Chorea in Systemic Lupus Erythematosus and "Lupus-Like" Disease: Association With Antiphospholipid Antibodies

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CHOREA, in association with systemic lupus erythematosus (SLE), is a recognized but rare manifestation of CNS involvement. As it manifests clinically, the chorea in no way differs from that occurring in other conditions, ie, associated with rheumatic fever (Sydenham's or Huntington type). By 1985, there have only been 70 reported cases of SLE and related disorders.[1-12] Of these, at least four[1-4] appeared during pregnancy (chorea gravidarum), while in one patient[5] it appeared in the postpartum period with psychosis. The chorea occurred either as an isolated phenomenon or with other CNS symptomatology.[6]

Although CNS involvement in SLE is common, occurring in 50% to 70% of cases,[7] chorea has been reported in <2% of these patients. It usually appears early in the course of the disease,[6] and may precede the diagnosis of SLE by as long as 7 to 8 years in some cases,[8,9] while in others it may present as long as 12 years after the initial manifestations of SLE.[10,11] In a number of patients, chorea was ascribed to acute rheumatic fever, but in retrospect, this may have been a prodrome of SLE.

In the reports to date, the duration of chorea has varied from days to years, but there has been no close relationship to SLE disease activity.

We recently reported a syndrome consisting of multiple thromboses, recurrent abortions, and CNS disease.[12] This constellation of features has been strongly associated with the presence of antiphospholipid antibodies[13] and often occurs in the absence of other classical features of SLE.

In our clinical studies, it became apparent that a number of patients with chorea had increased anticardiolipin antibody levels. In this report, we discuss the clinical and serologic details of the first 12 patients with chorea and SLE or "lupus-like" disease, nine of whom had elevated anticardiolipin antibody levels and the lupus anticoagulant.

MATERIALS AND METHODS

Patients

The 12 patients documented represent a retrospective study of 400 patients observed over a 5-year period (1980 to 1985) with a diagnosis of SLE or "lupus-like" disease seen at our clinic in London, and of 100 similar patients attending the Lupus Clinic of the University Hospital (Utrecht, The Netherlands) giving a frequency of 2.4%.

The SLE patients fulfilled at least four of the American Rheumatism Association (ARA) classification criteria for diagnosis.[14] Patients with "lupus-like" disease had symptoms and signs compatible with SLE, but did not fulfill all of these criteria. Approximately 20% to 30% of patients referred to our lupus clinic seem to fall into this latter category, which also contains a high percentage of patients demonstrating antiphospholipid antibodies.

Methodology

All patients had the standard investigations performed for SLE.[15] The lupus anticoagulant activity was measured by the modified mixing partial thromboplastin time with kaolin (PTTK) by the method of Proctor and Rapaport[16] or by a modified mixing activated partial thromboplastin time (APTT).[17] Antibodies to cardiolipin were measured in serum stored at −20°C by an enzyme-linked immunosorbent assay (ELISA) technique described elsewhere by Gharavi et al,[18] using a modification of the original radioimmunoassay developed by Harris et al.[13] In brief, plates were coated with cardiolipin (50 μg/mL) and blocked for two hours with 10% adult bovine serum (ABS) in PBS. Patient sera were diluted 1:50 in 10% ABS/PBS and incubated for three hours. The plates were washed and enzyme labeled affinity purified antihuman IgG or IgM in 10% ABS/PBS was added and incubated for 90 minutes. The plates were washed three times with PBS and 50 μL of 1 mg/mL substrate (P-nitrophenyl/

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phosphate disodium hexahydrate, Sigma, London) in diethanolamine buffer, pH 9.8 was added. After 45 minutes of incubation in the dark, absorbance was measured by a Titretek multiscanner (Flow Laboratories, London). Results were reported in APL units, as described in the International Workshop to standardize the anti-cardiolipin antibody test held in London, April 1986.[19]

ILLUSTRATIVE CASES

Patient No. 5 (Lupus-Like Disease)

An Indonesian woman, born in 1949, was admitted in 1979 with pneumonia, thrombocytopenia ($85 \times 10^{9/1}$), Coombs' positive hemolytic anemia (Hb 6.3 g/dL), hypergammaglobulinemia (14.2 g/L), an increased serum creatinine (278 μmol/L) and mild proteinuria (0.3 g/24 h). The rheumatoid factor and Venereal Disease Research Laboratory (VDRL) test were negative and "lupus-type" anticoagulant was detected (APTT, 53 seconds; control, 35 seconds). One year later the patient developed hypertension (190/110 mmHg) which responded to labetolol.

