ORIGINAL RESEARCH PAPER

Blood-brain barrier damage as a risk factor for corticosteroid-induced psychiatric disorders in systemic lupus erythematosus

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Summary

To clarify the incidence of and risk factors for corticosteroid-induced psychiatric disorders (CIPDs) in patients with systemic lupus erythematosus (SLE), we conducted a prospective study of 161 consecutive episodes in 155 inpatients with a SLE flare who were treated with corticosteroids. A subgroup of these patients, those who experienced a total of 22 episodes with current overt central nervous system manifestations of SLE (CNS-SLE), were excluded from follow-up. Results of clinical, laboratory, and neurologic tests (including electroencephalography, magnetic resonance imaging of the brain, and cerebrospinal fluid [CSF] analysis), performed within a week before corticosteroid administration, were assessed with regard to development of CIPDs. Within 8 weeks of corticosteroid administration, a diagnosis of CIPD was made for 14 (10.1%) of 139 episodes in 135 patients with a non–CNS-SLE flare. Using multiple logistic regression analysis, we identified positive $Q_{albumin}$ (CSF/serum albumin ratio; an indicator of blood-brain barrier [BBB] damage) (odds ratio [OR], 33.3; 95% confidence interval [CI], 3.64–304; $p = 0.002$) and low serum levels of complements (OR, 0.91; 95% CI, 0.83–1.00; $p = 0.047$) as independent risk factors for CIPDs. Positive $Q_{albumin}$ was detected in 45% (5 of 11) of episodes in which CIPDs developed. 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 (Jonckheere-Terpstra test, $p < 0.001$). Although no causal links have been proven, the results from the present study raise the possibility that BBB damage may be associated with SLE- and corticosteroid-induced behavioral changes.

Keywords: corticosteroid-induced psychiatric disorders; systemic lupus erythematosus; blood-brain barrier; $Q_{albumin}$; complements; central nervous system lupus

1. Introduction

Corticosteroids are the cornerstone of treatment for various inflammatory and immunologically mediated disorders, such as systemic lupus erythematosus (SLE). Despite widespread use, corticosteroid treatment is frequently associated with adverse psychiatric effects, including affective disorders, psychotic disorders, and delirium (Wolkowitz et al., 1997; Patten and Neutel, 2000). SLE is associated with a high incidence of psychiatric manifestations (West, 1994; Ainiala et al., 2001; Brey et al., 2002; Hanly et al., 2004).

It is unknown whether this association is a direct consequence of systemic autoimmunity and inflammation (eg, entry of immune cells and molecules into the central nervous system [CNS]), an indirect effect (eg, an epiphenomenon associated with accumulation of toxic metabolites), or a consequence of immunosuppressive therapy with corticosteroids (Kohen et al., 1993; Denburg et al., 1994; Wolkowitz et al., 1997)—because of similar or identical psychopathology (ACR Ad Hoc Committee on Neuropsychiatric Lupus Nomenclature, 1999; Patten and Neutel, 2000) and because no diagnostic gold standard of CNS manifestations of SLE (CNS-SLE) exists (West, 1994; ACR Ad Hoc Committee on Neuropsychiatric Lupus Nomenclature, 1999). Hypoalbuminemia has been demonstrated to be a risk factor for corticosteroid-induced psychiatric disorders (CIPDs) in SLE patients (López-Medrano et al., 2002; Chau and Mok, 2003), but the proposed mechanism remains speculative.

In general, brain damage or disease of any etiology may predispose a person to substance-induced psychiatric disorders such as delirium (Lipowski, 1990). Several abnormal findings associated with CNS involvement in SLE, including abnormal electroencephalographic findings, magnetic resonance images of the brain, and cerebrospinal fluid (CSF) findings, are observed in SLE patients, regardless of whether they exhibit current overt neuropsychiatric symptoms (West, 1994). Although this clinical or subclinical CNS involvement due to SLE

might predispose a patient to CIPDs, to our knowledge, no clinical studies from this viewpoint have been reported.

The purpose of the present study was to clarify the incidence of and risk factors for CIPDs in SLE patients, especially with regard to potential CNS involvement in SLE.

2. Methods

2.1. Study design

First, to identify the incidence of CIPDs in SLE patients, we prospectively followed for 8 weeks consecutive inpatients with a non–CNS-SLE flare who were treated with corticosteroids. Second, to identify risk factors for CIPDs, we evaluated clinical, laboratory, and neurologic variables within a week before corticosteroid administration and compared them between groups that developed CIPDs and those that did not. Finally, to evaluate potential CNS involvement in SLE in patients developing CIPDs, we compared neurologic variables for these patients and for patients with active CNS-SLE.

