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Psychiatric Manifestations of Systemic Lupus Erythematosus: Clinical Features, Symptoms, and Signs of Central Nervous System Activity in 43 Patients

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Introduction

Psychiatric abnormalities are a common manifestation of systemic lupus erythematosus (SLE). Substantial differences in the prevalence of psychiatric symptoms in patients with SLE (from 17% to 75%) have been reported (13, 37). This wide range can be accounted for by disparate methods employed in various studies, such as differences in assessment techniques and selection of subjects (32, 36, 62), and by the absence of a reliable marker and well-accepted diagnostic criteria for neuropsychiatric manifestation of SLE in the central nervous system (CNS) (6, 24).

Psychiatric disorders in patients with SLE may be due primarily to activity of SLE in the CNS or may result from complications of SLE, such as infection, uremia, electrolyte abnormalities, or its treatment, such as corticosteroids. Also, psychiatric abnormalities in patients with SLE may be secondary to a primary psychiatric disorder (for example, bipolar disorder) or to psychological stress associated with a chronic and potentially lethal disease (such as adjustment disorders). Symptoms of each of the above conditions are managed differently (6, 24, 36, 62).

Few studies have reported on the psychiatric manifestations of SLE using a multidisciplinary approach and subjects with active SLE. Because criteria for the psychiatric manifestations of SLE are not available, we undertook the present study to validate the diagnosis of SLE-associated psychiatric manifestations with the hope of improving clinical management of affected patients. We restricted our sample population to patients with SLE when the disease is flaring and based our diagnosis on a multidisciplinary clinical approach including laboratory and radiologic exams to measure CNS activity.

We evaluated 43 inpatients with active SLE by a multidisciplinary approach applying standardized psychiatric instruments and diagnostic criteria along with neuroimaging and electrophysiologic measures to answer the following research questions: 1) What features of psychopathology are present in patients with active SLE? and 2) In these patients, what is the relationship between psychiatric disorders and symptoms and signs suggesting activity of SLE in the CNS? Our a priori hypothesis was that, in patients with active SLE, those with psychiatric manifestations would have more symptoms and signs of CNS activity than those without psychiatric manifestations.

Methods

Patient selection

Forty-six female inpatients admitted between 1988 and 1991 to the rheumatologic and internal medicine ward of Hospital das Clinicas of the University of São Paulo Medical School were studied. All met revised criteria for SLE (57) and for SLE disease activity according to the Lupus Activity Criteria Count (LACC) (58) (that is, activity was present in at least 1 organ other than the brain and was associated with abnormal lab tests). Subjects underwent rheumatologic, psychiatric, neurologic, ophthalmo-

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logic, neuroradiologic, electrophysiologic, and laboratory evaluations. Exclusion criteria were history of drug or alcohol abuse, head injury with post-traumatic amnesia lasting longer than 24 hours, other cerebral or systemic diseases, and medications (other than corticosteroids or immunosuppressants) that could cause an organic mental syndrome. Three patients were excluded: 2 had psychiatric disorders attributed to the use of corticosteroids and the psychiatric disorder of the 3rd patient was attributed to metoclopramide (49). Therefore, 43 patients were included in the final analyses. The study was approved by the human subjects committee of the hospital, and all patients gave written informed consent.

Psychiatric evaluation

All patients were evaluated by the same psychiatrist (E.C.M.). The psychiatric evaluation consisted of a clinical evaluation; a semi-structured interview; the Present State Examination (PSE) (64); a measurement of cognitive state (Mini-Mental State Examination [MMSE]) (23); and an assessment of depression (Hamilton Depression Rating Scale [HAM-D]) (33). The PSE was completed in all but 4 patients and was analyzed by the CATEGO 4 computer program (63, 64). Psychiatric diagnoses were made according to the *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edition—Revised (DSM-III-R) (3).

Patients were categorized as either with (Psychiatric Group) or without (Nonpsychiatric Group) psychiatric disorders based on the clinical psychiatric examination. This clinical impression was then compared to the PSE index of definition (ID). An ID ≥ 5 indicates psychiatric disease (63, 64). Except for 2 patients with dementia, all patients with psychiatric diagnosis showed an ID ≥ 5, and all patients without current psychiatric diagnosis had an ID <5.