In December 1981, at the age of 32 years, the patient was admitted with the sudden onset of left-sided chorea, hyperreflexia, rigidity, slowness of movement, and akinesia. The antinuclear antibody (ANA) was weakly positive (1:10) and the Crithidia luciliae test for anti-dsDNA antibodies was also positive. A computed tomography (CT) brain scan showed severe brain atrophy. Although the choreiform movements diminished over 4 weeks, they did not disappear until 7 months later, in July 1982. The patient complained of persistent dizziness and became progressively more apathetic. By April 1983, the chorea was absent, but hyperreflexia, rigidity, and bilateral Babinski signs were noted.

In July 1983, the patient commenced having grand mal seizures that continued intermittently over the next year and a half. The EEG showed diffuse and severe abnormalities. There was a gradual and continuing loss of higher intellectual function. At this time, the lupus anticoagulant was again found to be positive.

In June 1984, the blood pressure was still elevated (diastolic blood pressure 110 mmHg), but renal function and proteinuria were stable. In July 1985, the patient was admitted because of a sudden right-sided hemiplegia, and a left-sided cerebral infarction was confirmed on CT scan. She eventually had to be placed in an institution for the chronically ill, bedridden and completely inactive.

Patient No. 7 (SLE)

A white, 12-year-old girl presented in 1977 with a seronegative polyarthralgia, leucopenia (37×10^9/L), mild thrombocytopenia (140×10^9/L), a positive ANA test (1:1000), a biological false positive VDRL test, and hypergammaglobulinemia. In 1978, a thrombosis of the left femoral artery occurred, and although blood counts, renal function, and serum complement levels were normal, a Crithidia luciliae test for anti-dsDNA was positive and SLE was diagnosed. An endarterectomy was performed and the circulation of the left foot normalized. Anticoagulant therapy was given for 6 months.

In November 1979, bilateral chorea suddenly occurred and the patient was admitted to the hospital. The chorea diminished on therapy with haloperidol (2×1.5 mg/d). Two weeks after admission, severe loin pain and hematuria, diagnosed as renal infarction, occurred, followed by recurrent convulsions and coma. Pyramidal and extrapyramidal tract signs were found on examination. The EEG was diffusely abnormal and lupus erythematosus (LE) cells were found to be positive. Diphenylhydantoin (4×75 mg d) was started and the dose of prednisolone was kept constant at 60 mg/d. The patient regained consciousness after four days, but bilateral chorea was a persisting neurologic abnormality. This dominated her daily life, and treatment with haloperidol or pimozide, administered for prolonged periods in varying doses, was unsuccessful. The intensity and hemilocation of the chorea varied. In September 1981, a CT brain scan, a radionucleide brain scan, and lumbar puncture (LP) were unremarkable. On several occasions, low platelet counts (100×10^9/L) and low levels of C4 (12% to 34%; normal range, 37% to 161%) were noted. Antibodies to extractable nuclear antigen (ENA) were absent. In August 1982, an attempt to influence the chorea with an increased dose of prednisolone (60 mg/d) was unsuccessful.

In March 1984, a mild right-sided hemiparesis occurred and a CT brain scan showed a large parietocentral infarction. Treatment was restarted with prednisolone (60 mg/d) together with oral anticoagulants. Over the next year and a half, the neurologic symptoms gradually disappeared with a marked improvement of the chorea, which had appeared to be almost therapy-resistant in the pre-stroke period.

Patient No. 8 (SLE)

