

## Recurrent stroke and multi-infarct dementia in systemic lupus erythematosus: association with antiphospholipid antibodies

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**SUMMARY** Four patients with recurrent stroke and multi-infarct dementia are presented in whom the dementia was progressive and severe. Three of the patients developed the dementia during the course of an illness which was punctuated by repeated episodes of cerebral infarction demonstrated by computed tomographic (CT) scans. The fourth patient presented with an illness dominated by progressive and deteriorating higher mental functions, which culminated in a major stroke 18 months later. Three patients fulfilled the American Rheumatism Association (ARA) criteria for the classification of systemic lupus erythematosus, the fourth had a 'lupus-like' disease. All had livedo reticularis, severe migraines, and also demonstrated antibodies to phospholipids. All four patients suffered deep vein thromboses.

The occurrence of thrombotic cerebral occlusions is well known in systemic lupus erythematosus (SLE), and because cerebral vasculitis has been shown to be relatively uncommon, other factors have assumed importance in its pathogenesis. Progression to dementia in association with recurrent strokes in three patients with SLE, and one with lupus-like disease is recorded. All four patients demonstrated the presence of antiphospholipid antibodies during their illness ('lupus anticoagulant', anticardiolipin antibodies in four, two with false positive Venereal Disease Research Laboratory tests (VDRLs)).

### Patients and methods

#### PATIENTS

The four patients represented all those presenting with recurrent stroke and dementia in association with the lupus anticoagulant and antibodies to cardiolipin seen at the lupus clinic of St Thomas's Hospital, London, over a 2 year period, 1983–1986, out of a population of 400 patients, giving an incidence of 1%.

Accepted for publication 13 March 1987.

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The patients with SLE fulfilled at least four of the ARA criteria for the diagnosis<sup>1</sup>; the patient with lupus-like disease (patient one) had symptoms and signs compatible with SLE but did not fulfil these criteria.

#### METHODOLOGY

All patients underwent the standard investigations performed for SLE. The lupus anticoagulant activity was measured by the modified mixing partial thromboplastin time with kaolin by the method of Proctor and Rapaport.<sup>2</sup> Antibodies to cardiolipin were measured in serum stored at  $-20^{\circ}\text{C}$  by an enzyme linked immunosorbent assay (ELISA) technique described elsewhere by Gharavi *et al.*,<sup>3</sup> using a modification of the original radioimmunoassay developed by Harris *et al.*<sup>4</sup> In brief, plates were coated with cardiolipin (50  $\mu\text{g}/\text{ml}$ ) and blocked for two hours with 10% adult bovine serum (ABS) in phosphate buffered saline (PBS). Patient sera were diluted 1:50 in 10% ABS/PBS and incubated for three hours. The plates were washed and enzyme labelled, 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  $\mu\text{l}$  of 1 mg/ml substrate (*p*-nitrophenyl phosphate disodium hexahydrate, Sigma Chemicals

Ltd) in diethanolamine buffer, pH 9.8, was added. After 45 minutes incubation in the dark, absorbance was made by a Titretex multiscanner (Flow Laboratories, UK) and the results reported as a binding index, taken as the ratio of the optimal absorbance of patients' serum to a mean absorbance of 40 normal control sera.

### Case reports

#### CASE 1

This 52 year old patient was first diagnosed as having SLE in 1983 at the age of 49. In August 1979 she developed right sided weakness, a right sided homonymous hemianopia, right sided hemianaesthesia, right facial paralysis. The electroencephalogram and CT scans were negative.

Between February 1980 and 1981 she suffered multiple cerebral infarcts with at least six lesions seen on CT scan. Concurrently she complained of severe 'migraine-like' headaches, an erythematous macular rash, myalgias, Raynaud's phenomenon, sicca symptoms, and suffered one deep vein thrombosis. On hospital admission she was found to have marked livedo reticularis, the Schirmer's test was positive bilaterally, and blood tests showed a positive antinuclear factor, false positive VDRL (*Treponema pallidum* haemagglutination test (TPHA) negative), a positive lupus anticoagulant and antibodies to cardiolipin. The C3 levels were reduced at 480 µg/l (normal 700 µg/l) but the C4 and CH<sub>50</sub> were within normal limits. Deoxyribonucleic acid (DNA) binding was 3%, RA latex and antibodies to extractable nuclear antigens were persistently negative. The Coombs' test was weakly positive. There was no thrombocytopenia.

Treatment was started with prednisolone, but the minor cerebral episodes continued. Anticardiolipin (aCL) antibody levels remained persistently high despite plasma exchange, and the lupus anticoagulant also remained positive. Warfarin was commenced together with the prednisolone, and dipyridamole 100 mg three times a day was also added. Towards the end of 1983 shortly after stopping the warfarin she developed a further deep vein thrombosis.