Subjective cognitive impairment, defined as forgetfulness and difficulty concentrating severe enough to interfere with social or occupational functioning, as reported by the patient, a relative, or both, was also assessed.

Evaluation of SLE systemic and CNS disease activity

All patients were evaluated by a rheumatologist (R.M.R.P.) and a neurologist (R.H.). Forty-two (98%) patients had ophthalmologic examinations (L.C.F.S.). A neurologic abnormality was attributed to SLE activity when 1) connected with disease flare (for example, migraine or seizures connected in time with a disease flare), and 2) other causes of the neurologic abnormality were excluded. Only abnormalities affecting the CNS were considered. Ophthalmologic signs considered to be associated with SLE disease activity included retinal hemorrhages, cotton-wool spots, evidence of vasculitis, and optic atrophy in patients otherwise free of risk factors for these findings (6 patients with arterial hypertension were excluded from the ophthalmologic study population).

Laboratory evaluation included serum and cerebral spinal fluid (CSF) exams. Serum antinuclear antibodies were detected by indirect immunofluorescence on rat liver and HEp-2 cells; antibodies to U1-RNP and Sm were detected by hemagglutination (51); anti-native DNA were detected by indirect immunofluorescence with *Crithidia lucilliae* (1); and anti-Ro/SSA were detected by immunodiffusion (50). CSF glucose and protein were determined in 33 patients.

Computer Tomography (CT) of the brain was performed on 40 (93%) patients with a 3rd-generation scanner using a 256×256 matrix that included the region from the cranial base to the vertex. Each scan was read by 2 neuroradiologists (N.G.B. and R.H.G.) blind to the patient's history. A 3rd neuroradiologist was consulted as a blind evaluator to resolve discordant findings. Two blinded observers (R.E.G. and E.C.M.) quantified the widths of cortical sulci using a linear measure (34) and the ventricular brain ratio (VBR) (55) by planimetry. Twelve normal exams from the hospital files (patients without abnormalities on physical, neurologic, and CT examination), matched for patients gender, age, and education, were used as controls. Reliability was excellent, both between neuroradiologists (Kappa ≥ 0.79, $p < 0.0001$) in qualitative analysis and between observers ($r = 0.76$, $p < 0.0001$) in quantitative analysis.

All patients had electroencephalography (EEG) using a Beckmann 200-A EEG, 16 channels with activation proofs. Each exam was read by a electroencephalographist (J.M.N.) blind to the patients history. All patients were initially evaluated by a rheumatologist and sent to other physicians (psychiatrist, neurologist, ophthalmologist, neuradiologist, electroencephalographist) who were blind to their clinical manifestations of SLE. Wherever possible, all clinical assessments, laboratory studies, CT, and EEG were obtained during the same week.

Statistical analysis

Nonparametric methods (10) were used to analyze categorical and badly skewed continuous variables. Statistical procedures included the chi-squared test, the Fisher Exact test, the Kappa reliability test for categoric variables, the Wilcoxon-Mann-Whitney U test, and the Kruskall-Wallis 1-way analysis of variance. Pearson correlations were used to examine the relation of continuous variables.

Results

Twenty-seven patients (63%) were diagnosed with psychiatric disorders (Psychiatric Group), and 16 (37%) patients presented no current psychiatric diagnosis (Nonpsychiatric Group). The 2 groups did not differ on most demographic or clinical characteristics, including social class (U: 205.5; $p = 0.78$); educational level (U: 174.0; $p = 0.28$); severity of disease (U for number of positive criteria for SLE: 233.5; $p = 0.66$; U for number of organ systems involved: 186.5; $p = 0.44$); familial prevalence of psychiatric disease ($p = 0.53$).

