Diagnostic Reliability of Cerebral Spinal Fluid Tests for Acute Confusional State (Delirium) in Patients with Systemic Lupus Erythematosus: Interleukin 6 (IL-6), IL-8, Interferon-α, IgG Index, and Q-Albumin

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ABSTRACT. ***Objective.*** Acute confusional state (ACS) is an uncommon but severe central nervous system (CNS) syndrome in systemic lupus erythematosus (SLE) defined by clinical manifestations. To develop useful and reliable diagnostic tools for ACS, we evaluated the association of cerebral spinal fluid (CSF) tests with ACS and their predictive values for the diagnosis of ACS in SLE.

Methods. We performed a prospective study using a cohort of 59 patients with SLE and compared those with and without ACS. Associations between ACS and each CSF test [interleukin 6 (IL-6), IL-8, interferon-α, IgG index, and Q-albumin] were statistically evaluated. Each patient underwent all CSF evaluations.

Results. ACS was diagnosed in 10 patients (ACS group), SLE-related CNS syndromes except ACS in 13, and no CNS syndromes in 36 (non-CNS group). CSF IL-6 levels in the ACS group were significantly higher than those in the non-CNS group ($p < 0.05$). A positive IgG index ($p = 0.028$) was significantly associated with ACS. No other test showed a significant association with ACS. The positive and negative predictive values for the diagnosis of ACS in SLE were 80% and 85% for elevated CSF IL-6 levels (≥ 31.8 pg/ml), and 75% and 83% for the IgG index, respectively.

Conclusion. No single CSF test had sufficient predictive value to diagnose ACS in SLE, although CSF IL-6 levels and the IgG index showed statistical associations with ACS. Use of CSF tests combined with careful history and clinical examinations is recommended for proper diagnosis of ACS in SLE. (First Release Sept 15 2007; J Rheumatol 2007;34:2010–7)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS CENTRAL NERVOUS SYSTEM
CEREBROSPINAL FLUID

Central nervous system (CNS) lupus is a serious and potentially life-threatening manifestation of systemic lupus erythematosus (SLE), occurring in 37%–95% of cases, and is associated with an increased risk of death[1]. The American College of Rheumatology (ACR) has developed a standardized nomenclature system that provides case definitions for 19 neuropsychiatric (NP) syndromes associated with SLE, including reporting standards and recommendations for laboratory and imaging tests[2]. Acute confusional state (ACS), which is one of the 19 NP syndromes in ACR nomenclature, is equivalent to "delirium," as defined in the Diagnostic and Statistical Manual of Mental Disorders (4th edition) and in the International Classification of Diseases and Related Health Problems (9th revision) as an observable state of impaired consciousness, cognition (including perception), mood, affect, and behavior[2]. "Encephalopathy" or "acute organic brain syndrome" has also been used to describe the same clinical state. Although ACS has been reported as one of the most severe and frequent CNS syndromes in SLE[3,4], because of the lack of a diagnostic gold standard it is often hard to differentiate ACS from primary mental disorders not related to SLE or drug-induced delirium at their onsets[2,5].

In the diagnosis of CNS syndrome in SLE, regular cerebral spinal fluid (CSF) tests, magnetic resonance imaging (MRI), and electroencephalography (EEG) are commonly

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used in conjunction with neurological or psychological examinations[1]. The IgG index[6-9] and Q-albumin[6,9,10], and levels of interleukin 6 (IL-6)[11-14], IL-8[12-14], interferon-α (IFN-α)[15], and antibodies to neuronal cells[16] were reported to increase in the CSF of patients with CNS lupus, including those with ACS, and have been used clinically as supplemental diagnostic examinations in some hospitals. Recent reports have also reported other potential diagnostic intrathecal markers of neuropsychiatric SLE (NPSLE)[13,14,17-19]. However, little is known about their diagnostic reliability in CNS lupus or ACS. To implement appropriate treatment and properly estimate patient prognosis, useful and reliable diagnostic tools are needed for the classification of patients into disease categories.

We conducted a prospective study in a cohort of SLE patients with or without CNS syndromes to characterize ACS in SLE and to evaluate the accuracy and usefulness of existing CSF tests in the diagnosis of ACS with SLE.