2.2. Study population

From August 1999 to December 2004, we prospectively followed consecutive SLE patients who were treated with corticosteroids for the first time or in augmented doses in the Rheumatologic Unit of Tokyo Women's Medical University Aoyama Hospital. In total, 161 courses of corticosteroids were administered for 161 episodes of first or recurrent manifestations of SLE in 155 patients (150 women, 5 men). Six patients required a second hospitalization because of another manifestation of SLE, and received a second course of therapy during the study period. Of the 161 episodes, 75 (47%) occurred in patients whose SLE had not been previously treated with corticosteroids. The mean dosage of corticosteroids administered was 50.8 mg/day

(standard deviation [SD], 19.6; range, 15–150) or 0.98 mg/kg/day (SD, 0.40; range, 0.27–2.59) as prednisolone. In addition, IV methylprednisolone pulse therapies were initially conducted in 48 (30%) of 161 episodes: 0.5 g/day for 3 days in 20 episodes and 1 g/day for 3 days in 28 episodes. Patients who showed any symptoms due to CNS-SLE at the time of administration of corticosteroids were excluded from follow-up, whereas patients with only peripheral neurologic symptoms were included. All patients in this study were Japanese and fulfilled the American College of Rheumatology 1982 revised criteria for SLE (Tan et al., 1982).

2.3. Definition of CIPDs and psychiatric evaluation

CIPDs were defined as new-onset psychiatric symptoms that developed within 8 weeks of initiation or augmentation of corticosteroid therapy and that resolved completely through a reduction in corticosteroid dosage and without additional immunosuppressive agents, as defined in a previous study (Chau and Mok, 2003). The psychiatric events in our unit were evaluated at regular intervals (once a week) by experienced psychiatrists (K.N. and M.O.) using the criteria for substance-induced disorders in the *Diagnostic and Statistical Manual of Mental Disorders,* 4th edition (DSM-IV) (American Psychiatric Association, 1994). Except for substance-induced sexual dysfunction and sleep disorder, the following phenomenological subtypes of substance-induced psychiatric disorders from the DSM-IV were used: substance-induced delirium, persisting dementia, persisting amnestic disorder, psychotic disorder, mood disorder, and anxiety disorder. According to the DSM-IV, the disturbances must be severe enough to cause clinically significant distress or impairment in social functioning for a diagnosis to be made. To identify delirium, we used information gathered through administration of the Mini-Mental State Examination (Folstein et al., 1975) and the Delirium Rating Scale (Trzepacz et al., 1988) in the assessment of psychiatric events. All sources of available information, including hospital staff, doctors, family, and medical records, were used for the psychiatric evaluation.

To address the possibility of development of CNS-SLE, we conducted laboratory and neurologic tests, including brain magnetic resonance imaging (MRI), electroencephalography (EEG), and CSF analysis, as soon as psychiatric events occurred. Psychiatric symptoms that were suspected to be due to other secondary causes, such as infection, metabolic derangement, or adjustment disorder, were also excluded. In case the psychiatric symptoms resolved through use of psychotropic agents, a diagnosis of CIPD was given if the symptoms did not relapse after discontinuation of the agents during a dose reduction of corticosteroids.

2.4. Study flow

Fig. 1 is a flow diagram of the study.

Of the 161 SLE episodes, 22 in 20 patients were diagnosed as current overt CNS-SLE at baseline (active CNS-SLE group), accompanied by the following syndromes: acute confusional state (delirium) in six episodes (27%), aseptic meningitis in four (18%), headache (excluding tension headache) in four (18%), mood disorder in three (14%), myelopathy in two (9%), cerebrovascular disease in one (5%), diabetes insipidus in one (5%), and psychotic disorder in one (5%). This active CNS-SLE group was excluded from follow-up.

One hundred thirty-five patients who did not show any current CNS-associated symptoms at baseline and who experienced a total of 139 episodes were followed prospectively. Within 8 weeks of corticosteroid administration, 20 psychiatric events had newly developed in 20 episodes in 20 patients. Of the 20 psychiatric events, 14 were diagnosed as CIPDs according to our definition (CIPD group); in six events, CIPDs could not be distinguished from CNS-SLE because a further augmentation in corticosteroid dosage or additional IV cyclophosphamide pulse therapy was conducted, owing to worsening of SLE. These six psychiatric events included delirium in two episodes, psychotic disorder in two, mood disorder in one, and anxiety disorder in one. No psychiatric events due to other secondary causes (infection, metabolic derangement,

or adjustment disorder) were observed.

In the other 119 episodes, no psychiatric symptoms developed during the 8-week follow-up. Of these 119 episodes, 97 for which patients received ≥ 40 mg/day prednisolone made up the group with no psychiatric events so that we could track the effect of corticosteroid dosage, because all patients with CIPDs received ≥ 40 mg/day prednisolone.