Except for serositis, which was found more frequently in the Nonpsychiatric Group than the Psychiatric Group (Psychiatric Group: 1 patient, 4%; Nonpsychiatric Group: 6 patients, 38%; $p = 0.007$), no statistical difference was found between the 2 groups regarding their general clinical evaluation, including malar rash and discoid rash ($p = 1.0$); mucocutaneous vasculitis ($p = 0.75$); arthritis, arthralgia (0.35); lymphopenia ($p = 1.0$); renal disease ($p = 0.75$); leukopenia ($p = 1.0$); anemia ($p = 1.0$); and thrombocytopenia ($p = 0.14$). The serum laboratory evaluation also did not differ significantly

between the 2 groups (cells LE: p = 1.0; low complement level: p = 0.53; anti-DNA native: p = 0.36; anti-U1 RNP: p = 0.75; anti-RO/SS-A: p = 1.0; anti-SM: p = 1.0).

Likewise, groups did not significantly differ regarding the rheumatologic treatment, including use of corticosteroids (CE) and immunosuppressants (IS) before (CE: p = 1.0; IS: p = 0.09) or during the study period (CE: p = 0.52; IS: p = 0.69). One-third of the patients in both groups had never taken CE and were not taking this medication during the study period. However, the Psychiatric Group was older (Psychiatric Group: mean ± standard deviation (SD) = 31.78 y ± 10.71; Nonpsychiatric Group: mean ± SD = 23.44 y ± 5.5; U: 328; p = 0.005) and had a longer disease duration than the Nonpsychiatric Group (Psychiatric Group: mean ± SD = 92.96 mo ± 93.405; Nonpsychiatric Group: mean ± SD = 28.03 mo ± 25.75; U: 327; p = 0.005).

The 2 groups were compared in terms of their symptoms and signs suggesting CNS activity (i.e., neurologic and ophthalmologic evaluation, CSF exam, CT, and EEG) to 1) determine the features of psychopathology in patients with active SLE, and 2) determine the relationship between psychiatric disorders and other symptoms and signs suggesting activity of SLE in the CNS.

Features of psychopathology in patients with active SLE

The DSM-III-R psychiatric diagnoses are listed in Table 1. Organic mood disorder with depressive symptoms was the most frequent diagnosis (19/43; 44%). The HAM-D scores in the 19 patients with depression were significantly higher than in the Nonpsychiatric Group (Psychiatric Group: mean ± SD = 17.16 ± 7.23; Nonpsychiatric Group: mean ± SD = 2.12 ± 1.80; U: 301.5, p < 0.0001).

Fourteen (52%) of the 27 patients in the Psychiatric Group developed psychiatric symptoms before or during the 2 years after the onset of SLE. In 1 patient the psychiatric manifestation started 2 months before the other SLE systemic symptoms, and in 5 patients the psychiatric and other SLE symptoms were concurrent. Thirteen (48%) patients started their psychiatric symptoms at least 2 years after the onset of SLE. Sadness (11 patients, 41%), irritability (10 patients, 37%), and subjective cognitive impairment (7 patients, 26%) were the most frequent 1st symptom reported by patients in the Psychiatric Group.

Twelve patients (44%) in the Psychiatric Group and 1 patient in the Nonpsychiatric Group reported a psychiatric episode before the study period (p = 0.01). Nine patients in the Psychiatric Group reported past symptoms compatible with a different psychiatric syndrome when compared to the current manifestation. Seven patients had depression followed or preceded by delirium or dementia. One patient had a hallucinatory state followed by depression. Another patient had an organic delusional syndrome followed by depression. The Nonpsychiatric Group patient described a past episode of depression.

TABLE 1. Prevalence of psychiatric diagnoses in 43 patients with active SLE

Current Psychiatric Diagnosis*	Number of Patients (n=43) No. (%)
Organic mood (depressive) disorder	19 (44)
Delirium	3 (7)
Dementia	2 (5)
Organic mental disorder NOS†	2 (5)
Organic hallucinosis	1 (2)
Total with psychiatric disorders	27 (63)
None	16 (37)

* DSM-III-R diagnoses (reference 3).

† NOS = not otherwise specified (2 patients with mild cognitive impairment).