MATERIALS AND METHODS

Patients. This was a prospective study of a cohort of 59 patients with SLE (with or without NP syndromes) enrolled from August 1994 through October 2003. These patients were admitted to the Aoyama Hospital of Tokyo Women's Medical University during this period and had 4 or more ACR (formerly, the American Rheumatism Association) revised criteria for the classification of SLE[20]. In our institute, patients who were suspected to have SLE or newly diagnosed as SLE were usually admitted for systemic evaluation regardless of the severity of their diseases. However, not only patients with newly diagnosed SLE but also those whose disease (NP syndrome or other manifestations of SLE) flared were enrolled in the study. A total of 137 patients with SLE gave informed consent to the study, including CSF tests during the above period. Among these 137 patients, those who had non-SLE-related NP manifestation (due to infection, uremia, electrolyte imbalance, hypoxia, brain tumor, trauma, primary mental disease, or drugs; n = 45) or histories of NP involvement (n = 33) were excluded. These patients were excluded not only because we wanted to compare patients with recently diagnosed active ACS to non-NPSLE patients, but also because these conditions might affect current manifestations or laboratory data, including CSF tests. Ultimately, 59 patients were enrolled into the study. At the time of their admission to hospital, each patient completed a standardized medical history, including medication use, and underwent physical examinations, including neurologic and rheumatologic examinations. Psychiatric examinations were employed if necessary. Serologic profiling was done using standard immunoassays in each patient. The activity of SLE was measured using the SLE Disease Activity Index (SLEDAI)[21]. Treatment with corticosteroids or immunosuppressive drugs was instituted, if necessary, after the evaluations on admission were completed. A non-NPSLE patient at admission who later developed NPSLE was reevaluated at the onset of the NP syndrome (a mood disorder in this patient) and was classified into the CNS group. In this reevaluated patient all the data at the time of reevaluation including the results of CSF tests were used for analyses. The subjects were first classified into the CNS group or the non-CNS group according to the presence or absence of CNS syndromes. Then the CNS group was further classified into the ACS group (patients with ACS with or without other NP syndromes) or the non-ACS CNS group (patients with CNS syndromes except ACS). Diagnostic criteria for these groups are described below in detail. The Helsinki Declaration was followed throughout the study.

Diagnosis of CNS lupus. Although ACR nomenclature and case definitions include 12 CNS syndromes and 7 peripheral nervous system syndromes[2], we focused on only the 12 CNS syndromes because of substantial differences in anatomical, functional, and clinical aspects between the central and peripheral nervous systems. Slight or mild cognitive dysfunction without significant clinical impairment as revealed by detailed neuropsychological tests described below in the section "Diagnosis of acute confusional state (ACS)" [i.e., less than the median of normal controls (using published normative data) by 2 SD in 2 or more areas of cognitive function without significant clinical impairment[22]] was excluded from CNS syndromes in the study (n = 3). Tension headache (episodic tension-type headache) was also excluded.

The final clinical diagnosis and classification of various NP syndromes for the study were made by both a rheumatologist (M. Hara) and a psychiatrist (K. Nishimura), according to the standardized ACR nomenclature and case definitions for neuropsychiatric lupus syndromes[2]. These were based on the medical history and neuropsychological examinations by rheumatologists, as well as an experienced neurologist (S. Uchiyama, Tokyo Women's Medical University) and psychiatrist (K. Nishimura), and were supported by conventional laboratory tests, the appropriate complementary tests (CSF tests, brain MRI, and EEG), and their clinical courses. Among CSF tests, intrathecal pressure, appearance, differential cell counts, protein and glucose level, and conventional bacteriological examinations were routinely used as diagnostic tools. CSF levels of IL-6, IL-8, or IFN-α, and the IgG index and Q-albumin were not used for the diagnosis of NP syndromes because none of these, except the IgG index, is employed as a laboratory evaluation in the ACR case definitions for NP syndromes in SLE[2].

Diagnosis of acute confusional state. ACS was defined by the presence of disturbance of consciousness or level of arousal with reduced ability to focus, maintain, or shift attention, and one or more of the following developing over a short period of time (hours to days) and tending to fluctuate during the course of the day: (1) acute or subacute change in cognition that may include memory deficit and disorientation; and (2) a change in behavior, mood, or affect[2]. Disturbed consciousness was ascertained with clinical observation, mental status, and neurologic examination. Cognitive function was evaluated with the Mini Mental Status Examination[23] and the ACR-suggested battery[2], including instruments such as the WAIS-R/Digit Span (Forward)[24], Trail Making Test (Part B)[25], WAIS-R/Digit Span (Backward)[24], Wisconsin Card Sorting Test[25], Rey Auditory-Verbal Learning Test[24], WAIS-R/Block Design[24], Animal Naming Test[25], WAIS-R/Similarities[24], Trail Making Test (Part A)[25], and WAIS-R/Digit Symbol Substitution Test[24]. Mood and behavioral dysfunction were ascertained with clinical observation, history by patient and others, and standardized instruments (e.g., the Profile of Mood States[26]). However, these tests were not performed routinely in all the patients and the diagnosis of cognitive, mood, or behavioral dysfunction was made on the basis of clinical assessment using the ACR definitions[2] rather than formal neuropsychological testing, especially in some of the patients with disturbance of consciousness, such as ACS, who had difficulties in taking these tests. The influence of disturbance on daily life and previous occupational and social functioning was determined from the individual or from informants.