A 60-year-old white woman was diagnosed as having myasthenia gravis at the age of 24, and had been treated with pyridostigmine bromide (Mestinon, Roche, UK). In 1963, at the age of 38, SLE was diagnosed because of polyarthritis, pericarditis, thrombocytopenia (80×10^9/L), a positive ANA (1:100), and a positive LE cell preparation. The patient was treated with prednisolone (10 mg/d). In 1973, a deep venous thrombosis of the left leg occurred and in 1978, hypertension (blood pressure 205/110 mmHg) was found and treated with a beta-blocking agent (Tenormin). In 1981, the patient noticed macroscopic hematuria and a prolonged APTT was found. This was proven to be due to a "lupus-type" anticoagulant (APTT, 74 seconds; control, 39 seconds). Between October 1982 and October 1983, the patient had three transient ischemic attacks (TIAs) with paraesthesia in the right part of the face and tongue together with aphasia. Angiography revealed no abnormalities. Treatment with prednisolone (10 to 12.5 mg on alternate days) was continued in addition to anti-hypertensive treatment. Several further TIAs occurred with episodes of depersonalization. On admission to the hospital in October 1985, the patient demonstrated chorea of the extremities, head, and tongue. No other neurologic abnormalities were found. Laboratory findings included a normochromic, normocytic anemia (Hb 11 g/dL), weakly positive Coombs' test, leucopenia (1.7×10 g/L), thrombocytopenia (62×10g/L), a slightly elevated serum creatinine (156 μmol/L) without proteinuria and a normal urine sediment, and hypergammaglobulinemia was present (20.7 g/dL). The ANA was positive (1:100), as were tests for anti-dsDNA antibodies (Crithidia luciliae test), ENA (Ro), and anti-acetylcholine receptor antibodies. Tests for lupus

anticoagulants were positive. CT and NMR scans were normal. Treatment with oral anticoagulants was started. Although the choreiform movements were still present, they were markedly diminished at follow-up 3 months later.

RESULTS

Six patients (patients no. 7 to 12) fulfilled the ARA classification for SLE, while the other six had clinical features and/or laboratory features suggestive of SLE, but less than four of the ARA criteria for the diagnosis of SLE. These latter six patients (patients no. 1 to 6) were referred to as having "lupus-like" disease.

The clinical and laboratory features of our group of patients are given in Table 1. One patient (patient no. 3) had a history of chorea and polyarthralgia several years before the onset of other symptoms. At that time, there were no other features suggestive of rheumatic fever (eg, carditis or increased antistreptolysin (ASLO) titers), and it is probable that this represented the initial manifestation of the illness.

Venous or arterial occlusions were observed in four patients. Most patients (ten of 12) suffered from polyarthralgias or polyarthritis, and arthritis was recurrent in two patients. Glomerulonephritis was present in four of 12 patients. (Biopsy proven in two; in the other two, clotting abnormality had prevented this investigation.) Vasculitis (skin) was evident in four of 12 patients during illness, while Sjogren's syn-

Table 1. General Clinical Symptomatology and Laboratory Features

Patient No.	Sex	Age	Related to Phospholipid Syndrome	Other Major Clinical Symptoms	Laboratory Features DNA	ENA	ANA
"Lupus-like" diseases							
1	F	36*	Thrombocytopenia Thrombophlebitis Recurrent abortions (5) Retinal vein thrombosis	Raynaud's	–	+(Ro)	+(1:2,560)
2	F	29*	Thrombocytopenia DVTs (2) PE (1)	Polyarthritis Raynaud's Vasculitis (splinters)	–	+(Ro)	+(1:40)
3	F	28*	—	Polyarthritis	–	+(La)	+(1:10,000)
4	F	24*	—	Polyarthralgias Glomerulonephritis (biopsy proven)	–	–	+(1:100)
5	F	36	Thrombocytopenia	?Glomerulonephritis (no biopsy)	–	–	+(1:10)
6	F	31	Recurrent Abortions (2) Thrombocytopenia (ITP)	Choroiditis and retinal detachments	–	–	+(1:40)
Systemic lupus erythematosus							
7	F	20†	Thrombocytopenia Peripheral arterial occlusion Renal infarction	Polyarthralgias	–	–	+(1:100)
8	F	60†	Thrombocytopenia DVT (x2)	Polyarthritis Pericarditis ?Glomerulonephritis (no biopsy)	–	+(Ro)	+(1:100)
9	F	37†	—	Psychosis Polyarthralgias Raynaud's Discoid LE Polymyositis	–	–	+(1:10)
10	F	21†	Thrombocytopenia	Vasculitis (splinters)	–	+(Ro)	+(1:80)
11	F	37†	PE (1)	Polyarthralgias Glomerulonephritis (biopsy proven) Pleurisy	+	+(Ro)	+(1:40)
12	F	39†	—	Psychosis Vasculitis (skin) Discoid LE Aseptic necrosis of hips	–	+(Ro)	+(1:20)

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolus.

*Age in 1986.

†Age in 1985.

drome, Raynaud's phenomenon, and polyserositis were uncommon (two patients with each). Thrombocytopenia was present in seven patients. Most patients were DNA-negative (11 of 12), while all were ANA-positive, several in low titer only (three of 12). Antibodies to ENA were present in five of 12 patients (four, Ro-positive, one La-positive [a patient with Sjogren's syndrome]).