2.5. Laboratory and neurologic tests

All tests were performed within a week before administration of corticosteroids. On the basis of previous reports about CIPDs (Wolkowitz et al., 1997; Patten and Neutel, 2000; López-Medrano et al., 2002; Chau and Mok, 2003) and CNS-SLE (Hirohata and Miyamoto, 1990; Shiozawa et al., 1992; West, 1994; ACR Ad Hoc Committee on Neuropsychiatric Lupus Nomenclature, 1999; Trysberg et al., 2000), and pathophysiological interest, potential relevant laboratory and neurologic variables were selected. Apolipoprotein E status and past or family history of psychiatric illness, possible risk factors for behavioral change, were not assessed. Antiphospholipid antibodies, relevant immunological markers of CNS-SLE (West, 1994; ACR Ad Hoc Committee on Neuropsychiatric Lupus Nomenclature, 1999), were defined as positive if at least one anticardiolipin β_2-glycoprotein I complex or lupus anticoagulant was positive. Other relevant immunological markers of CNS-SLE (eg, antiribosomal P antibody [Kohen et al., 1993; West, 1994; ACR Ad Hoc Committee on Neuropsychiatric Lupus Nomenclature, 1999]) were not assessed in this study.

Neurologic tests, including brain MRI, EEG, and CSF analysis, were performed in patients who were admitted to our unit for the first time, 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 (West, 1994) or in the absence of an abnormal electroencephalogram

or MRI lesions (Oda et al., 2005). Informed consent was obtained from all patients who underwent these neurologic tests in the present study.

Brain MRI was performed in 126 of the 161 episodes. MRI findings were defined as abnormal when any abnormal-intensity lesion or cerebral atrophy was found. EEG was performed in 128 of the 161 episodes. Electroencephalographic findings were defined as abnormal when the electroencephalogram showed epileptiform activity, slow waves, abnormalities of amplitude, or deviations from normal patterns and was subdivided into several basic patterns. Borderline records were not included.

Paired samples of CSF and serum were collected in 121 of the 161 episodes under sterile conditions after atraumatic lumbar and venous punctures. After centrifugation, cell-free supernatant was collected from CSF and serum and stored in aliquots at −80°C until analysis. Albumin and immunoglobulin G (IgG) concentrations in CSF and serum were determined by rate nephelometry using standard kits. Biochemical analysis of these CSF samples included determinations of IgG index and $Q_{albumin}$ as well as analysis of interleukin (IL)-6, IL-8, and interferon (IFN)-α , which have been reported to be associated with active CNS-SLE (Hirohata and Miyamoto, 1990; Shiozawa et al., 1992; West, 1994; Trysberg et al., 2000).

The IgG index (normal < 0.70) was used as a measure of intrathecal IgG synthesis and was calculated using the following formula: (CSF IgG/serum IgG)/(CSF albumin/serum albumin). The integrity of the blood-brain barrier (BBB) was assessed by $Q_{albumin}$, which was calculated using the following formula: (CSF albumin × 10^3)/serum albumin. The $Q_{albumin}$ is age-dependent. The upper reference limit is 5.0 for patients less than 15 years old, 6.5 for patients aged 16–40 years, 8.0 for patients aged 41–60 years, and 8.0–9.0 for patents older than 61 years (Andersson et al., 1994). Therefore, we defined $Q_{albumin} \geq 9.0$ as positive. Concentrations of IL-6 and IL-8 in the CSF were measured by solid-phase sandwich

enzyme-linked immunosorbent assay (ELISA) using the Human IL-6 QuantiGlo® ELISA Kit (R&D Systems, Minneapolis, MN) and the Human Interleukin-8 Easia™ ELISA Kit (BioSource, Camarillo, CA) according to the manufacturers' protocols. IFN-α in the CSF was measured by radioimmunoassay using the Interferon-α Kit® (Abbott Laboratories, Abbott Park, IL) according to the manufacturer's protocol. IL-6 values < 0.15 pg/ml, the lowest limit of the assay, were considered to be 0.15 pg/ml, and IFN-α values < 10 IU/l, the lowest limit of the assay, were considered to be 10 IU/l.

2.6. Statistical analyses

The nonparametric Mann-Whitney *U* test was used to identify differences between groups for continuous variables, and categorical variables were compared by the Fisher exact test. Because our samples included a substantial number of data sets with missing values from neurologic tests, including brain MRI, EEG, and CSF analysis, we analyzed the variables in two steps to identify independent risk factors for CIPDs. In the first step, a univariate analysis was performed. In the second step, a multiple logistic regression analysis was performed, with forward stepwise variable selection. In this regression analysis, we used data sets that showed statistical significance in the first step. Regression coefficients were used to calculate the odds ratio (OR) and the 95% confidence interval (CI) of the OR. Trend analysis for the levels of $Q_{albumin}$ among the group with no psychiatric events, the group with CIPDs, and the active CNS-SLE group was performed using the Jonckheere-Terpstra test. In all statistical analyses, *p* values less than 0.05 were taken to indicate statistical significance. We performed all analyses using the SPSS software package (version 14.0J; SPSS Inc., Chicago, IL).