Cerebrospinal fluid test. Lumbar punctures were performed at the time of admission to hospital according to standard procedures. Levels of IL-6 and IL-8 in CSF were measured by solid-phase sandwich ELISA using the Human IL-6 QuantiGlo® ELISA Kit (R&D Systems, Minneapolis, MN, USA) and the Human Interleukin-8 Easia™ ELISA Kit (Biosource, Camarillo, CA, USA) according to the manufacturer's protocol. IFN-α in CSF was measured by radioimmunoassay using the Interferon-α Kit® (Abbott Laboratories, Abbott Park, IL, USA) according to the manufacturer's protocol. The lower measuring limits of each kit were 0.15 pg/ml, 10 pg/ml, and 10 IU/ml for IL-6, IL-8, and IFN-α, respectively.

Paired CSF and serum samples from each patient were assayed for IgG and albumin levels by rate nephelometry on a Behring Nephelometer II (Dade Behring, Newark, DE, USA) with commercially available standard and monospecific antisera (Dade Behring), according to the manufacturer's instructions. The CSF IgG index (normal < 0.70) was used as a measure of intrathecal IgG synthesis and calculated by using the following formula: [CSF IgG (mg/dl)/serum IgG (mg/dl)]/[(CSF albumin (mg/dl)/serum albu-

min (mg/dl)][27]. The integrity of the blood-brain barrier was assessed by the Q-albumin (normal < 9.0) using the following formula: [CSF albumin (mg/dl) × 10^3]/[serum albumin (mg/dl)][27]. These cutoff values had been generally used in the laboratory of our hospital mainly in the diagnosis of other diseases such as multiple sclerosis[6,27].

Statistical analyses. Diagnostic tests evaluated in our study were correlated with the final clinical diagnosis for each case. Three group comparisons were analyzed by the Kruskal-Wallis test or the Steel-Dwass multiple comparison test for continuous variables and chi-square test for categorical variables. Two-group comparisons were analyzed by the Mann–Whitney U-test for continuous variables and Fisher's exact test for categorical variables. Values of $p < 0.05$ were considered statistically significant. Accuracy, positive predictive value (PPV), and negative predictive value (NPV) of the CSF tests, which had shown significant statistical difference between ACS and non-CNS groups, were also calculated. The relationship between IL-6 and IL-8 levels was evaluated using simple regression and Spearman rank correlation. All statistical analyses were performed using SPSS statistical software (version 14.0J; SPSS Inc., Tokyo, Japan).

RESULTS

Clinical characteristics of the patients. Of the 59 patients with SLE enrolled in the study, 57 were women and 2 were men. Patients had a median age of 31 years (range 15–64 yrs). The median disease duration since diagnosis of SLE was 1 year (range 0–20 yrs). The patients were all Japanese with the exception of 1 Chinese woman. Current CNS syndromes were observed in 23 patients (CNS group) including 10 ACS (ACS group), while the remaining 36 patients did not have either a current CNS syndrome or a history of a CNS syndrome (non-CNS group). Table 1 shows the number of patients with each type of CNS syndrome. Neurologic disorders alone, psychiatric disorders alone, and both disorders were diagnosed in 7, 13, and 3 patients, respectively. All 3 of the patients with both disorders had ACS and seizure disorders. The most frequent manifestation of psychiatric disorders was ACS (n = 10), while that of neurologic disorders was "seizures and seizure disorders" (n = 5). Detailed clinical characteristics of the patients with ACS are summarized in Table 2.

ACS was the most frequent CNS syndrome in SLE in the present study, as in some other studies[3,4]; it has been recognized as one of the most severe CNS syndromes in SLE[3,4]. Therefore, demographic, clinical, and laboratory characteristics were compared between the patients with ACS (ACS group, n = 10), those with CNS syndromes except ACS (non-ACS CNS group, n = 13), and those without CNS syndromes (non-CNS group, n = 36). Sex, age, disease duration, clinical features of SLE, prevalence of lymphocytopenia, presence of antinuclear antibodies and antiphospholipid antibodies, and levels of serum anti-DNA antibody or total complement activity (CH50) did not differ significantly between the 3 groups. Although the SLEDAI score was significantly different between the 3 groups ($p < 0.0001$), "the SLEDAI score without CNS syndrome" score (the clinical variables of SLEDAI score other than CNS syndrome were evaluated and summed up for each patient) was not (Table 3).

