13 %)	0.317
Cerebrospinal fluid tests			
Positive IgG index (normal <0.70)	5/18 (28 %)	14/77 (18 %)	0.269
Positive Q-albumin (normal<9.0)	6/16 (38 %)	2/73 (3 %)	0.000[a]
Interleukin-6 (pg/ml)[h]	1.4 (0.7–3.2)	2.2 (1.0–4.9)	0.196
Interleukin-8 (pg/ml)[h]	44.6 (24.1–74.6)	40.3 (26.7–78.3)	0.761
Interferon-a (IU/l)[h]	1.7 (0–18.3)	0 (0–14.8)	0.442

Data are number/number assessed (%) or median (interquartile range)

RIA radioimmunoassay, *ELISA* enzyme-linked immunosorbent assay

[a] Significant variables

[b] Levels <10 U/ml, the lowest limit of the assay, were calculated as 10 U/ml

[c] Antinuclear antibody (ANA) values were converted into the following binary logarithm: $\log_2(\text{ANA}/40)$

[d] Antiphospholipid antibodies include anticardiolipin β_2-glycoprotein I complex and lupus anticoagulant

[e] All detected abnormalities in both groups were small subcortical lesions

[f] Diffuse continuous bisynchronous slow waves were detected in three episodes, and θ bursts in one

[g] Diffuse continuous bisynchronous slow waves were detected in seven episodes, θ bursts in two, and sharp waves in two

[h] Interleukin (IL)-6, IL-8, and interferon (IFN)-a in the cerebrospinal fluid were determined in 19 episodes of new-onset psychiatric disorders and in 80 episodes of no psychiatric events. Values below the lowest limit of the assay were calculated as the value of the lowest limit: IL-6 as 0.15 pg/ml, IFN-a as 10 IU/l

Results

Incidence and clinical characteristics of new-onset psychiatric manifestations after corticosteroid therapy

During the 8 weeks of corticosteroid administration, new psychiatric events occurred in 20 (14.4 %) of the 139 episodes, accompanied by delirium in 2 events (10 %), psychotic disorders in 3 (15 %), anxiety disorders in 1 (5 %), and mood disorders in 14 (70 %), which involved depressive features in 2, manic features in 10, and mixed features in 2. No individual patient had more than one psychiatric diagnosis. All 20 events developed within 4 weeks (mean 12 days, range 2–28 days) of corticosteroid administration. The mean dosage of corticosteroids administered was 0.98 mg/kg/day (range 0.24–1.39 mg/kg/day) as prednisolone. No episodes occurred because of other secondary causes such as infection or metabolic derangement or because of a psychological reaction, e.g., adjustment disorder. Other medications used in parallel, such as trimethoprim/sulfamethoxazole (patient no. 8), beraprost (patient no. 1), or famotidine (patient no. 13), were not considered as likely secondary causes, because these medications were continuously used before and after the psychiatric episodes.

Risk factors of new-onset psychiatric manifestations after corticosteroid therapy

Table 1 shows the results of the univariate analysis of risk factors for new-onset psychiatric disorders after corticosteroid therapy. According to multiple logistic regression analysis, positive Q-albumin (OR 18.2, 95 % CI 2.64–127, $p = 0.003$) and serum C3 level (OR 1.05, 95 % CI 1.01–1.08, $p = 0.01$) were significant independent risk factors.

Events fitting the definition of corticosteroid-induced psychiatric disorder (CIPD)

Of the 20 psychiatric events, 14 were suitable for the definition of CIPD, as reported elsewhere [13] (Table 2). The mean interval between steroid administration and CIPD manifestation was 12.5 days (range 2–28 days). The mean dosage of corticosteroids administered was 1.03 mg/kg/day (range 0.82–1.40 mg/kg/day). A psychotic disorder occurred in one event and mood disorders occurred in 13 events, including depressive episodes in 2, manic episodes in 9, and mixed episodes (i.e., simultaneous symptoms of both depression and mania) in 2. All psychiatric events resolved completely after corticosteroid dosage reduction to a mean of 0.69 mg/kg/day (range 0.27–0.88 mg/kg/day). Neurological/immunological findings prior to corticosteroid therapy in these 14 patients are shown in Table 3.