3. Results

3.1. Incidence, clinical characteristics, and courses of CIPDs

CIPDs occurred in 14 (10.1%) of 139 episodes in 135 SLE patients without current overt CNS manifestations, as discussed in Methods. In all 14 events, CIPDs developed within 4 weeks (mean, 12.5 days; range, 2–28 days) of corticosteroid administration. The mean dosage of corticosteroids administered was 51.4 mg/day (range, 40–60 mg/day) or 1.03 mg/kg/day (range, 0.82–1.40 mg/kg/day) as prednisolone. Psychotic disorders occurred in one event (7%), and mood disorders occurred in 13 events (93%), including depressive features in two (14%), manic features in nine (64%), and mixed features in two (14%). No events with delirium, persisting dementia, persisting amnestic disorder, or anxiety disorder were observed. All psychiatric events resolved completely after corticosteroid dosage reduction to a mean of 32.5 mg/day (range, 15–45 mg/day) or a mean of 0.69 mg/kg/day (range, 0.27–0.88 mg/kg/day).

3.2. Risk factors for CIPDs

To identify risk factors for CIPDs, we compared clinical characteristics and findings of laboratory and neurologic tests performed within a week before corticosteroid administration, and we considered whether CIPDs developed. We analyzed those variables in two steps. Table 2 shows the results of the univariate analysis performed in the first step. Serum levels of the complements CH50 ($p = 0.033$), C3 ($p = 0.026$), and C4 ($p = 0.028$) and the intrathecal level of IL-6 ($p = 0.042$) were lower in the CIPD group than in the group with no psychiatric events. Positive $Q_{albumin}$ was more frequently observed in the CIPD group than in the group without psychiatric events ($p = 0.001$).

In the second step, we performed a multiple logistic regression analysis by the forward stepwise selection method using three data sets as risk factors: serum CH50 level (which represented serum complements), intrathecal level of IL-6, and positive $Q_{albumin}$. Of the three

variables, positive $Q_{albumin}$ and serum CH50 level were significant independent risk factors. The OR for positive $Q_{albumin}$ was 33.27 (95% CI, 3.64–304, $p = 0.002$), and the OR for CH50 level was 0.91 (95% CI, 0.83–1.00, $p = 0.047$).

3.3. Latent CNS involvement in SLE in patients who developed CIPDs

Neurologic tests revealed several findings of latent CNS involvement in SLE even before corticosteroid administration in patients who developed CIPDs. Abnormalities shown by brain MRI ($p = 0.013$) and EEG ($p = 0.024$) were less frequently noted in the CIPD group than in the active CNS-SLE group (Table 3), whereas the frequencies of positive IgG index ($p = 0.494$) or positive $Q_{albumin}$ ($p = 0.500$) in the two groups were not different. In particular, positive $Q_{albumin}$, one of the independent risk factors for CIPDs, was detected in approximately half the CIPD group (5 of 11, 45%) and half the active CNS-SLE group (11 of 21, 52%). The intrathecal level of IL-6 was lower in the CIPD group than in the active CNS-SLE group ($p = 0.003$), but the levels of IL-8 ($p = 0.124$) and IFN-α ($p = 0.862$) were not different between the two groups.

Next, levels of $Q_{albumin}$ were compared among the three groups, using the Jonckheere-Terpstra test for linear trend (Fig. 2). Compared with the group with no psychiatric events, a higher level of $Q_{albumin}$ was found in the CIPD group and an even higher level in the active CNS-SLE group ($p < 0.001$).

4. Discussion

This prospective cohort study had three major findings. First, the incidence of CIPDs, according to the strict definition used, in SLE episodes without overt CNS manifestations was 10.1%. Second, independent risk factors for CIPDs were positive $Q_{albumin}$ (an indicator of BBB damage) and hypocomplementemia. Third, positive $Q_{albumin}$ was detected in approximately half the

episodes with CIPDs or with active CNS-SLE, although compared with episodes in which no psychiatric events developed, levels of $Q_{albumin}$ were higher in episodes with development of CIPDs, and even higher in episodes with active CNS-SLE.

The incidence of CIPDs demonstrated in the present study was derived from a strict definition of CIPD with regard to chronological relation to administration of corticosteroids, as well as with regard to outcome—namely, complete recovery by dosage reduction of corticosteroids, without use of additional immunosuppressive agents. This definition was employed because CNS-SLE also may manifest after corticosteroid administration (Wysenbeek et al., 1990). In fact, one of our patients developed an acute confusional state leading to coma, within a few days after methylprednisolone pulse therapy. The patient demonstrated diffuse MRI lesions in the brain and high intrathecal levels of IL-6 and IFN-α, which all improved in parallel with the patient's recovery through reaugmentation of immunosuppressive therapy.