Cerebrospinal fluid. Levels of IL-6, IL-8, and IFN-α were measured in the CSF of all 59 patients enrolled in the study (10 in the ACS group, 13 in the non-ACS CNS group, and 36 in the non-CNS group). We investigated the diagnostic value of the CSF levels of these cytokines and chemokine for ACS. The intrathecal level of IL-6 [median (25th, 75th percentile)] in the ACS group [5.05 (2.08, 69.2) pg/ml] was significantly higher than that in the non-CNS group [1.49 (0.74, 3.13) pg/ml], with statistical significance ($p < 0.05$, Steel-Dwass multiple comparison test; Figure 1A). However, those in the non-ACS CNS group [1.97 (0.80,

Table 1. CNS syndromes of SLE patients (n = 59).

Manifestations of CNS lupus*	n	%	SLEDAI, median	SLEDAI Without CNS score, median
Total	23	39		
Neurologic disorders	10	17	12.5	8.5
Aseptic meningitis	1	2	14	14
Cerebrovascular disease	1	2	10	2
Demyelinating syndrome	0	0	NA	NA
Headache**	2	3	26	18
Movement disorder (chorea)	0	0	NA	NA
Myelopathy	1	2	11	11
Seizures and seizure disorders	5†	8	11	3
Psychiatric disorders	16	27	14.5	10
Acute confusional state	10	17	18.5	10.5
Anxiety disorder	1	2	7	7
Cognitive dysfunction††	0††	0	NA	NA
Mood disorders	4	7	8	8
Psychosis	1	2	38	30

* Based on ACR case definitions for neuropsychiatric syndromes in SLE. ** Excluding tension headache (episodic tension-type headache). † Three patients also had acute confusional state. †† Excluding slight or mild cognitive dysfunction without significant clinical impairment as revealed by detailed neuropsychological tests. NA: not applicable.

Table 2. Characteristics of the patients with ACS in SLE.

Case	Sex	Age, yrs	Duration of SLE, yrs	SLEDAI	SLEDAI without CNS Score	Clinical Features	SLE-Related CNS Syndrome
1	F	15	0	33	17	Fever, malar rash, arthritis, oral ulcer, hair loss, leukocytopenia, thrombocytopenia	ACS, seizure disorder
2	F	32	0	15	8	Arthritis, pericarditis, systemic sclerosis	ACS
3	M	19	0	26	19	Fever, discoid rash, arthritis, pleuralitis, oral ulcer, hair loss, leukocytopenia, thrombocytopenia	ACS
4	F	46	5	19	11	Fever, renal disorder	ACS
5	F	52	3	9	1		ACS, seizure disorder
6	F	43	0	18	10	Malar rash, renal disorder	ACS
7	F	45	9	14	6	Other rash, renal disorder	ACS, seizure disorder
8	F	43	0	23	23	Hair loss, vasculitis, renal disorder, thrombocytopenia	ACS
9	F	51	0	11	3	Fever, malar rash	ACS
10	F	62	0	22	14	Fever, malar rash, arthritis, dermatomyositis	ACS

ACS: acute confusional state; SLE: systemic lupus erythematosus; SLEDAI: SLE Disease Activity Index.

Table 3. Characteristics of the 59 patients with or without ACS in SLE. Except where indicated otherwise, values of continuous data are the median (25%, 75% percentile).

Characteristics	ACS Group, n = 10	Non-ACS CNS Group, n = 13	Non-CNS Group, n = 36	p†
Female/male	9/1	13/0	35/1	0.400*
Age at evaluation, yrs	44 (34.8, 49.8)	28 (22, 31)	30 (23,45.3)	0.119
Clinical features (%)				
Malar rash/discoid rash	6 (60)	7 (54)	10 (28)	0.084
Oral or nasal ulcers	1 (10)	0 (0)	3 (8)	0.536*
Arthritis	4 (40)	3 (23)	15 (42)	0.485*
Serositis	2 (20)	2 (15)	1 (3)	0.134*
Renal disorder	5 (50)	6 (46)	11 (31)	0.401
Vasculitis	1 (10)	0 (0)	1 (3)	0.400*
Antinuclear antibody (%)	10 (100)	13 (100)	35 (97)	0.723*
Antiphospholipid antibodies (%) ††	2 (20)	2 (15)	9 (25)	0.762*
Lymphocytopenia (< 1500/mm^3); %	8 (80)	12 (92)	26 (72)	0.321
SLEDAI	19 (14.3, 22.8)	10 (10, 14)	8 (4, 10)	< 0.001
SLEDAI without CNS score	11 (6.5, 16.3)	10 (6, 13)	8 (4, 10)	0.219
Anti-DNA antibody (RIA; IU/ml)	12 (6, 35.3)	10 (5, 109)	10 (2.5, 45.5)	0.897
CH50 (U/ml)	35.0 (14.4, 407.3)	27.0 (< 10, 36.9)	33.0 (24.1, 37.3)	0.583