The neurologic symptomatology is given in Table 2. Chorea was the earliest sign of CNS involvement in nine of 12 patients. Four patients with antiphospholipid antibodies developed cerebral infarction as demonstrated by CT scanning, while a further three suffered from TIAs. However, CT scanning performed on six patients at the time of chorea was normal in five, whereas the other showed severe cortical atrophy. This patient developed dementia simultaneously with the appearance of chorea (case no. 5). In case no.

Table 2. Neurologic Symptomatology in Patients With "Lupus-Like" Disease

Patient No.	Chorea				Neurologic Symptomatology (Chronologic)
	Age of Onset	Episodes	Duration	Localization	
1	25	1	Months	Generalized	Chorea (CT: ND) Epilepsy Migraine TIAs Memory loss
2	21	1	Months	Generalized	Chorea (CT: ND) TIAs Migraine Cerebral infarct (CT: neg)
3	14	2	Weeks	Generalized	Chorea (CT: ND) Memory loss Cerebral infarct (CT: neg) Migraines Dyslexia Chorea-athetosis
4	18	6	Days-weeks	Generalized Left-sided Right-sided	Chorea (CT: neg) Memory loss Migraine TIA (1 episode)
5	32	1	Months	Left-sided	Chorea (CT: severe cortical atrophy) Vertigo Dementia Epilepsy Cerebral infarct (CT: pos)
6	20	1	Months	Left-sided	Chorea Polyneuritis ↓ Mental function
7	14	1	Years	Generalized	Chorea (CT: neg) Epilepsy Coma Cerebral infarct (CT: pos)
8	60	1	Months	Generalized	Myasthenia Gravis TIAs Chorea (CT and NMR: neg)
9	34	2	Months	Generalized	Chorea Brain stem/cerebellar (CT: pos) Coma
10	20	1	Months	Left-sided	↓Mental function Chorea (CT: ND)
11	32	1	Months	Generalized	Migraine (CT: ND) Chorea/personality changes
12	17	1	Months	Generalized	Chorea (CT: neg)

Abbreviations: ND, not done; Neg, negative; Pos, positive.

8, an NMR scan was also negative at the time of chorea.

Antiphospholipid Antibodies

Antiphospholipid antibodies include the VDRL, lupus anticoagulant, and anticardiolipin antibodies (IgG and IgM) (Table 3). Nine of 12 patients had antiphospholipid antibodies in serum at some stage of their illness. Of these, samples were obtained in six patients at the time of chorea, and five of six had antiphospholipid antibodies. Three patients demonstrated antiphospholipid antibodies some time after chorea occurred. Sera from these patients had not been tested at the time of chorea.

DISCUSSION

Several comprehensive reviews of the association between chorea and SLE, including isolated case reports, have been published over the past 10 years. Lusins and Szilagyi[20] published their own three cases and reviewed 28 from the world literature in 1975, followed by a review of 34 and a further three new cases by Herd et al.[21] The most recent reviews were those of Bruyn and Padberg[6] and Bouchez et al who commented on the association of the "lupus anticoagulant" with chorea in their three patients.[22] Although Bruyn and Padberg collected 52 cases, not all were adequately documented. They summarized the neuropathologic findings in 11 patients, three of whom had lesions involving the basal ganglia accompanied by thrombotic occlusion of vessels. Occlusions involving more distant cortical vessels were found in the other eight patients. In addition to these changes, infarcts, diffuse scattered petechial hemorrhages, subarachnoid hemorrhage, fibrinoid degeneration of arteries with perivascular infiltration, subpial hemorrhagic infarction, and vasculitis were also seen.

As only 20% of all reported cases of chorea had pathologic examinations, it is difficult to draw definite conclusions, and previous investigators could only speculate as to its pathogenesis.