Because of the strict definition used, the incidence of CIPDs in the present study might be underestimated. In a previous study of SLE using the same definition of CIPDs (Chau and Mok, 2003), a lower incidence of CIPDs was reported (4.8%, vs. 10.1% in this study). In that study, however, CIPDs were not evaluated by a psychiatrist. Mild memory impairment, which occurs frequently in patients undergoing corticosteroid therapy (Wolkowitz et al., 1997), may be also underestimated in our study, because no detailed assessments using neuropsychological tests were performed.

Although the results from the present study indicate that BBB damage is a strong risk factor for CIPDs in patients with SLE, no causal links have been proven. Because corticosteroids, being hydrophobic molecules, readily cross an intact BBB (Joels and de Kloet, 1992), the increased permeability of the BBB may result in an increased risk of CIPDs. BBB damage is believed to be relevant to the pathogenesis of CNS-SLE (Abbott et al., 2003). A recent model of CNS-SLE demonstrated that increased permeability of the BBB is instrumental in allowing

circulation of potentially pathogenic antibodies across to the CNS, causing subsequent neuronal damage and behavioral impairment (Huerta et al., 2006). Our findings suggest that BBB damage is likely to lead to both kinds of neuropsychiatric manifestations, but overt CNS signs are indicative of greater BBB damage, although our data cannot prove any causal association.

BBB damage has been demonstrated in 30%–37% of patients with CNS-SLE (Winfield et al., 1983; Kelly and Denburg, 1987; McLean et al., 1995). However, this damage may be transient and underestimated because of corticosteroid treatments, which are known to reduce BBB leakage—for instance, in multiple sclerosis (Rosenberg et al., 1996; Abbott et al., 2003). The BBB damage as defined by positive $Q_{albumin}$ shown in the present study might also be underestimated, because 17 (81%) of the 21 CNS-SLE episodes and five (45%) of the 11 CIPD episodes occurred in patients whose SLE had been previously treated with corticosteroids (data not shown).

The dopaminergic diathesis may be behind the development of CIPDs in SLE patients. SLE induces damage in nigrostriatal and mesolimbic dopaminergic pathways (Garcia-Moreno and Chacon, 2002; Ballok et al., 2004), and corticosteroids appear to increase dopaminergic function (Wolkowitz, 1994). This situation suggests that development of CIPDs could be predicted by baseline levels and changes in homovanillic acid (HVA), a major metabolite of dopamine, in the CSF, as some previous investigators (Wolkowitz, 1994) have hypothesized. Regrettably, CSF levels of HVA were not obtained in the present study.

Hypocomplementemia was one of the independent risk factors for CIPDs in the present study. However, other parameters indicating active SLE (eg, anti-DNA antibody or circulating immune complex) were not associated with CIPDs. Although the underlying mechanism is unclear, careful observation is required in SLE patients with hypocomplementemia, because a previous survey (Chau and Mok, 2003) also suggested this association in patients with SLE. Low intrathecal levels of IL-6 were associated with CIPDs, but significance could not be reached after

multivariate adjustment. Inversely, elevated intrathecal levels of IL-6 were associated with the active CNS-SLE group, a finding that is consistent with previous reports (Hirohata and Miyamoto, 1990; Trysberg et al., 2000). The underlying mechanism by which lower levels of IL-6 might lead to CIPDs remains speculative.

Hypoalbuminemia was not associated with CIPDs in the present study, a result that is inconsistent with two previous reports on SLE (López-Medrano et al., 2002; Chau and Mok, 2003). In contrast with corticosteroid-binding globulin, albumin has a low affinity for corticosteroids, and for practical purposes albumin-bound corticosteroids should be considered free (biologically active) and thus mostly in the unbound form (Chrousos and Margioris, 2001). Therefore, a hypoalbuminemic state may not necessarily expose patients to more adverse effects, including CIPDs.

The strengths of our study are the prospective cohort design, the adoption of strict criteria for CIPDs, and the use of multivariate methods to identify risk factors for CIPDs in SLE patients. However, our study has two important limitations. First, our samples included data sets with missing values from neurologic tests, including brain MRI, EEG, and CSF analysis. In particular, the proportion of missing values for $Q_{albumin}$ was 35% of the total number of episodes (111) in the CIPD group and the group with no psychiatric events combined, but there were no differences in this proportion between the two groups (3/14 [21%] in the CIPD group vs. 36/97 [37%] in the group with no psychiatric events; $p = 0.371$). Second, the power in this study was relatively low for detecting risk factors for CIPDs.

In conclusion, although no causal links have been proven, the results from the present study raise the possibility that BBB damage may be associated with SLE- and corticosteroid-induced behavioral changes. Future studies should be conducted with larger samples to clarify the underlying pathogenesis of CIPDs, especially from the viewpoint of BBB function.