Of the 13 events presenting as mood disorders, 10 events (77 %) were unipolar episodes during one therapy course, while three events (23 %) were bipolar episodes during one therapy course. One mixed episode (patient no. 13) and the manic episode (patient no. 16) recovered after being succeeded by major depressive episodes. Another mixed episode (patient no. 17) recovered after being succeeded by a manic episode followed by a major depressive episode.

Events not fitting the CIPD definition—differentiation with CNS-SLE

Of the 20 psychiatric events, six were unsuitable for the definition of CIPD because augmentation therapies were performed after the occurrence of psychiatric events, e.g., re-augmentation of steroid dosage or additional immunosuppressive agents (Table 4). Two psychiatric events (patients no. 10 and 20) were diagnosed as CNS-SLE triggered by corticosteroid therapy on the basis of abnormal neurologic and immunological findings indicating CNS involvement (Table 3), which existed even prior to the corticosteroid administration and improved in parallel with these patients' recoveries through treatment augmentation with additional immunosuppressive therapy.

Patient no. 10 developed delirium after 8 days of corticosteroid administration of 0.59 mg/kg/day as prednisolone. She had already demonstrated an EEG abnormality of diffuse continuous bisynchronous slow waves (3–7 Hz θ) on the 6th day of corticosteroid administration. Additionally, after the manifestation of delirium, she showed hypoperfusion in the left temporal and left occipital areas as depicted by single photon emission computed tomography (SPECT), as well as markedly elevated levels of serum anti-ribosomal P antibody (over 480 U/ml, normal <37), which has been reported to be associated with active CNS-SLE [21]. Intravenous cyclophosphamide pulse therapy (500 mg/day) was performed, while the same dosage of corticosteroid was maintained. Afterwards, EEG findings dramatically improved and her psychiatric episode also gradually disappeared. This case has been reported elsewhere [24].

Patient no. 20 developed delirium on the third day of methylprednisolone (0.5 g/day) pulse therapies that were additionally performed for pancytopenia after 20 days of corticosteroid administration up to 1.35 mg/kg/day as prednisolone for lupus nephritis, pericarditis, and pleuritis. Three days later, she developed coma and seizures. On the 7th day of the initial corticosteroid administration, she had already shown an EEG abnormality with diffuse continuous bisynchronous slow waves (3–7 Hz θ) and abnormal

Table 2 Clinical features and outcome of events suitable for the definition of corticosteroid-induced psychiatric disorders

Patient no	Age, years/sex	Main target symptoms of corticosteroid therapies	SLEDAI-2 K at baseline	Interval[a], days	Neuropsychiatric features	PSL dose, mg/kg/day, at			Duration[b] (days)	Outcome
						Baseline	Administration	Recovery		
1	53/F	Myositis, hematologic disorder	9	14	Mood disorder, manic	0.08	1.08	0.88	30	Recovery
3	30/F	Arthritis, hematologic disorder	5	7	Mood disorder, manic	0.10	0.83	0.62	40	Recovery
4	50/F	Hematologic disorder, arthritis	16	21	Mood disorder, manic	0.00	1.30[c]	0.86	21	Recovery
5	29/F	Vasculitis, rash	15	14	Psychotic disorder	0.00	0.97	0.79	30	Recovery
6	22/F	Nephritis, arthritis, hematologic disorder	18	4	Mood disorder, depressive	0.00	0.89[d]	0.29	90	Recovery
8	21/F	Hematologic disorder, nephritis	8	16	Mood disorder, depressive	0.51	1.21[c]	0.66	90	Recovery
9	40/F	Nephritis, arthritis, hematologic disorder	16	20	Mood disorder, manic	0.00	1.39	0.69	60	Recovery
11	29/F	Arthritis, rash, hematologic disorder	10	3	Mood disorder, manic	0.00	0.91	0.74	35	Recovery
12	36/F	Nephritis, arthritis, hematologic disorder	22	5	Mood disorder, manic	0.10	1.02[d]	0.82	40	Recovery
13	19/F	Nephritis, rash	12	2	Mood disorder, mixed[e]	0.27	0.91	0.27	240	Recovery
16	30/F	Serositis, arthritis, rash	15	10	Mood disorder, manic[e]	0.00	1.08	0.76	60	Recovery
17	22/F	Serositis, hematologic disorder, arthritis	10	28	Mood disorder, mixed[f]	0.00	0.87	0.40	90	Recovery
18	62/F	Nephritis, rash	22	18	Mood disorder, manic	0.08	0.92	0.69	14	Recovery
19	25/F	Arthritis, nephritis	22	13	Mood disorder, manic	0.31	0.82	0.66	28	Recovery

