The accuracy of diagnosing neuropsychiatric systemic lupus erythematosus in a series of 49 hospitalized patients

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Abstract

Objective

Neuropsychiatric manifestations in patients with systemic lupus erythematosus (SLE) originate from immune-mediated disease (primary neuropsychiatric SLE) or from other pathogenetic mechanisms indirectly related to SLE (secondary neuropsychiatric SLE). The objective of this study is to describe the clinical practice of diagnosing NP-SLE and to assess how often the diagnosis of primary NP-SLE is changed to secondary NP-SLE and vice versa during the follow-up period in a large series of hospitalized SLE patients.

Materials and methods

Data was collected by means of retrospective evaluation of the charts of 191 SLE patients admitted during the period 1986 to 1995.

Results

Of 191 admitted SLE patients, 49 had developed neuropsychiatric signs and symptoms. At admission 30 patients were classified as having primary NP-SLE and 19 patients secondary NP-SLE. During follow-up the diagnosis was changed to primary NP-SLE in 2 patients initially diagnosed as suffering from secondary NP-SLE, and in two patients from primary to secondary NP-SLE. Seizures, cognitive deterioration, psychosis and organic brain syndrome were the most frequent manifestations in primary NP-SLE, whereas in secondary NP-SLE headache, seizures, paresis and organic brain syndrome prevailed. 47% of the primary NP-SLE patients were re-admitted to hospital because of recurrent neuropsychiatric manifestations within 4.5 years, while 10% died due to primary NP-SLE. The prognosis of secondary NP-SLE was dependent on the diagnosis.

Conclusion

In the large majority of patients the initial diagnosis of primary or secondary NP-SLE made upon their admittance to hospital is confirmed during the long-term follow-up.

Key words

Systemic lupus erythematosus, neurological diseases, diagnosis, prognosis.

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Introduction

The neurologic and psychiatric manifestations in SLE can be divided into primary and secondary neuropsychiatric SLE (NP-SLE). Primary NP-SLE is regarded as an immune-mediated disease leading to direct neuronal damage or vascular injury, whereas secondary NP-SLE can be attributed to other pathogenetic mechanisms indirectly induced by SLE (1, 2).

Immunosuppression is the keystone of therapeutic intervention in primary NP-SLE, except in the case of thromboembolic events that can be attributed to the presence of antiphospholipid antibodies. In these patients anticoagulant rather than immunosuppressive therapy is warranted. In secondary NP-SLE the therapy should be targeted at the relevant pathophysiology. In both groups of patients seizures and psychosis should initially be treated with symptomatic therapy.

The manifestations in both categories are diverse in nature and can vary from headache to coma (1, 2). In this respect clear diagnostic criteria have not been formulated. As a result the lifetime incidences reported in various studies range from 11% to 69% (1). No laboratory tests or imaging techniques are available to firmly support the diagnosis of primary NP-SLE (3) and it is therefore difficult to discriminate between primary and secondary NP-SLE.

Because of the therapeutic implications, it is essential that the initial diagnosis is correct. To study the clinical practice patterns of diagnosing NP-SLE and to assess their accuracy in distinguishing between primary and secondary NP-SLE, the charts of hospitalized SLE patients with CNS symptoms followed at the Leiden University Medical Center were analyzed with respect to the clinical characteristics, the diagnosis upon presentation and the diagnosis after follow-up.

Methods

During the period from January 1986 to December 1995, a total of 191 SLE patients were admitted to the wards of rheumatology, neurology, internal medicine and renal diseases of Leiden University Medical Center, a tertiary referral center for the southwestern part of The Netherlands, serving an area of ± 2 million inhabitants. The patients were identified from the hospital's automated information system.

The charts of these patients were retrospectively evaluated. All 191 patients fulfilled at least four of the criteria for SLE, and 49 of them had developed neuropsychiatric signs and symptoms. The signs and symptoms present at the first admission for a neuropsychiatric event and the clinical diagnosis of primary or secondary NP-SLE made by a team of rheumatologists and neurological or psychiatric consultants, were noted. The SLE Disease Activity Index (SLEDAI) for each patient was calculated based on a physical examination, and anamnestic and laboratory parameters determined at admission (4). Although the SLEDAI score tends to be lower when assessed retrospectively, its assessment of disease activity has been reported to be accurate (5). We also documented the radiological findings and SLE criteria met by each patient. Their follow-up was retrospectively monitored by studying their readmission and outpatient records.