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Figure Captions

Figure 1. Flow diagram of the study.

Figure 2. Levels of $Q_{albumin}$ in the group with no psychiatric events, the CIPD[a] group, and the active CNS-SLE[b] group compared using the Jonckheere–Terpstra test for linear trend.

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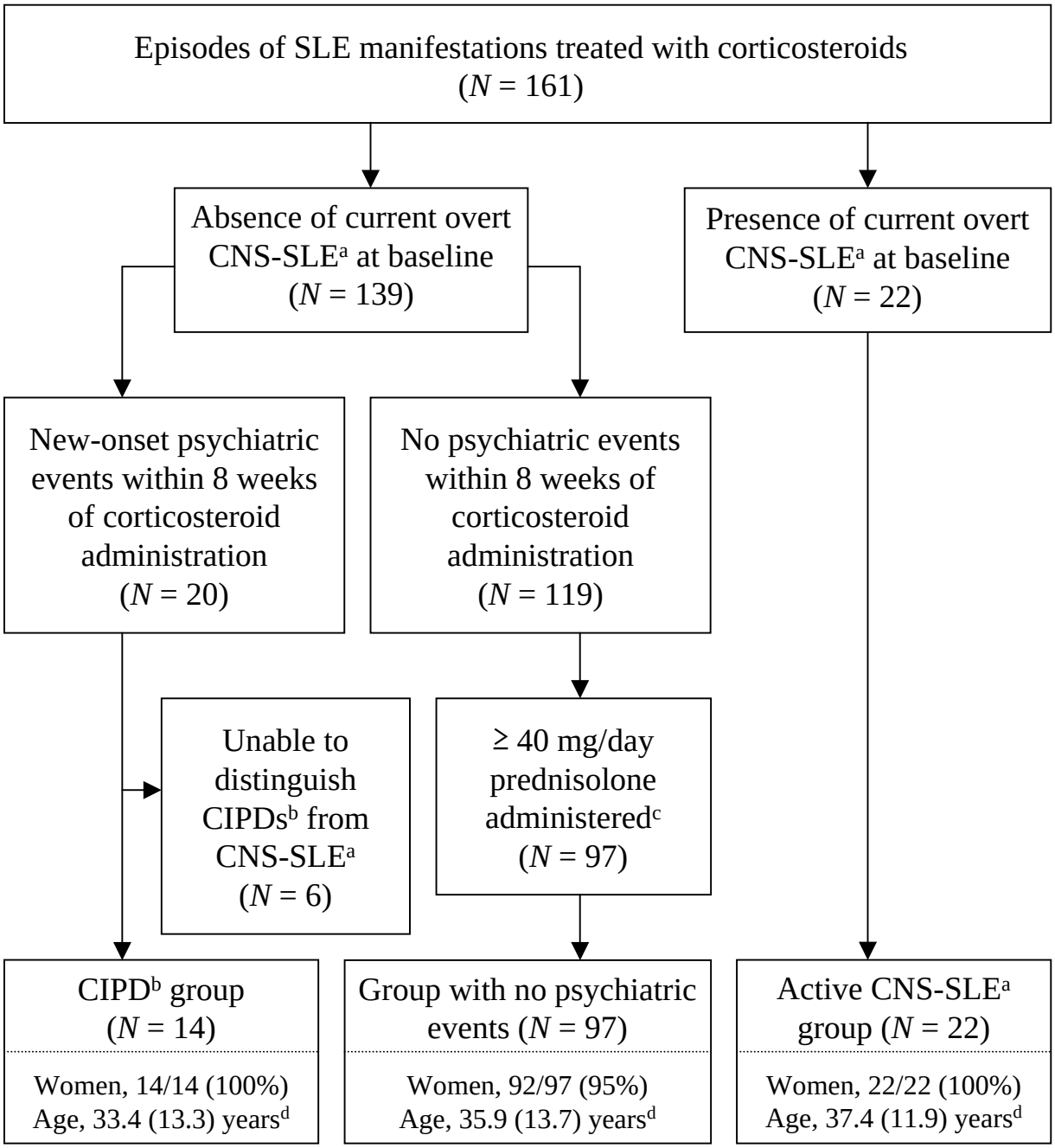

Figure 1.

N means number of episodes, not number of patients.
[a]CNS-SLE = central nervous system manifestations of systemic lupus erythematosus.
[b]CIPD = corticosteroid-induced psychiatric disorder.
[c]To track the effect of corticosteroid dosage with the CIPD group because all patients with CIPDs received ≥40 mg/day prednisolone.
[d]Means (standard deviations).