SLEDAI-2 K systemic lupus erythematosus disease activity index 2000, *PSL* prednisolone

[a] Interval between steroid administration and neuropsychiatric manifestation

[b] Duration of psychiatric events

[c] Methylprednisolone (0.5 g/day) initially administered for 3 days

[d] Methylprednisolone (1 g/day) initially administered for 3 days

[e] Recovered via major depressive episode

[f] Recovered via manic episode and major depressive episode

Table 3 Neurological/immunological findings prior to corticosteroid administration in SLE patients with new-onset psychiatric manifestations after corticosteroid therapy

Patient no	EEG	Brain MRI	IgG index (normal <0.7)	Q-albumin (normal <9.0)	CSF or other findings related to CNS involvement
Events fitting the CIPD definition					
1	Abnormal[a]	Small subcortical HIAs	0.73[c]	11.7[c]	Mild elevation of CSF protein (57 mg/dl)
3	Normal	Normal	0.57	3.1	Normal CSF
4	Normal	Normal	0.50	9.9[c]	Mild evalation of CSF protein (59 mg/dl)
5	Normal	Normal	0.90[c]	NA	Normal CSF
6	Normal	Normal	0.49	2.8	Normal CSF
8	Normal	Normal	0.36	12.2[c]	Normal CSF
9	Normal	Small subcortical HIAs	0.52	3.8	Normal CSF
11	Normal	Normal	0.54	10.2[c]	Normal CSF
12	Normal	Normal	0.64	4.1	Normal CSF
13	Normal	Normal	0.54	3.7	Normal CSF
16	Normal	Normal	0.50	11.8[c]	Marked elevation of CSF IFN-alpha (136.3 IU/l); Mild evalation of CSF protein (63 mg/dl)
17	Normal	Normal	NA	NA	CSF; NA
18	Normal	Small subcortical HIAs	0.38	6.3	Normal CSF
19	Normal	Normal	NA	NA	CSF; NA
Events not fitting the CIPD definition					
Diagnosed as CNS-SLE					
10	Abnormal[a]	Normal	0.52	7.5	Markedly elevated level of serum anti-ribosomal P antibody (over 480 U/ml, normal <37); hypoperfusion in the left temporal, occipital area as depicted by SPECT
20	Abnormal[a]	Multiple subcortical HIAs	0.88[c]	21.3[c]	Marked elevations of IL-6 (144.9 pg/ml) and IFN-alpha (128.7 IU/l) in the CSF
Unable to make a definite diagnosis					
2	Normal	Normal	0.90[c]	4.1	Normal CSF
7	Abnormal[b]	Normal	0.64	5.2	Normal CSF
14	Normal	Small subcortical HIAs	0.44	7.1	Normal CSF
15	Normal	Normal	0.73[c]	3.8	Normal CSF

EEG electroencephalography, *MRI* magnetic resonance imaging, *CSF* cerebrospinal fluid, *CNS* central nervous system, *CIPD* corticosteroid-induced psychiatric disorder, *HIA* high-intensity area, *NA* not available, *IFN* interferon, *IL* interleukin, *SPECT* single photon emission computed tomography