Relationship between psychiatric disorders and other symptoms and signs suggesting activity of SLE in the CNS

Psychiatric Group patients exhibited subjective cognitive impairment more frequently than Nonpsychiatric Group patients (Table 2). These cognitive symptoms were associated with the duration of SLE (χ^2 = 5.50, df = 1, p = 0.03), neurologic abnormalities (χ^2 = 16.87, df = 1, p = 0.0001), and psychiatric symptoms (as measured by higher scores on the PSE; χ^2 = 14.67, df = 1, p = 0.0007).

Presence of at least 1 neurologic abnormality in the CNS was found more frequently in the Psychiatric Group patients (23/27, 85%) than in the Nonpsychiatric Group patients (0/16, p < 0.0001) (Table 2). Migraine without aura was the most frequent neurologic manifestation; seizures were next in frequency. Psychiatric symptoms measured by higher scores on the PSE were related to the presence of neurologic abnormalities (χ^2 = 16.71, df = 2, p = 0.0002). Ophthalmologic abnormalities tended to be more frequent in the Psychiatric Group, although the numbers were not statistically significant (Table 2). There was no significant correlation between ophthalmologic abnormalities and use of corticosteroids (χ^2 = 1.01, df = 1, p = 0.32).

The CT findings are also shown in Table 2. The most common alterations were widened cortical sulci, ventricular enlargement, and calcifications. Widened cortical sulci were prevalent across the 2 groups, including more than half of the Nonpsychiatric Group patients (Table 2). Correlation between widened cortical sulci and use of corticosteroids was

TABLE 2. Symptoms and signs suggesting SLE activity in CNS in 43 patients with active SLE with and without psychiatric disorders

	Psychiatric Group (n=27) No. (%)	Nonpsychiatric Group (n=16) No. (%)	Significance*
Subjective cognitive impairment†	23 (85)	1 (6)	$p < 0.0001$
Neurologic abnormalities†			
Total	23 (85)	0	$p < 0.0001$
Migraine	22 (81)	0	$p < 0.0001$
Seizures	8 (30)	0	$p = 0.02$
Past neurologic episode	12 (44)	3 (19)	$p = 0.1$
Ophthalmologic abnormalities†			
Total	10 (45)†	2 (14)§	$p = 0.08$
Vascular alterations	6 (27)‡	1 (7)§	$p = 0.21$
Cotton-wool spots	7 (32)‡	1 (7)§	$p = 0.12$
Hemorrhages	6 (27)‡	0§	$p = 0.06$
CT abnormalities†			
Qualitative Analysis			
Widened cortical sulci	13 (54)‖	10 (63)	$p = 0.75$
Ventricular enlargement	12 (50)‖	5 (31)	$p = 0.33$
Calcifications	8 (33)‖	1 (16)	$p = 0.06$
Quantitative analysis			
Widened cortical sulci	13 (54)‖	7 (44)	$p = 0.75$
VBR (mean ± SD)**	10.09 ± 4.72‖	9.9 ± 1.78	$p = 0.39$
CSF			
Protein elevation (>30 mg/dL)	6 (25)‖	1 (13)¶	$p = 0.64$
Pleocytosis (>5 cells/mm^3)	3 (13)‖	1 (13)¶	$p = 1.0$
Low glucose (60% of serum)	1 (4)‖	0¶	$p = 1.0$
EEG abnormalities	7 (26)	1 (6)	$p = 0.22$

Abbreviations: VBR = ventricular brain ratio; CSF = cerebral spinal fluid.
* All p values are from the Fisher Exact test, except for VBR, which is from Kruskall-Wallis; analysis of variance = 1.86.
** VBR of normal control group (mean ± SD) = 10.15 ± 2.15.
† See methods section for definition of terms.
‖ n=24.
‡ n=22.
§ n=14.
¶ n=8.

not significant (qualitative analysis, $\chi^2 = 1.42$, df = 1, $p = 0.23$; quantitative analysis, $\chi^2 = 0.96$, df = 1, $p = 0.33$). Furthermore, 10 patients who had never taken corticosteroids showed widened cortical sulci (8 patients in the Psychiatric Group and 2 patients in the Nonpsychiatric Group).

No statistical difference was found among the 2 groups regarding their CSF exams or EEG alterations (Table 2).