† Chi-square test or Kruskal-Wallis test. †† Antiphospholipid antibodies include lupus anticoagulant, anticardiolipin antibodies, and anti-ß$_2$-glycoprotein I antibodies. * 20% or more of cells have expected count less than 5. ACS: acute confusional state; SLE: systemic lupus erythematosus; CNS: central nervous system; SLEDAI: SLE Disease Activity Index; RIA: radioimmunoassay.

4.60) pg/ml] and non-CNS group were not significantly different (p > 0.05). To discriminate the ACS group from the non-CNS group, we calculated the diagnostic accuracies with several cutoff values for levels of CSF IL-6 and compared them. When we arbitrarily set the cutoff value at 31.8 pg/ml for IL-6, the highest diagnostic accuracy for ACS was obtained; the accuracy, PPV, and NPV were 85%, 80%, and 85%, respectively. In addition, we observed that the levels of CSF IL-6 were positively correlated with the SLEDAI score (rho = 0.315, p = 0.015) but not with "the SLEDAI score without CNS syndrome" (rho = 0.161, p = 0.225).

The level of CSF IL-8 [ACS group, 63.2 (39.4, 124); non-ACS CNS group, 44.6 (26.6, 96.8); non-CNS group, 31.9 (22.3, 42.2)] and IFN-α [ACS group, 17.6 (2.6, 31.2); non-ACS CNS group, 0 (0, 13.2); non-CNS group, 13.7 (0, 25.4)] in CSF did not differ significantly between the groups