[a] Diffuse continuous bisynchronous slow waves, predominant θ

[b] θ bursts

[c] Positive

CSF findings with marked elevations of intrathecal IL-6 (144.9 pg/ml) and IFN-α (128.7 IU/l), both which have been reported to be associated with active CNS-SLE [18–20], mild positive IgG index (0.88, normal <0.7), and marked positive Q-albumin (21.3, normal <0.9). Brain MRI showed multiple T2 high-intensity lesions at the time of occurrence of delirium. This severe CNS-SLE case recovered through re-augmentation of steroid dosage up to 1.79 mg/kg/day as well as three episodes of intravenous cyclophosphamide pulse therapy (500 mg/day). EEG, CSF, and MRI findings were also normalized.

The other four events, presenting as an anxiety disorder (patient no. 2), a mood disorder with manic features (patient no. 7), and psychotic disorders (patients no. 14 and no. 15), all disappeared through re-augmentation of immunosuppressive therapies targeting other symptoms of

Table 4 Clinical features and outcomes of events unsuitable for the definition of corticosteroid-induced psychiatric disorder

Patient no	Age, years/sex	Main target symptoms of corticosteroid therapies	SLEDAI-2 K at baseline	Interval[a], days	Neuropsychiatric features	PSL dose (mg/kg/day), at		Augmentation of immunosupressive therapies after psychiatric events occurred		Main target of augmentation therapies	Duration[b], days	Outcome
						Baseline	Administration	PSL	IVCY			
Diagnosed as CNS-SLE												
10	56/F	Arthritis, hematologic disorder, rash	12	7	Delirum	0.00	0.59	Maintenance of same steroid dosage	Yes, 500 mg/day, once	Delirium	23	Recovery
20	26/F	Serositis, hematologic disorder, nephritis	12	23	Delirum, coma, seizures	0.00	1.35[c]	Re-augmentation of steroid dosage up to 1.79 mg/kg/day	Yes, 500 mg/day, three times	Delirum, coma, seizures	90	Recovery
Unable to make a definite diagnosis												
2	24/F	Arthritis, rash	24	2	Anxiety disorder	0.00	0.24	Re-augmentation of steroid dosage up to 1.46 mg/kg/day	No	Autonomic disorder	60	Recovery
7	31/F	Nephritis, enteritis, arthirtis	8	5	Mood disorder, manic	0.18	1.18[d]	Re-augmentation of steroid dosage up to 1.96 mg/kg/day	No	Movement disorder	14	Recovery
14	23/F	Nephritis, rash	18	21	Psychotic disorder	0.22	1.11[e]	Reduction in steroid dosage	Yes, 500 mg/day, twice	Nephritis	50	Recovery
15	26/F	Nephritis, hematologic disorder, rash	23	16	Psychotic disorder	0.00	1.01[e]	Reduction in steroid dosage	Yes, 500 mg/day, twice	Nephritis	300	Recovery

SLEDAI-2 K systemic lupus erythematosus disease activity index 2000, *PSL* prednisolone, *IVCY* intravenous cyclophosphamide

[a] Interval between steroid administration and neuropsychiatric manifestation

[b] Duration of psychiatric events

[c] Delirium occurred on the third day of additional methylprednisolone (0.5 g/day) administration

[d] Methylprednisolone (1 g/day) initially administered for 3 days

[e] Methylprednisolone (0.5 g/day) initially administered for 3 days

SLE, and were not diagnosed as CNS-SLE because of insufficient evidence of CNS involvement. Therefore, they could not be identified as CIPDs, CNS-SLE, or the coexistence of both conditions.