To determine whether the severity of psychiatric symptoms was related to CNS activity, we divided the 27 patients with psychiatric manifestations into 2 groups: 18 patients with major psychiatric disorders (e.g., delirium, dementia, organic hallucinosis, delusional syndromes, major depressive syndromes) comprised the Major Group; 9 patients with mild depressive symptoms comprised the Minor Group. All statistical analyses reported above were repeated for the 3 groups (Major, Minor, Nonpsychiatric), which were comparable on all sociodemographic variables, and duration and severity of SLE.

All depressed patients in the Major Group had Ham-D scores of 17 or higher; those in the Minor Group had scores of 5–16. Patients in the Major Group had lower scores on the MMSE compared to those in the Minor Group and in the Nonpsychiatric Group (lower score implies more severe cognitive abnormalities; Kruskall-Wallis = 10.649, $p = 0.005$). Psychotic symptoms were present only in the Major Group.

When the distinction was made between patients with major and minor psychopathology, those in the Major Group showed significantly more ophthalmologic abnormalities and calcifications on CT (mainly in the basal ganglia) compared with those in both the Minor Group and the Nonpsychiatric Group. Similarly, once the VBR values were categorized into 3 levels (high, medium, and low), high values were significant more frequent in the Major Group patients than in Minor Group patients, Nonpsychiatric Group patients, and normal controls (Table 3).

Major and Minor Groups did not differ significantly regarding the presence of subjective cognitive impairment and neurologic abnormalities (Table 3). The 2 groups with psychiatric symptoms were also similar in terms of the time intervals between the onset of SLE and the beginning of

TABLE 3. Symptoms and signs suggesting SLE activity in CNS in 43 patients with active SLE with major, minor, or no psychiatric disorders

	Psychiatric Disorder			
	Major (n=18) No. (%)	Minor (n=9) No. (%)	None (n=16) No. (%)	Significance*
Subjective cognitive impairment†	17 (94)[a]	6 (66)[b]	2 (12)[ab]	p = 0.001
Neurologic abnormalities†				
Total	16 (89)[a]	7 (77)[b]	0[ab]	p = 0.001
Migraine	16 (89)[a]	6 (67)[b]	0[ab]	p = 0.0001
Seizures	6 (33)[a]	2 (22)[b]	0[ab]	p = 0.04
Ophthalmologic abnormalities†				
Total	9 (60)[ab]‡	1 (14)[b]§	2 (13)[a]‡	p = 0.03
Vascular alterations	6 (40)[ab]‡	0[b]§	1 (7)[a]‡	p = 0.02
Cotton-wool spots	6 (40)‡	1 (14)§	1 (7)‡	p = 0.07
Hemorrhages	5 (33)[ab]‡	1 (14)[b]§	0[a]‡	p = 0.05
CT abnormalities†				
Qualitative analysis				
Calcifications	8 (53)[ab]‡	0[b]	1 (6)[a]	p = 0.001
Quantitative analysis				
VBR‖	9 (60)[ab]	3 (33)[b]	2 (12.5)[a]	p = 0.02

Abbreviations: VBR = ventricular brain ratio.
* p Values for comparison of all 3 groups by chi-squared test with df = 2, except for VBR, df = 4.
† See methods section for definition of terms.
‡ n=15.
§ n=7.
‖ High values on VBR (VBR categorized into 3 levels: high, medium, and low; none of normal controls presented high values).
[a,b] Values that differ significantly ($p < 0.05$) share same superscript letter.

psychiatric symptoms (Major Group: mean ± SD = 60.80 mo ± 72.29; Minor Group: mean ± SD = 55.11 mo ± 32.80; U = 75.0; p = 0.78) and presence of past psychiatric episodes ($\chi^2 = 0.68$, df = 1, p = 0.41).

Table 4 shows correlations among depressive symptoms, measured by Ham-D, and psychotic symptoms, measured by PSE (PSE subscores for delusional and hallucinatory, and behavior and speech syndromes), and several variables studied. Depressive symptoms significantly correlated with age, disease duration, different past psychiatric syndrome, subjective cognitive impairment, migraine, seizure, and calcifications on CT. Presence of psychotic symptoms correlated with subjective cognitive impairment, migraine, ophthalmologic abnormalities, and calcification. Interestingly, a negative correlation was found between patients with current use of corticosteroids and psychotic symptoms.