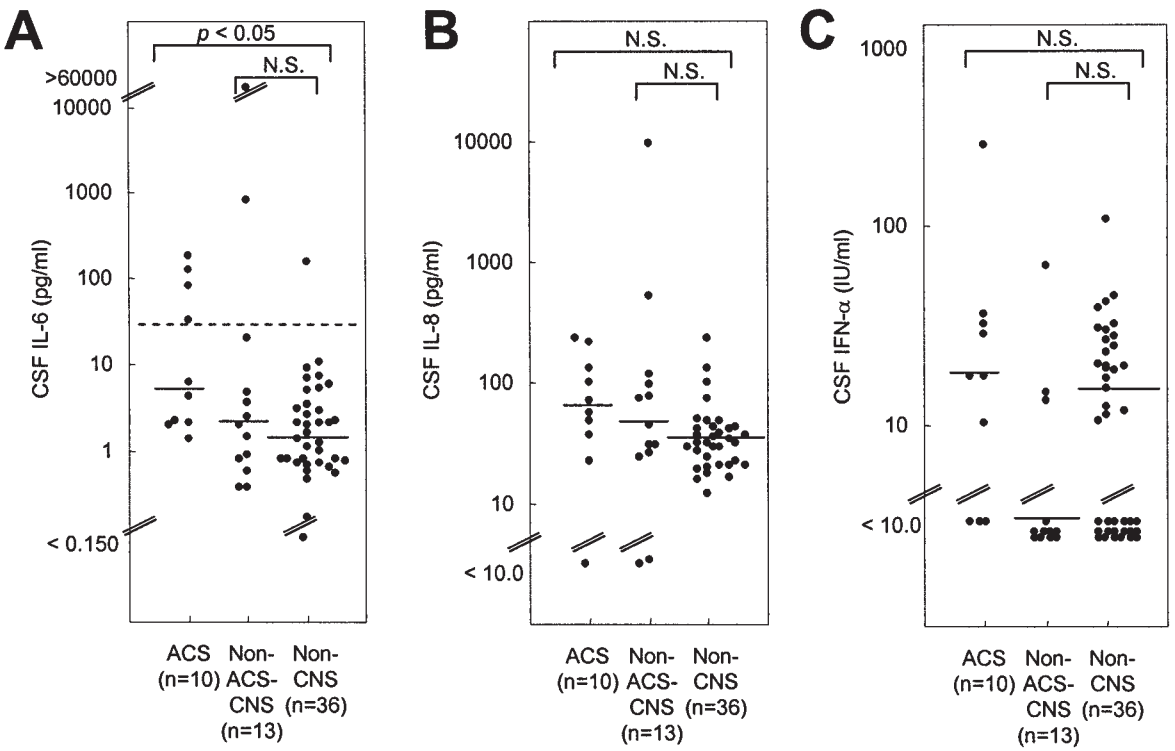

Figure 1. A current acute confusional state (ACS) was diagnosed in 10 patients with SLE (ACS group), while 13 patients with SLE had CNS syndromes except ACS (non-ACS CNS group) and 36 patients with SLE had neither a current CNS syndrome nor a history of CNS syndrome (non-CNS group). Levels of CSF IL-6 (A), IL-8 (B), and IFN-α (C) of the ACS, non-ACS-CNS, and non-CNS patients were measured. Horizontal bars represent median values in each group. The median value of IFN-α in non-ACS CNS patients was lower than the limit of the measuring kit (i.e., 10 IU/ml). Data points above or below the upper or lower parallel slanted lines indicate data that were out of the measurement range of each cytokine or chemokine kit. Horizontal broken line (A) indicates an arbitrary cutoff value (31.8 pg/ml), which gives the highest diagnostic accuracy for the diagnosis of ACS in SLE to the measurement of CSF IL-6, as described in the Results section. P values were calculated by Steel-Dwass multiple comparison test. NS: not significant.

(Figure 1B, 1C). Levels of IL-8 or IFN-α were not statistically correlated with the SLEDAI score or "the SLEDAI score without CNS syndrome" (data not shown).

The IgG index, which is an indicator of intrathecal immunoglobulin synthesis, was calculated in all 59 patients enrolled in the study, and the diagnostic values of the IgG index for ACS were determined. The frequency of patients with a positive IgG index (≥ 0.70) in the ACS group (3/10, 30%) was significantly higher than that in the non-CNS group (1/36, 3%), which was statistically significant (p = 0.028, Fisher's exact test), whereas the frequency in the non-ACS CNS group (2/13, 15%) was not (p = 0.168). This resulted in an accuracy of 83%, PPV 75%, and NPV 83% for the IgG index in the diagnosis of ACS in SLE.

The Q-albumin, which is an indicator of blood-brain barrier function, was calculated in all 59 patients enrolled. The frequency of patients with a positive Q-albumin (≥ 9.0) in the ACS group (3/10, 30%) was higher than but not statistically different from that in the non-CNS group (2/36, 6%) (p = 0.061 for ACS vs non-CNS, Fisher's exact test). This resulted in an accuracy of 80%, PPV 60%, and NPV 83% for Q-albumin in the diagnosis of ACS in SLE.

Association between cerebrospinal fluid tests. We then examined the association between the above CSF tests in all 59 subjects in the study (Figure 2). We observed that the levels of CSF IL-6 were positively correlated with levels of IL-8 (rho = 0.359, p = 0.005; Figure 2A). The levels of CSF IL-6 were higher in patients with positive IgG index than in those with negative IgG index (p = 0.004; Figure 2B), but they were not significantly different between patients with positive and negative Q-albumin (p = 0.613, data not shown). Conversely, the levels of CSF IL-8 were higher in patients with positive Q-albumin than in those with negative Q-albumin (p = 0.006; Figure 2C), but they were not significantly different between patients with a positive and negative IgG index (p = 0.219, data not shown). Finally, the frequency of a positive IgG index was not significantly different between patients with positive and those with negative Q-albumin (p = 0.224, data not shown).

Because no single CSF test showed sufficient predictive value for the diagnosis of ACS in SLE, we statistically analyzed whether a combination of any 2 of the tests could be a more useful diagnostic tool. Based on the above analyses, we picked 2 independent variables: CSF IL-6 and Q-albumin. When a criterion for ACS in SLE was defined as "positive for either CSF IL-6 (IL-6 level ≥ 31.8 pg/ml) or Q-