Discussion

As one of the particularly difficult clinical situations in the treatment of patients with SLE, it has been empirically well known that new-onset neuropsychiatric symptoms in SLE patients on corticosteroids could be due to CNS-SLE and not to a CIPD [10]. However, to our knowledge, no reports have definitely demonstrated the fact that corticosteroid therapy worsens or triggers CNS-SLE. A small literature review of ten cases of acute CNS complications in SLE patients after corticosteroid pulse therapy showed that psychosis occurred in four patients, seizures in three, and hemiplegia in four [25]. However, there was little pathophysiological information in this review. Tabata, et al. [26] reported a pediatric SLE case who showed neuropsychiatric manifestations within 2 days after corticosteroid pulse therapy. While both of these reports showed only a chronological relationship between corticosteroid administration and psychiatric manifestations, the two cases diagnosed as CNS-SLE in the present case-series had not only this chronological relationship, but also evidence of abnormal CNS findings even before the psychiatric manifestation. This fact suggests that the CNS symptoms worsened during the course of corticosteroid therapy (or were triggered by corticosteroid therapy) and only improved with the augmentation of treatment by immunosuppressive therapies.

Further, our study suggests that delirium (acute confusional state) tends to represent CNS-SLE, requiring augmentation of immunosuppressive therapy. A recent review of CIPDs in contrast to CNS-SLE by Bhangle et al. [12] has concluded that imaging and EEG abnormalities, the coexistence of non-CNS manifestations of SLE, and the presence of serious disturbances in memory and concentration (including delirium or acute confusional state) are more suggestive of CNS-SLE than CIPDs. Meanwhile, mood disorders, predominantly with manic features, tend to represent CIPDs. Recent studies [27, 28] have suggested that manic symptoms are the most commonly observed response to acute therapy with relatively high doses of corticosteroids, while depression is likely more common than mania during long-term treatment with corticosteroids [29]. These findings are consistent with the results from the present study.

Both of the CNS-SLE cases in the present case-series demonstrated EEG abnormalities (diffuse slow activities) even prior to psychiatric manifestations, while only 1 of the 14 CIPD cases and 1 of the 4 cases that could not be etiologically identified showed EEG abnormalities. Some immunological abnormalities associated with CNS-SLE were also obtained in both of the CNS-SLE cases, but they were inconsistent. Other clinical features did not seem to be different between the patients developing CIPDs and CNS-SLE. Thus, our study suggests that EEG abnormalities may possibly be predictive of CNS-SLE manifestations after corticosteroid therapy.

In a previously published study [13] we identified positive Q-albumin, an indicator of blood–brain barrier damage, as an independent risk factor for CIPDs. Compared with episodes in which no psychiatric events occurred, a higher level of Q-albumin was found in episodes in which CIPDs developed, and an even higher level was noted in episodes with active CNS-SLE which manifested before corticosteroid administration [13]. In this case-series, one of the two CNS-SLE cases also demonstrated a markedly higher level of Q-albumin compared with the mean levels seen in CIPD cases.

Of the 13 CIPD events presenting mood disorders in the present case-series, 4 events showed bipolar episodes (manic/mixed episodes recovering via major depression) in one therapy course. Wada et al. [30] have reported in a retrospective chart review on nine patients with first-onset mood symptoms after corticosteroid use. The patients had clinical courses of recurrent bipolar disorder after that. Further careful observation is needed in such patients.

The chief limitation of the present study is that this was an observational study of the presentation and treatment of SLE patients with illness episodes severe enough to warrant hospitalization. No scientific hypothesis was prespecified or tested in the course of the study. However, the strengths include the careful description of the presentation and treatment of unselected, consecutive cases in the hospital setting.

In conclusion, delirium may be suggestive of CNS-SLE, while mood disorders may be more suggestive of CIPDs. EEG abnormalities may possibly be predictive of CNS-SLE. Careful differential diagnosis and treatment are required. Furthermore, the present observational consecutive case-series study suggests that corticosteroid therapy can trigger or worsen CNS-SLE. However, neither our cases nor the literature cited substantially support this concept, which nonetheless remains an interesting possibility worthy of consideration.

Acknowledgments The authors thank Professors Naoshi Horikawa, Masako Hara, and Naoyuki Kamatani for helpful comments on the manuscript.

Ethical standard The authors declare that they acted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Conflicts of interest The authors declare no conflicts of interest.

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