TABLE 4. Pearson correlations of depressive and psychotic symptoms with demographic and clinical variables in 43 patients with active SLE

	Depressive Symptoms*	Psychotic Symptoms†‡
Age	0.44§	0.20
Disease duration	0.34‖	0.13
Different past psychiatric syndrome	0.58¶	0.55¶
Subjective cognitive impairment	0.59‖	0.48§
Neurologic abnormalities	0.71¶	0.41§
Migraine	0.65¶	0.44§
Seizure	0.41§	0.22
Ophthalmologic abnormalities	0.21	0.41§
Calcification	0.45§	0.36‖
VBR enhanced	0.29	0.26
Current CE use	0.01	−0.31‖
Previous CE use	0.25	−0.04

Abbreviations: VBR, ventricular brain ratio; CE = corticosteroids.
* Based on Hamilton Depression Rating Scale (ref. 33).
† Based on Present State Examination (ref. 64).
‡ Because presence of psychotic symptoms is a binary variable indicating presence of either none or one or more psychotic syndromes on PSE, these correlations are point biserial r's.
§ $p < 0.01$.
‖ $p < 0.05$.
¶ $p < 0.001$.

Discussion

Our study design improves on previously published studies of the psychiatric manifestations of SLE in several ways: a) inclusion of only inpatients with evident signs of SLE disease activity enhancing the validity of a SLE-associated psychiatric diagnosis; b) use of a semi-structured psychiatric interview and reliable diagnostic criteria; c) inclusion of an ophthalmologic examination, looking for

signs of CNS activity; d) use of qualitative and quantitative analyses of SLE CT findings, with a normal control group for contrast, and e) comparison of patients with mild depressive syndromes (usually considered to be an adjustment disorder) to patients with major psychiatric symptoms, more frequently attributed to SLE.

Because the sample was limited to inpatients in a university general hospital, the SLE symptoms seen probably were more severe than in other studies (22). As a consequence, the results may not reflect the worldwide pool of patients with SLE. Given the small number of subjects, Type II error is possible for comparisons between the 2 groups of psychiatric disorders (Major and Minor Groups). We were not able to include newer neuroimaging techniques, such as Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET), which might have provided more information than the CT for patients with SLE (52, 54). However, the wide availability of CT, the ease and simplicity with which it can be used, and the substantial body of reference studies ensure that CT will remain a clinical and research tool for many years (4).

Features of psychopathology in patients with active SLE

This study confirms that 1) psychiatric manifestations are frequent in patients with active SLE; 2) several kinds of psychiatric disorders occur as a CNS manifestation in patients with active SLE; and 3) frequently more than 1 psychopathologic syndrome occurs in the same patient during the advance of the disease (7, 8, 40, 47, 48 53, 60). Moreover, psychiatric disorders can appear at any time in the disease process.

The fact that the Psychiatric Group patients were older and had a longer disease duration than the Nonpsychiatric Group patients is consistent with other studies suggesting that psychiatric alterations tend to be more frequent as the disease progresses (47, 8, 30).

Depressive syndrome was the most frequent diagnosis, found in 19 (44%) patients. Depressive symptoms in SLE have been reported in 6.5% (13) to 86% (8) of patients in previous studies. Compared to studies reporting a lower prevalence of depression, the frequency of 44% for such symptoms in this study could be due to 1) failure in other studies to consider mild depressive symptoms as a CNS manifestation of SLE (21, 53) and 2) the use of different diagnostic criteria (37, 47, 48, 60). Three patients with depressive symptoms and mood-incongruent psychotic features probably would have received the diagnosis of schizophreniform syndrome instead of depression before the DSM-III-R (3) era.

Compared to studies reporting a higher prevalence of depression, the lower frequency (44%) of such symptoms in this study could be due to differences in sample features such as 1) the use of outpatients in other studies (40) (our study focused on inpatients, who had more severe disease than outpatients) and 2) the smaller number of subjects in other reported studies (8) than in the present study.