If during the first year of follow-up additional information emerged that challenged the initial diagnosis of primary or secondary NP-SLE, this was documented. If new neuropsychiatric signs and symptoms appeared after more than one year, these were considered to be unrelated to the earlier event and the initial classification was not changed. Chi-square testing was performed to detect differences in the frequencies of SLE manifestations between primary and secondary NP-SLE patients. Kaplan-Meier life table analysis was used to assess outcome.

Results

Characteristics of the patients

Twenty-nine of the 30 primary NP-SLE patients and 17 of the 19 secondary NP-SLE patients were female. The age at admission ranged from 16 to 67 years in the primary NP-SLE group (mean 36.3 years) and 15 to 80 years in secondary NP-SLE patients (mean 43.1 years). The time lapse between the diagnosis of SLE and the first NP-SLE event was on average 4.2 years (SEM 0.9) in the primary NP-SLE group versus 7.7 (SEM 2.5) in

the secondary NP-SLE patients. The mean follow-up time was 5.7 years (SEM 0.8) in primary NP-SLE patients and 3.2 years (SEM 1.0) in secondary NP-SLE patients.

The most common features in the primary NP-SLE group were seizures (9), cognitive deterioration (7), (transient) paresis (6) and psychosis or organic brain syndrome (5). A striking number of cases (i.e., 4) with paraparesis due to transverse myelitis or myelopathy were noted. Nine of the primary NP-SLE patients received intravenous cyclophosphamide, 7 azathioprine and 16 corticosteroids; in 10 patients no immunosuppressive therapy was initiated. In the secondary NP-SLE group the most frequent features were headache due to migraine (4), paresis and seizures due to hypertensive encephalopathy (3) and organic brain syndrome due to meningitis tuberculosa (2).

The mean non-CNS SLEDAI score in the primary NP-SLE patients was 7.2 (range 0 - 24) while in the secondary NP-SLE patients the mean score was 8.3 (range 0 - 28).

It was found that in clinical practice the diagnosis of primary NP-SLE was based on the presence of clear signs and symptoms that could not be attributed to hypertension, infection, generalized atherosclerotic disease, renal failure, hepatotoxicity, insufficient pulmonary function or pharmacologic derangements. Furthermore, thromboembolic events in the presence of anticardiolipin antibodies were considered to be evidence of primary NP-SLE. If, on the other hand, the signs and symptoms were mild and an alternative neurologic or psychiatric diagnosis such as migraine, epilepsy, depression or personality disorder could account for the symptomatology, the diagnosis was considered to be secondary NP-SLE.

Table II depicts the frequency of SLE manifestations in the patients. Chi-square testing showed no significant differences between the groups.

Imaging and laboratory tests

MRI scanning revealed abnormalities in 10 of 16 primary NP-SLE cases, consisting of generalized atrophy (n = 3), white matter lesions (n = 4), infarctions (n = 4), and in 2 of 3 patients with paraparesis (myelopathy) an increase in signal emission from the myelum. In the secondary NP-SLE cases, MRI scanning was abnormal in 3 of 9 cases. One scan showed a hemorrhagic stroke in a patient with hypertension, one showed an infarct in an elderly female with generalized atherosclerotic disease, and one scan showed multiple white matter lesions in a patient with encephalopathy due to hepatic failure.

Urinalysis in 11 of the 30 primary NP-SLE patients was abnormal; cellular casts, proteinuria and/or renal failure were present in these cases. In the secondary NP-SLE group, 10 of 17 patients had abnormal urine sediments, proteinuria or renal failure.

Anti-cardiolipin antibodies

The lower part of Table I-A shows the patients with anti-cardiolipin antibodies. In patients nos. 20-30 of the primary NP-SLE group, 4 had lesions on MRI or CT scan indicative of infarctions and possibly related to the presence of anti-cardiolipin antibodies (cases 21, 22, 24, and 28).