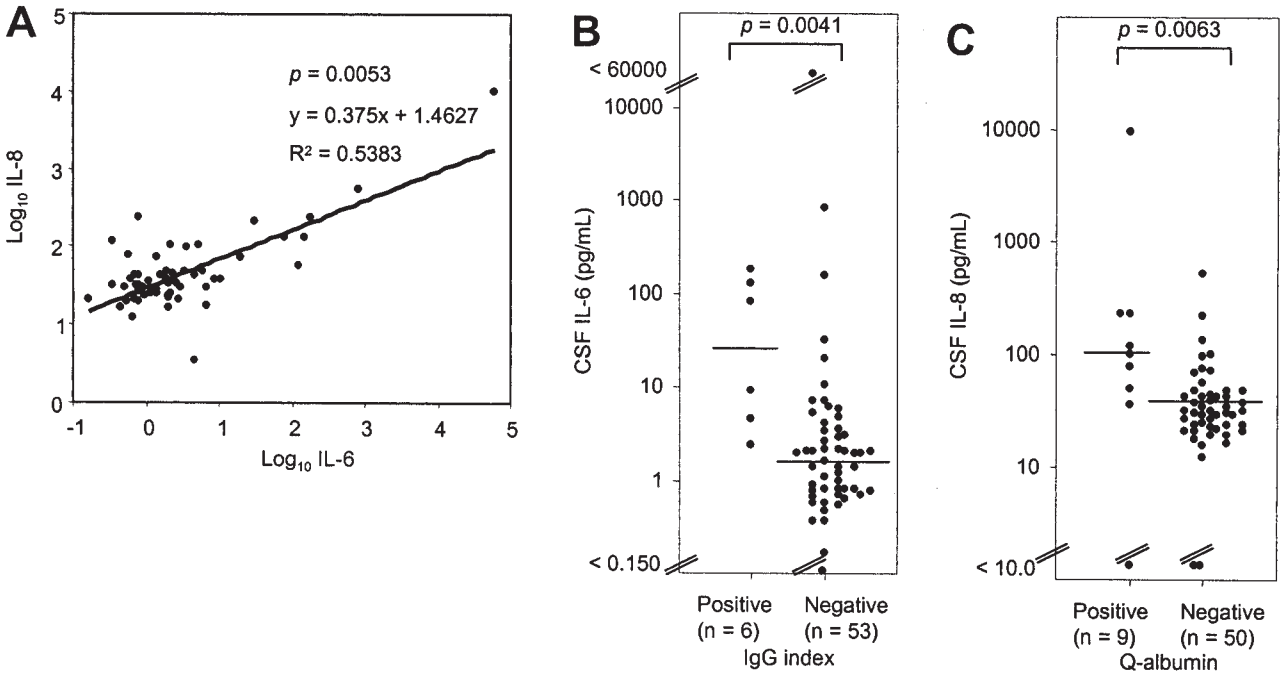

Figure 2. A current acute confusional state (ACS) was diagnosed in 10 patients with SLE (ACS group), while 13 patients with SLE had CNS syndromes except ACS (non-ACS CNS group) and 36 patients with SLE had neither a current CNS syndrome nor a history of CNS syndrome (non-CNS group). (A) Correlation between logarithmic levels of CSF IL-6 and IL-8. The relationship between IL-6 and IL-8 levels was evaluated using simple regression and Spearman rank correlation. Three cases with undetectable levels of either cytokine are not included in Figure 2. (B) CSF IL-6 levels of patients with positive or negative CSF IgG index (an indicator of intrathecal immunoglobulin synthesis; normal < 0.70). (C) CSF IL-8 levels of patients with positive or negative CSF Q-albumin (an indicator of blood-brain barrier function; normal < 9.0). Horizontal bars (B and C) represent median values in each group. Data points above or below the upper or lower parallel slanted lines indicate data that were out of the measurement range of each cytokine or chemokine kit. P values calculated by Mann–Whitney U test (B and C).

albumin," the accuracy, PPV, and NPV were 85%, 67%, and 89%, respectively, for the diagnosis of ACS in SLE. The combination of the 2 tests was found not to be a better diagnostic tool than either of the 2 alone.

DISCUSSION

We characterized ACS in SLE and evaluated the accuracy and predictive values of several existing CSF tests in the diagnosis of ACS in SLE. The CSF IL-6 level and positive IgG index showed statistically significant associations with the ACS group; however, neither had sufficient predictive value for the diagnosis of ACS in SLE. We also found that the elevation of CSF levels of IL-6 and IL-8 were significantly associated with the IgG index and Q-albumin, respectively, in patients with SLE. To our knowledge, this is the first report describing the predictive values of CSF tests for the diagnosis of ACS in SLE in a prospective study using a cohort of patients with or without NP syndromes.

Our study showed that CNS lupus including ACS was not associated with elevated "SLEDAI scores without CNS syndrome," elevated anti-DNA antibody levels, or decreased serum CH50 levels. The latter 2 are widely recognized and used clinically as reliable laboratory tests for estimating disease activity in patients with SLE[28,29]. Our data support the view that CNS syndrome in SLE may occur independently from and in the absence of serological activity or other organ involvement[30].