Seven (16%) patients of the Psychiatric Group presented objective cognitive symptoms (that is, delirium, dementia, or mild cognitive impairment) sufficient for the diagnosis of organic mental syndrome (3). This diagnosis is the most frequent among patients with SLE by most published accounts (13, 21, 48, 60).

Relationship between psychiatric disorders and other symptoms and signs suggesting activity of SLE in the CNS

The literature reports a high prevalence of neuropsychologic dysfunction in patients with SLE (16, 61). In the present study, subjective cognitive impairment occurred in the majority of the Psychiatric Group patients and was associated with psychiatric and neurologic abnormalities. The MMSE was not sufficiently sensitive to detect these abnormalities. Thus, new, simple, and specific instruments to detect mild cognitive impairments should be developed and validated to permit earlier diagnosis of CNS alterations in patients with SLE. The association between cognitive impairment and duration of illness found in this study has been reported (30), and is further evidence that mental function gradually deteriorates as the disease progresses.

The association between neurologic abnormalities and psychiatric manifestations found in this study has already been described (21, 26) and suggests that psychopathologic symptoms reflect CNS activity. There is some controversy in the literature about whether or not migraine can be a CNS manifestation of SLE (2, 5, 11, 35, 59). Migraine related to clinical activity of SLE was found frequently in the present study and was associated with higher VBR, calcifications, and subjective cognitive impairment. These findings suggest that migraine should be considered a manifestation of SLE and could indicate CNS activity of SLE in patients with psychiatric disorders.

The association between migraine and depression found in this work has also been reported in several studies (12, 43). Interestingly, these 2 disorders seem to share some common aspects, such as low levels of 5-hydroxytryptamine and of platelet 5-

hydroxytryptamine, and responsivity to antidepressant therapies (27).

Retinovascular abnormalities were present in 33% of patients, compared to 3% to 29% reported previously (28, 39). These symptoms were more frequent in the group with major psychiatric manifestations than in the groups with minor and nonpsychiatric manifestations, suggesting another parameter of activity in the CNS.

Other studies (9, 29, 38) have found widened cortical sulci to be the most common CT alteration in patients with SLE; they have been found even in asymptomatic patients (17, 25). Our study differed from the others in that widened cortical sulci could not be attributed to the use of corticosteroids. The fact that they were found in patients who had neither used steroids nor had neuropsychiatric manifestations suggests that widened cortical sulci could be due to subclinical SLE activity.

In the present study, ventricular enlargement was found more frequently in patients with major psychiatric manifestations than in those with minor and nonpsychiatric manifestations. However, this enlargement was not associated with psychiatric symptoms. Burns and colleagues (14, 15) also found a negative association between ventricular enlargement and psychiatric symptoms in patients with Alzheimer's disease.

Calcifications were more frequent in the Major Group than in the other groups, mainly in the basal ganglia. Calcification in the basal ganglia and paraventricular area has already been described in patients with SLE (20, 45, 46). The suggestion was that these alterations were due to microinfarcts (46). At autopsy in 1 deceased patient from the Major Group, a dystrophic calcification was related to a microinfarcted area. Neurocysticercosis was ruled out in all patients in the present study by CSF examination and by the observed features of CT calcifications (42, 56). The explanation for the association between calcification and psychotic symptoms is unknown but recognized; studies of different diseases also have described calcifications in basal ganglia associated with psychotic symptoms (14, 15, 18, 19).

Systemic clinical and laboratory exams used in this study, including CSF examination, did not help to characterize psychiatric manifestations. Similarly, EEG alterations were found in only 8 (19%) patients—less than observed in other studies (2, 31). Higher rates would probably have been found if the EEG exams had been done closer to the onset of the psychiatric manifestations and if sphenoidal electrodes had been used in all patients.