In the secondary NP-SLE group, case 47 was believed to be suffering from anti-phospholipid syndrome-related pathology, although the simultaneous presence of atherosclerosis complicated the diagnosis.

Accuracy of the initial diagnosis

At presentation, 30 of the 49 patients were diagnosed with primary NP-SLE while 19 were assessed to have secondary NP-SLE. The clinical data on the individual patients are presented in Table I. In two patients with secondary NP-SLE the diagnosis was changed during the follow-up to primary NP-SLE, while in two patients with primary NP-SLE the initial diagnosis was changed to secondary NP-SLE. In case no. 29 (Table I-B) the diagnosis was changed from “proximal muscle weakness and psychosis due to prednisone” to “transverse myelitis accompanied by psychosis” because of progressive disease. In patient no. 30 the conclusion was changed from “no diagnosis, depressive feelings” to “dementia due to SLE”. Two patients who were initially diagnosed as suffering from primary NP-SLE appeared to have meningitis tuberculosa (cases 48 and 49, Table I-D). In the remaining 17 patients with secondary NP-SLE the neurological deficits were assessed as originating from concomitant disease or from SLE in other organ systems.

Outcome

Our retrospective evaluation showed that 15 of 30 primary NP-SLE patients required re-admission to hospital because of recurrent neuropsychiatric manifestations. Kaplan-Meier analysis revealed that 47% of the patients were re-admitted within 4.5 years after their first CNS event with 8 patients still at risk. Four primary NP-SLE patients died. In three cases the cause of death was related to the neuropsychiatric disease. The fourth patient (case 1) died for unknown reasons at the age of 64 years, after 6.5 years of follow-up.

In the secondary NP-SLE group, the prognosis was dependent on the underlying disease. The patients with thrombotic thrombocytopenic purpura, meningitis tuberculosa and hepatic failure all died in hospital following their first admission, whereas the outcome of the patients with migraine was favourable.

Discussion

This study describes the clinical practice of diagnosing NP-SLE and the accuracy of the initial diagnosis within the setting of a university hospital. The results of this retrospective study suggest that the original diagnosis is usually accurate. During follow-up the diagnosis was changed in only 4 of 49 patients. Two patients (48 and 49) initially assigned to the primary NP-SLE group were actually suffering from meningitis tuberculosa. Patients 29 and 30 were assessed as having secondary NP-SLE, whereas during follow-up their diagnosis was changed to primary NP-SLE.

In retrospect, the diagnosis of secondary NP-SLE was disputable in 10 patients (nos. 29, 30, 34, 37-39 and 43-46). No positive tests can affirm the correctness of the diagnosis in these patients; hence they could have as easily been assigned to the primary NP-SLE group. However, during the follow-up of these patients, who were not given immunosuppressive treatment, only two (29 and

Table I.