While the CSF IL-6 level and IgG index showed a statistical association with ACS, the PPV of the CSF IL-6 level, IgG index, and Q-albumin (81%, 80%, 57%, respectively) and the NPV (81%, 81%, 81%, respectively) of these tests were not sufficient to support their practical use in the diagnosis of ACS in SLE. The combination of the 2 independent variables, CSF IL-6 level and Q-albumin, did not improve the diagnosis of ACS in SLE. Therefore, the combined use of these CSF tests with a careful history and clinical examination would be important for the definitive diagnosis of CNS lupus or ACS in SLE. These findings may also indicate that there is heterogeneity of the pathogenesis of ACS in SLE. Although ACS is a restricted syndrome, it could still involve several etiologies because its diagnosis is based on psychiatric symptoms[2]. Consequently, we conjectured that no single laboratory marker or diagnostic procedure had sufficient power for the definitive diagnosis of CNS lupus or ACS.

Although we did not have a non-SLE control group, it has been reported that CSF cytokines do not increase in healthy controls, while they do increase in some other dis-

eases such as multiple sclerosis (IL-6)[31], neuro-Behçet's syndrome (IL-6)[32], meningitis (IL-6 and IL-8)[33,34], stroke (IL-6)[35], and brain injury (IL-8)[36]. It should be noted here that measuring CSF IL-6 or IL-8 levels alone may not be useful to differentiate ACS or other NPSLE from non-SLE-related NP syndromes because those levels could increase in many other diseases. In the small number of patients among the non-CNS group, we unexpectedly found elevated CSF levels of IL-6 and IL-8 and a positive CSF IgG index and Q-albumin; this requires further investigation. While these values were not measured in SLE patients without NP syndromes in most other studies, one study reported that some SLE patients without overt CNS disease had levels of CSF IL-6 or IL-8 as high as those of patients with CNS lupus[12]; another study also reported that one of the non-NPSLE patients had a high level of CSF IL-6[37].

Analysis of levels of cytokines and chemokines in the CSF of patients with CNS lupus or NPSLE differed considerably among some reports[11-15,37]. The reason for these conflicting results is unclear, but could be related to the heterogeneity of patients with NPSLE, the method of measuring cytokines and chemokines, or the limited number of patients without CNS syndrome as controls. It is notable that data for various kinds of NPSLE were pooled in most of the published reports, which could also confound the results. Indeed, the level of CSF IL-6 did not show any significant difference between the non-ACS CNS group and the non-CNS group in our study population, while the ACS group was significantly associated with an elevated CSF IL-6 level.

We also found that the elevations of CSF IL-6 and IL-8 levels were significantly associated with the IgG index and Q-albumin, respectively, in patients with SLE. Rationales for this analysis include (1) that the elevation of CSF IL-6 and IL-8 levels may be related differently to the pathogenesis of ACS or NPSLE; and (2) that analyzing the relationships between CSF tests may lead to elucidation of novel molecular mechanisms of ACS or NPSLE. The increase of intrathecal IL-6 might activate the B cells in the CNS and enhance intrathecal IgG production in patients with a positive IgG index[38]. We also surmised that increases of intrathecal IL-8 levels in patients with a positive Q-albumin might enhance leukocyte transendothelial migration into the CNS through the impaired blood-brain barrier and further accelerate CNS inflammation, as presumed in patients with severe traumatic brain injury[36]. In addition, a positive correlation between CSF levels of IL-6 and IL-8 in patients with SLE may indicate the presence of a common mechanism for the elevation of CSF levels of IL-6 and IL-8, such as intrathecal inflammation.

CSF IL-6 did not relate to the overall SLE activity exclusive of CNS syndrome. To evaluate the relevance of high levels of CSF IL-6 to the activity of ACS, we studied the effects of treatments on the IL-6 levels in patients whom we could follow up (8 patients with ACS out of 10). The levels of CSF IL-6 decreased by more than 50% in 4 of the 5 patients in whom ACS had been ameliorated after treatments, while they did not change by more than 50% in 2 of the 3 patients in whom ACS had not been alleviated (data not shown). These results were just preliminary and could not be interpreted statistically because of the small number of cases and many confounding variables. However, they may indicate that levels of CSF IL-6 might be related to the activity of ACS in some patients. Further followup studies in larger number of patients are needed to clarify this.

No single CSF test had sufficient predictive value to diagnose ACS in SLE, although levels of CSF IL-6 and a positive CSF IgG index showed a statistically significant association. A further study to compare ACS in SLE and ACS-like psychiatric manifestations caused by non-SLE pathogenesis would lead to more precise assessment of the reliability of those tests as diagnostic tools for ACS in SLE.

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