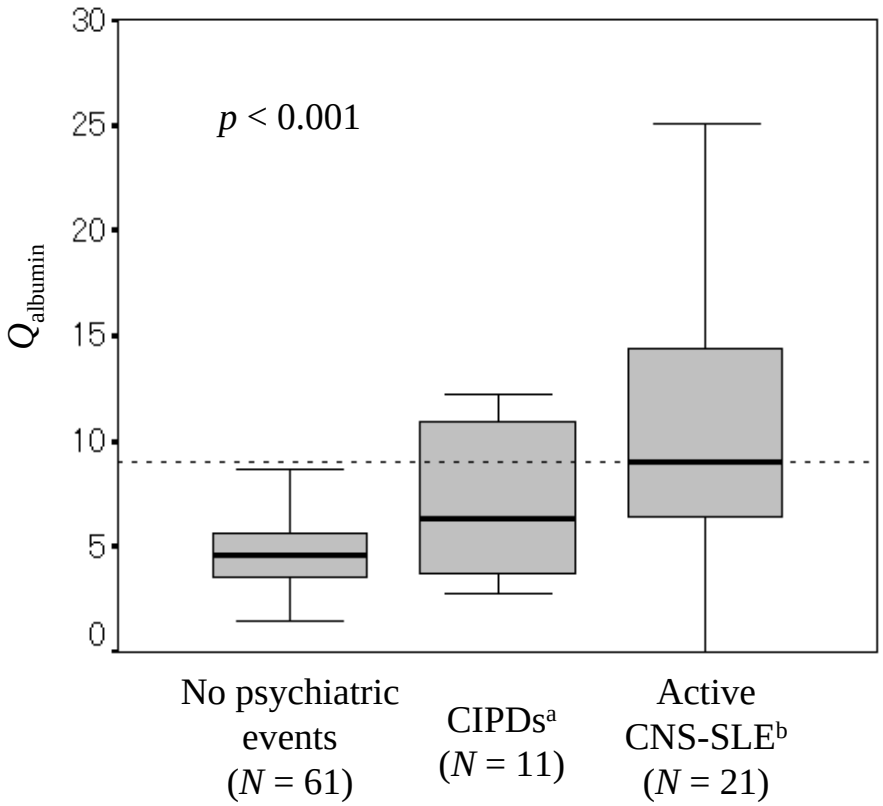

Figure 2.

Each box denotes medians with 25th–75th percentiles, with whiskers showing minimum and maximum values, excluding the following values more than 1.5 box lengths outside the box: 0.3, 10.6, and 12.5 in the group with no psychiatric events and 37.0 and 71.5 in the active CNS-SLE[b] group. *N* means number of episodes, not number of patients.

[a]CIPD = corticosteroid-induced psychiatric disorder.

[b]CNS-SLE = central nervous system manifestations of systemic lupus erythematosus.

Table 1. Univariate analysis of predictive factors for corticosteroid-induced psychiatric disorders in patients with systemic lupus erythematosus: clinical characteristics and corticosteroid therapy

Variable	Corticosteroid-induced psychiatric disorders *N* = 14	No psychiatric events[a] *N* = 97	*p* value
Disease duration after diagnosis, months	2.5 (0–41.8)	0 (0–60.0)	0.390
Cumulative clinical manifestations			
Nephritis	8/14 (57%)	74/97 (76%)	0.117
Hematological disorder	9/14 (64%)	48/97 (50%)	0.228
Arthritis	8/14 (57%)	42/97 (43%)	0.246
Mucocutaneous disorder	7/14 (50%)	43/97 (44%)	0.453
Serositis	2/14 (14%)	13/97 (13%)	0.598
Peripheral neurologic disorders	1[b]/14 (7%)	0/97 (0%)	0.126
Corticosteroid therapy			
First-time corticosteroid therapy	8/14 (57%)	48/97 (50%)	0.402
Duration of corticosteroid therapy at admission, months	2.0 (0–62.8)	0 (0–60.0)	0.707
Baseline dose/body weight, mg/kg/day	0 (0–0.10)	0 (0–0.23)	0.292
Initiation/augmentation dose/body weight, mg/kg/day	0.99 (0.90–1.11)	0.89 (0.77–1.12)	0.106
Dose/body weight escalation relative to baseline, mg/kg/	0.92 (0.79–1.07)	0.82 (0.61–0.98)	0.082
Methylprednisolone pulse therapy	3/14 (21%)	27/97 (28%)	0.443

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

[a]Corticosteroids were administered at a dosage of ≥40 mg/day as prednisolone.