A. Primary neuropsychiatric systemic lupus erythematosus (NP-SLE) patients.

No.	Sex	Age at admis.	Dis. dur.	Clinical presentation	CT/MRI brain (unless stated otherwise)	Renal disorders	SLEDAI†	Aca*	Initial therapy**
1	F	40	2.5	Seizures, transient hemiparesis	CT: normal	Proteinuria	9	ND	Cs, Aza, Aed
2	M	51	1.7	Cognitive deterioration, vision derangements	CT: atrophy, infarction	-	1	ND	-
3	F	24	0.1	Psychosis	-	Proteinuria	12	ND	-
4	F	33	16.8	Paresis	CT: normal	Proteinuria	5	ND	-
5	F	67	10.6	Hemiparesis, decreased consciousness	CT: atrophy, infarctions	Renal failure	0	ND	↑ Cs
6	F	24	1.0	Cognitive deterioration and psychosis	CT and MRI: normal	Proteinuria, hematuria, cellular casts	9	ND	↑ Cs, iv Cyc
7	F	42	0.1	Cognitive deterioration	CT: atrophy, hypodense lesions	-	1	ND	-
8	F	21	2.9	Seizures and psychosis	CT: normal	-	4	ND	Cs
9	F	58	10.9	Paraparesis	MRI: high signal emission myelum	-	5	ND	Cs, iv Cyc
10	F	34	2.5	Paresthesia, inability to speak, vertigo, vision derangements	CT: infarction	-	1	ND	Cs, Aza
11	F	35	1.6	Headache, vision derangements, attributed to pseudotumor cerebri	CT: normal	Proteinuria, hematuria, cellular casts	20	ND	↑ Cs, Aza
12	F	57	8.4	Chorea	-	-	0	-	Oac, Aps
13	F	46	9.5	Cerebellar ataxia	MRI: atrophy, white matter lesions	-	1	-	Iv Cyc, antiplatelet
14	F	17	0.1	Seizures, paresis, decreased consciousness	CT: normal	-	15	-	Cs, iv Cyc
15	F	17	0.1	Seizures and polyneuropathy	MRI: normal	-	12	-	-
16	F	43	3.4	Paraparesis	MRI: high signal emission myelum	-	2	-	Iv Cyc
17	F	18	2.1	Seizures	MRI: normal	Proteinuria, hematuria, cellular casts	15	-	↑ Cs, Aza, Aed
18	F	35	8.1	Seizures and organic brain syndrome	MRI: atrophy; CT: infarctions	-	2	-	Cs, iv Cyc, Oac, Aed, Aps
19	F	24	2.9	Seizures	MRI: infarction	-	3	-	↑ Cs, ↑ Aza, Aed
20	F	39	0.1	Paresis, vision derangement, unconsciousness	CT and MRI: normal	Proteinuria, hematuria, cellular casts, renal failure	22	+	Cs, Aza
21	F	22	0.4	Cognitive deterioration	MRI: multiple infarctions	-	1	+	Oac
22	F	33	4.2	Cognitive deterioration	MRI: atrophy, infarctions, white matter lesions	-	5	+	↑ Cs, iv Cyc (already had Oac)
23	F	43	1.4	Coma, facial nerve palsy	CT: contrast pattern fitting sterile meningitis	-	3	+	↑ Cs
24	F	16	0.7	Seizures	MRI and CT: multiple infarctions	Proteinuria, hematuria, cellular casts	19	+	↑ Aza, Oac, Aed
25	F	61	0.9	Paraparesis	MRI: normal myelum	-	6	+	Iv Cyc, Oac
26	F	63	16.2	Seizures	CT: normal	-	0	+	-
27	F	23	0.1	Cognitive deterioration, decr. consciousness	MRI: multiple white matter lesions	Proteinuria	24	+	Cs, antiplatelet
28	F	24	6.1	Hemiparesis	MRI: multiple white matter lesions; CT: infarctions	Proteinuria, hematuria, cellular casts, renal failure	10	+	Cs, iv Cyc, Oac

B. Primary neuropsychiatric systemic lupus erythematosus (NP-SLE) patients, initially misclassified as having secondary NP-SLE.

No.	Sex	Age at admis.	Dis. dur.	Clinical presentation	CT/MRI brain (unless stated otherwise)	Renal disorders	SLEDAI†	Aca*	Initial therapy**
29	F	24	6.8	Proximal muscle weakness and psychosis	CT: normal	-	2	+	Aps
30	F	55	5.3	Depression	MRI: normal	-	2	+	-