Implications

We assume that the psychiatric manifestations observed in the Major Group could be diagnosed as an organic mental disorder related to SLE for several reasons: 1) the presence of a disease (SLE) that could cause an organic mental syndrome and the exclusion of other causes of organic mental syndromes (e.g., infection, uremia, electrolyte abnormalities); 2) the temporal relationship between the beginning of psychiatric symptoms and clinical and laboratory evidence of SLE activity; 3) the presence of psychopathologic features similar to those found in organic mental syndromes, such as objective (7 patients) and subjective (17 patients) cognitive symptoms, visual hallucinations (4 patients) and poorly organized delusions (5 patients), and past episode of a different psychiatric syndrome (9 patients) (19, 41); and 4) the presence of important symptoms and signs of CNS activity (neurologic and ophthalmologic abnormalities, ventricular system enlargement, and calcifications identified by CT scan).

The relationship of psychiatric symptoms to the physiopathologic process of SLE in the CNS remained obscure in the Minor Group (those with mild depressive syndromes). These alterations could also be secondary to an adjustment reaction to a chronic disease. However, patients of the Minor Group were closer to those of the Major Group than to those of the Nonpsychiatric Group in terms of CNS activity (for example, subjective cognitive impairment and neurologic abnormalities). Major and Minor groups also presented similar time intervals between onset of SLE and beginning of psychiatric symptoms, and similar frequency of past psychopathologic episodes. Thus, we propose that the mild depressive symptoms observed in the Minor Group might be a prodromic, residual, or mild manifestation of SLE in the CNS. As mentioned earlier, Type II error should be considered when analyzing these findings, given the small numbers of patients in each group.

Our findings confirmed our a priori hypothesis. In patients with active SLE, those with psychiatric manifestations have symptoms or signs of CNS activity, such as neurologic and subjective cognitive impairment, more frequently than those without psychiatric manifestations. Major psychopathology is also associated with ophthalmologic abnormalities and brain calcifications, and widened cortical sulci in CT may be an early or subclinical sign of CNS disease activity.

Summary

Forty-three female inpatients with active systemic lupus erythematosus (SLE) were studied by a multidisciplinary team to answer the following research questions: 1) What are the features of the

psychopathology in patients with active SLE? and 2) In these patients, what is the relationship between psychiatric disorders and symptoms and signs suggesting activity of SLE in the CNS? Our a priori hypothesis was that, in patients with active SLE, those with psychiatric manifestations would have more symptoms and signs of CNS activity than those without psychiatric manifestations.

Psychiatric evaluation consisted of standardized psychiatric instruments and diagnostic criteria. The assessment of SLE systemic and central nervous system (CNS) activity consisted of rheumatologic, neurologic, and ophthalmologic evaluations; serum and cerebral spinal fluid (CSF) analysis; brain computerized tomography (CT); and electroencephalogram (EEG).

Twenty-seven patients (63%) presented psychiatric symptoms (Psychiatric Group), and 16 (37%) patients presented no current psychiatric diagnosis (Nonpsychiatric Group). These groups were compared in terms of the above variables. Depressive syndrome was the most frequent diagnosis (44%) followed by delirium (7%) and dementia (5%). Psychiatric symptoms were associated with subjective cognitive impairment (85%) and neurologic abnormality (85%). Widened cortical sulci was the most frequent CT alteration and was equally common in both groups. No statistical difference was found between the 2 groups regarding their general clinical evaluation, serum and CSF exams, or EEG alterations.

To determine whether the severity of psychiatric symptoms was related to CNS activity, we divided the 27 patients with psychiatric manifestations into 2 groups: the Major Group—18 patients with major psychopathology, and the Minor Group—9 patients with mild depressive syndromes. The group with major psychopathology had significantly more ophthalmologic abnormality (60%), brain calcification (53%), and ventricular system enlargement on CT when compared to the Minor and Nonpsychiatric Groups.

In summary, psychiatric manifestations in patients with active SLE are frequently associated with symptoms or signs of CNS activity, such as neurologic (mainly migraine) and subjective cognitive impairment. Major psychopathology in these patients was also associated with ophthalmologic abnormalities and brain calcifications. Widened cortical sulci in CT, found also in patients without psychiatric and neurologic symptoms, may be an early or subclinical signs of CNS disease activity in patients with SLE.

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