[b]Polyneuropathy

Table 2. Univariate analysis of predictive factors for corticosteroid-induced psychiatric disorders in patients with systemic lupus erythematosus: laboratory and neurologic variables

Variable	Corticosteroid-induced psychiatric disorders *N* = 14	No psychiatric events[a] *N* = 97	*p* value
Laboratory tests			
White blood cell count, cells/mm^3	4800 (3250–6975)	5000 (3500–6950)	0.766
Red blood cell count, $\times 10^6$/mm^3	3.96 (3.47–4.32)	3.98 (3.56–42.2)	0.954
Hemoglobin, g/dl	11.7 (9.7–12.9)	11.4 (10.0–12.2)	0.625
Platelet count, $\times 10^4$/mm^3	20.7 (15.5–25.3)	21.4 (15.9–26.5)	0.972
Serum albumin, g/dl	3.1 (2.8–3.7)	3.3 (2.9–3.7)	0.508
Serum creatinine, mg/dl	0.7 (0.6–0.9)	0.7 (0.6–0.8)	0.537
Serum potassium, mEq/l	4.1 (3.9–4.3)	3.9 (3.7–4.1)	0.103
CH50 level, U/ml[b]	16 (10–24)	24 (13–34)	0.033*
C3 level, mg/dl	42 (38–65)	63 (46–76)	0.026*
C4 level, mg/dl	6 (2–11)	11 (4–16)	0.028*
Immune complex, C1q, μg/ml	7.2 (4.7–15.5)	6.7 (3.6–10.3)	0.337
Antinuclear antibody[c]	6 (5–8)	5 (4–7)	0.053
Anti-DNA antibody, U/ml (RIA[d])	41.0 (17.0–85.3)	47.0 (10.5–162.5)	0.852
Anti-ds-DNA IgG antibody, U/ml (ELISA[e])	27.5 (6.6–81.5)	28.1 (5.6–105.4)	0.853
Positive anti-Sm antibody (ELISA[e])	3/14 (21%)	17/92 (19%)	0.518
Positive antiphospholipid antibodies[f]	1/13 (8%)	13/78 (17%)	0.364
Neurologic tests			
Magnetic resonance images of the brain, abnormal[g]	3/12 (25%)	22/70 (31%)	0.470
Electroencephalogram, abnormal	1[h]/14 (7%)	10[i]/71 (14%)	0.423
Cerebrospinal fluid tests			
Positive IgG index (normal < 0.70)	2/12 (17%)	10/62 (16%)	0.624
Positive $Q_{albumin}$ (normal < 9.0)	5/11 (46%)	2/61 (3%)	0.001*
Interleukin-6, pg/ml[j]	0.95 (0.64–1.99)	2.05 (1.10–4.57)	0.042*
Interleukin-8, pg/ml[j]	57.0 (20.1–75.8)	41.4 (28.2–76.3)	0.940
Interferon-α, IU/l[j]	10.2 (0–19.9)	10 (0–13.1)	0.259

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

*Significant variable.

[a]Corticosteroids were administered at ≥ 40 mg/day as prednisolone.

[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: $\log_2$(ANA/40).

[d]RIA = radioimmunoassay.

[e]ELISA = enzyme-linked immunosorbent assay.

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

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

[h]Diffuse continuous bisynchronous slow waves.

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

[j]Interleukin (IL)-6, IL-8, and interferon (IFN)-α in the cerebrospinal fluid were determined in 13 episodes of corticosteroid-induced psychiatric disorders and in 63 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-α as 10 IU/l.

Table 3. Neurologic investigations in patients with corticosteroid-induced psychiatric disorders vs. active CNS-SLE[a]

Neurologic investigations	Corticosteroid-induced psychiatric disorders $N = 14$	Active CNS-SLE[a] $N = 22$	p value
Magnetic resonance images of the brain, abnormal	3[b]/12 (25%)	15[c]/21 (71%)	0.013*
Electroencephalogram, abnormal	1[d]/14 (7%)	9[e]/21 (43%)	0.024*
Cerebrospinal fluid tests			
Positive IgG index (normal <0.70)	2/12 (17%)	5/21 (24%)	0.494
Positive $Q_{albumin}$ (normal <9.0)	5/11 (45%)	11/21 (52%)	0.500
Interleukin-6, pg/ml[f]	0.95 (0.64–1.99)	2.65 (1.93–136.0)	0.003*
Interleukin-8, pg/ml[f]	57.0 (20.1–75.8)	65.4 (39.6–147.0)	0.124
Interferon-α, IU/l[f]	10.2 (0–19.9)	1.3 (0–22.2)	0.862

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

*Significant variable.

[a]CNS-SLE = central nervous system manifestations of systematic lupus erythematosus

[b]Small subcortical lesions.

[c]Small subcortical lesions were detected in 11 episodes and mid-sized to large high-intensity lesions in four episodes.

[d]Diffuse continuous bisynchronous slow waves.

[e]Diffuse continuous bisynchronous slow waves were detected in seven episodes and θ bursts in two episodes.

[f]Interleukin (IL)-6, IL-8, and interferon (IFN)-α were determined in 13 episodes of corticosteroid-induced psychiatric disorders and in 22 episodes of active CNS-SLE. 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-α as 10 IU/l.