C. Secondary neuropsychiatric systemic lupus erythematosus (NP-SLE) patients.

No.	Sex	Age at admis.	Dis. dur.	Clinical presentation	Diagnosis	CT/MRI brain (unless stated otherwise)	Renal disorders	SLEDAI†	Aca*	Initial therapy**
31	F	36	2.2	Headache, decreased consciousness, seizures	Hypertensive encephalopathy due to renal failure	CT: normal	Proteinuria, hematuria, cellular casts, renal failure	17	ND	-
32	F	31	1.2	Confusion	Neurologic disorder due to mycoplasma pneumonia	MRI and CT: normal	-	4	ND	-
33	F	30	12.4	Hemiparesis, decreased consciousness, seizures	Hemorrhagic cerebrovascular accident and seizures	MRI and CT: hemorrhagic cerebrovascular accident	Proteinuria and cellular casts	9	ND	Aed
34	M	80	33.7	Depression	Depression	-	-	0	ND	-
35	F	15	0.1	Paresis, seizures, decreased consciousness	Hypertensive encephalopathy due to renal failure	CT: normal	Hematuria, renal failure	10	ND	↑ Cs, iv Cyc, Aed
36	F	37	10.5	Cognitive deterioration, polyneuropathy	M. Wernicke-Korsakow	CT: atrophy	-	6	ND	-
37	F	34	0.9	Headache, derangements of vision	Migraine	-	Proteinuria, hematuria, cellular casts	17	ND	-
38	M	50	17.5	Depression	Personality disorder	MRI: normal	Proteinuria	4	ND	↑ Cs
39	F	35	2.6	Seizures	Primary epilepsy	-	Hematuria	4	-	–
40	F	30	0.3	Cranial nerve palsy	Thrombotic thrombocytopenic purpura	MRI: normal	Proteinuria, hematuria, cellular casts	28	-	Cs
41	F	69	0.2	Paresis, decreased consciousness, seizures	Encephalopathy due to hepatic failure	MRI: multiple white matter lesions	ND	1	-	Aed
42	F	37	11.3	Seizures	Hypertensive encephalopathy due to renal failure	-	Proteinuria, hematuria, cellular casts, renal failure	20	-	Cs, Aza, iv Cyc
43	F	20	0.1	Headache, paresthesis, vision derangements	Migraine	MRI: normal	Proteinuria, hematuria, cellular. casts, renal failure	16	+	↑ Cs, Aza
44	F	34	6.3	Headache and decreased consciousness	Migraine	-	-	1	+	-
45	F	43	8.2	Headache	Migraine	MRI: normal	-	0	+	-
46	F	36	2.3	Transient diplopia and vertigo	-	MRI: normal	-	5	+	-
47	F	71	0.1	Paresis and cerebellar ataxia	Atherosclerotic stroke	MRI and CT: stroke in cerebello	-	0	+	Oac

D. Secondary neuropsychiatric systemic lupus erythematosus (NP-SLE) patients initially misclassified as having primary NP-SLE.

No.	Sex	Age at admis.	Dis. dur.	Clinical presentation	Diagnosis	CT/MRI brain (unless stated otherwise)	Renal disorders	SLEDAI†	Aca*	Initial therapy**
48	F	61	35.2	Depression, depersonalisation	Meningitis tuberculosa	CT: normal	Proteinuria	12	ND	↑ Cs
49	F	68	0.6	Headache, organic brain syndrome	Meningitis tuberculosa	CT: normal	ND	2	+	↑ Cs, iv Cyc

ND: not determined; †SLEDAI: Systemic Lupus Erythematosus Disease Activity Index without CNS items; *Aca: anticardiolipin antibodies.
**Initial immunosuppressive, anti-thrombotic and symptomatic therapy instituted after the CNS event: Oac: oral anticoagulants; Aps: antipsychotic drugs, Cs: corticosteroids; Aza: azathioprine; Aed: anti-epileptic drugs; iv Cyc: intravenous cyclophosphamide; Antiplatelet: platelet aggregation inhibitory drugs; (↑): increase.

Table II. SLE manifestations preceding the first admission for NP-SLE.

	Primary NP-SLE	Secondary NP-SLE	P-value
Skin lesions	55%	72%	0.31
Joint involvement	93%	89%	0.61
Renal disorders	37%	44%	0.59
Serositis	34%	33%	0.94
Vasculitis	28%	17%	0.39
Fever due to SLE	48%	61%	0.39
Thrombopenia	30%	44%	0.31
Leukocytopenia	35%	59%	0.12
ANA	96%	100%	0.41
Anti-dsDNA	81% (n = 21)	69% (n = 16)	0.39
Anticardiolipin antibodies	58% (n = 19)	60% (n = 10)	0.91
Complement consumption	81% (n = 16)	87% (n = 15)	0.68

30) developed major neuropsychiatric symptoms, thus suggesting that the initial classification was reasonably accurate.