The pathogenesis of CNS involvement in SLE is generally poorly understood. From neuropathologic studies in SLE patients with CNS manifestations, it can be concluded that although vascular changes are often found, vasculitis or a relationship to vasculitis elsewhere is absent.[23-25]

Recent reports suggest that antiphospholipid

Table 3. Antiphospholipid Antibodies

Patient No.	Date Sample Taken	VDRL	LA	ACLA IgG	ACLA IgM	Chorea
"Lupus-like" disease				(n – <5)	(n = <3.2)	
1	1984	+	+	65.4	18.3	Absent
2	1984	–	+	71.0	–	Absent
3	1984	–	+	9.8	20.1	Absent
4	1984 (June)	–	+	3.8	7.5	Absent
	1984 (Dec)	–	+	100.0	–	Present
5	1982	–	ND	12.5	5.8	Present
	1984	–	+	5.0	14.7	Absent
6	1984	–	–	–	–	Absent
Systemic lupus erythematosus				(n = <5)	(n = <3.2)	
7	1981	+	ND	18.5	–	Present
	1984 (Jan)	+	+	19.4	ND	Present
	1984 (April)	+	+	44.2	15.9	Present
8	1981	ND	+	ND	ND	Absent
	1985	–	+	100.0	–	Present
9	1982	ND	ND	–	–	Present
	1984	–	+	–	–	Absent
10	1983	–	+	ND	ND	Absent
	1984	–	+	19.7	74.5	Present
11	1984	–	–	–	–	Absent
12	1984	–	–	–	ND	Absent

Abbreviations: VDRL, Venereal Disease Research Laboratory; LA, lupus anticoagulant; ACLA, anticardiolipin antibody = results expressed as APL units; ND, not done.

antibodies occur in approximately 25% of SLE patients.[26] The clinical complications of SLE most frequently associated with the presence of these antibodies are stroke, recurrent thromboses (venous and other large vessel arterial), recurrent fetal loss, and thrombocytopenia. The association of chorea and the presence of antiphospholipid antibodies in this report is striking, being present in nine of our 12 patients with chorea.

Given reports of the strong association between thrombosis and antiphospholipid antibodies, it is tempting to postulate that chorea may be a result of thrombosis of small vessels supplying the basal ganglia. On the other hand, CNS tissue contains large quantities of phospholipid and it is conceivable that these antibodies may cause chorea by binding phospholipid in basal ganglia. The demonstration of normal CT and NMR scans in several patients supports this latter mechanism. The mechanism of action of these antiphospholipid antibodies remains obscure, but the concept of primary endothelial cell damage and impairment of production of endothelial cell products or damage to platelets are the main hypotheses offered.

Carreras et al[27] postulated that they may facilitate coagulation by preventing the release of arachidonic acid from blood vessel endothelium. Prostacyclin production is reduced and platelet aggregation might occur. Inhibition of prekallikrein (Fletcher Factor) and the resulting impairment of fibrin clearance was suggested by Angles-Cano et al,[28] and this has also been demonstrated in several patients by Sanfellipo and Drayna[29] and Elias and Eldor.[30]

Comp et al[31] have described IgG from two patients with lupus anticoagulant that inhibited the function of human thrombomodulin, the endothelial co-factor in the activation of protein C by thrombin. Thus, the feedback inhibition of coagulation by activated protein C is prevented. This has recently been verified by other workers in Paris.[32] There is also an association with thrombocytopenia and Harris et al[33] suggested that anticardiolipin antibodies may play a direct role in mediating platelet destruction. A recent editorial[34] suggests that lupus anticoagulants primarily damage platelets and increase their adhesiveness, thus initiating thrombosis.

TREATMENT

Both corticosteroids and neuroleptic drugs have been advocated. In one case, prednisolone was effective during several episodes, although spontaneous recovery was seen in this patient at a later date. The spontaneous disappearance of chorea in several other patients, as well as the absence of an effect of prednisolone in another, suggests that patients recover despite, rather than because of, treatment with corticosteroids. We recently commenced treating patients with chorea and antiphospholipid antibodies with oral anticoagulants, believing that chorea may be caused by thrombosis of small cerebral vessels, and in an attempt to prevent future cerebral infarction that occurred in five of our patients. The disappearance of longlasting, previously corticosteroid-resistant chorea in case no. 11 soon after the start of oral anticoagulants suggests that this therapy may have therapeutic value apart from a prophylactic role. In the patient reported by Hodges et al,[35] the dramatic disappearance of chorea within a few days after commencing aspirin also supports the value of therapy directed against blood vessel occlusion.

SUMMARY

Twelve patients with chorea from a population of 500 patients with SLE and "lupus-like" disease were reviewed. Clinical histories, including time relationships of chorea to the systemic illness and other neurologic manifestations, are reported. Chorea appeared early in the course of disease in most patients, but the development of cerebral infarctions or TIAs occurred subsequently in seven of nine patients demonstrating antiphospholipid antibodies. The relationship of chorea to the presence of these antibodies in nine of 12 patients and the therapeutic outcome are briefly discussed.

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