In this study, among a total of 191 SLE patients seen, 15.7% were admitted with primary NP-SLE and were subsequently followed for 5.7 years. This figure is in accordance with a similar study reporting that 18% of SLE patients admitted to a rheumatology department had experienced neuropsychiatric manifestations (6). The different neuropsychiatric manifestations associated with SLE have been reported in widely varying frequencies in the literature (1, 6, 7). Our data lies within the reported ranges, except for the symptom of transverse myelitis; we registered a frequency of 14% whereas the literature reports a frequency of 0 to 3% (1). Although the possibility of referral bias cannot be excluded, this discrepancy suggests that transverse myelitis might be more common than previously thought. There are no studies reporting the frequency of different symptoms of secondary NP-SLE as yet.

The value of magnetic resonance imaging in NP-SLE remains equivocal. Although a high correlation between active NP-SLE and MRI abnormalities has been reported (8), others have found apparent MRI abnormalities in SLE patients without neuropsychiatric manifestations (9). Moreover, MRI lesions have also been detected in elderly subjects without apparent neurological or autoimmune disease (3, 10). The pathological substrate of these lesions is thought to be gliosis, edema and demyelination associated with vasculitis (3) or simple lacunar spaces in the brain parenchyma filled with extracellular fluid. This last reported finding was based on a series of 8 postmortem MRI scans and the subsequent pathological examination (11). In our study the MRI scan proved to be abnormal in 10 of 16 primary NP-SLE cases. These figures indicate that, despite the conflicting results in the literature, in daily clinical practice MRI scanning can be contributory to the diagnosis of primary NP-SLE. This might be explained by the fact that the NP-SLE patients in our series had just experienced their first neuropsychiatric event. Such patients are less likely to have scarring of the brain tissue. Therefore, in this patient group MRI abnormalities might be better correlated with active NP-SLE than in a group of patients with a history of neuropsychiatric disease.

The frequency of symptoms indicative of nephritis in the primary NP-SLE group was lower than in the secondary NP-SLE group (11/ 30 versus 10/17 patients, $p = 0.14$). It has been reported that lupus nephritis and NP-SLE are at least in part mutually exclusive (12). However, it should be realized that the prevalence of two manifestations simultaneously will by definition be smaller than the prevalence of one single manifestation.

Primary NP-SLE is diagnosed after a mean SLE disease duration of 4.2 years. The mean time lapse between the onset of SLE and the development of lupus nephritis is approximately three years (13). The similarity of these figures supports the hypothesis that primary NP-SLE, like lupus nephritis, is a disease manifestation of SLE driven by active immunopathologic mechanisms.

Therapy in NP-SLE can be divided into three categories: immunosuppressive, anti-thrombotic and symptomatic treatment. In the patients described here, cognitive deterioration, transverse myelitis and myelopathy, cerebellar ataxia and organic brain syndrome were considered to be indications for therapy with intravenous cyclophosphamide. This is in accordance with the conclusions drawn from several case series of NP-SLE patients that advocated aggressive therapies (14-16). In a retrospective study of 48 consecutive patients with primary NP-SLE, therapy consisted in many cases of symptomatic treatment and in only one case of i.v. cyclophosphamide (6). This treatment regimen was justified by the relative good prognosis of the patients, in whom the CNS events turned out to be self-limiting and non-recurrent. In contrast, we found that 47% of our primary NP-SLE patients, despite more aggressive treatment, were re-admitted within 4.5 years after their first admission and that at least in 3 patients death could be attributed to the consequences of NP-SLE. Extensive reviews on this subject point to patient selection and the heterogeneous character of the manifestations as the most likely explanations for the discrepancies in various reported results (1, 17).

The present study describes the clinical practice of diagnosing NP-SLE and shows that primary NP-SLE can generally be differentiated from secondary NP-SLE at a patient's first admission for neuropsychiatric signs and symptoms. Hence, it should be possible to conduct prospective trials on primary NP-SLE patients to determine whether these patients would benefit more from an aggressive or a conservative treatment approach.

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