From 1983 onwards there was progressive deterioration of cerebral functions. She had poor immediate memory, dyscalculia, finger agnosia, a marked constructional apraxia, and expressive dysphasia. Poor serial 7s and a poor digit forward memory span were also evident. She was unable to distinguish blue and red. She had evidence of multiple infarcts on CT scanning involving the left occipital lobe, the left and right parietal lobes, and right frontal cortex (Fig. 1).

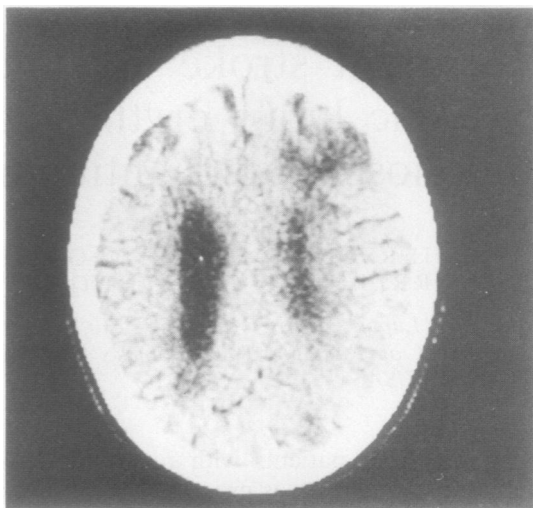


Fig. 1 Unenhanced axial CT scan showing a low attenuation area in the right frontal cortex. This does not enhance. The appearance is of a focal cortical infarct. Other scans at different levels obtained at the same time showed further areas of infarction in the left occipital cortex and both parietal cortices.

She was also found to have a diminished right femoral pulse and an absent left radial pulse, subsequently shown to be due to a subclavian artery occlusion on arteriography.

'Pulse' cyclophosphamide (500 mg) was administered on two occasions at the end of 1983 and early in 1984. Warfarin was recommenced and continued together with dipyridamole.

#### CASE 2

This 33 year old woman had 'rheumatic fever' and chorea at the age of 3 years. She continued complaining of polyarthralgias and at the age of 21 developed pleurisy.

In April 1977 (aged 26) she developed left subclavian vein thrombosis and on admission to hospital was found to have a Coombs' positive haemolytic anaemia. She was treated with prednisolone (80 mg/day) and was also given seven plasma exchanges. The steroids were reduced to a maintenance level of 5 mg twice a day in 1980.

In 1981 she developed a butterfly rash on the face, livedo reticularis, muscle weakness, and myalgia. The weakness progressed and was diagnosed as a Guillain-Barré syndrome, from which she made a full recovery within three to four weeks. A diagnosis of SLE was made in 1982, and she was also found to be mildly hypertensive (blood pressure 160/100-120 mmHg). Recurrent episodes of confusion accompa-

nied by profound weakness became a problem and she underwent a distinct personality change, with marked irritability and constant shouting at her family. She complained of severe migraines and dryness of her eyes, and alopecia became marked. Transient ischaemic attacks (TIAs) consisting of intermittent clumsiness of both hands, accompanied by an expressive dysphasia, were frequent, and it was noted that she had difficulty in making herself understood. She often spoke the wrong words and showed perseveration. Memory was also poor.

On admission to hospital in December 1984 she was mentally slow and had difficulty in describing her illness. Periods of confusion and memory loss were evident. She was Cushingoid, with marked livedo reticularis and mild butterfly rash. She was mildly hypertensive (blood pressure 140/95 mmHg) and a murmur of mitral incompetence was audible. Examination showed her respiratory and gastrointestinal systems were essentially normal. Neurological examination showed that she clearly had impairment of higher nervous control with focal deficits of left homonymous hemianopia and an expressive dysphasia.

She was found to have a retinal vein thrombosis on retinoscopy. The blood count was normal. The erythrocyte sedimentation rate (ESR) was 60 mm/

hour, antinuclear antibodies (ANA) were positive (1/640, speckled), the latex screen, autoantibodies, DNA binding, and antibodies to extractable nuclear antigens were negative. The lupus anticoagulant was present, and both IgG and IgM antibodies to cardiolipin were positive in high titre.

Echocardiography confirmed the presence of a mitral valve lesion and a ventilation/perfusion (V/Q) chest scan demonstrated possible pulmonary emboli. The CT scan demonstrated multiple cerebral infarcts (Fig. 2).

She was anticoagulated with warfarin. Dipyridamole and prednisolone were continued. She also continued to receive antihypertensive therapy.

### CASE 3

The patient first complained of polyarthralgias in 1966 at age 21 years, followed 11 years later by pleural effusions, leucopenia, and thrombocytopenia. SLE was diagnosed and treatment was started with prednisolone. Later in the same year she developed a severe discoid skin rash and almost total alopecia. In 1978, at the age of 35, she had a right deep vein thrombosis, which was treated with warfarin for four months. Intermittent migrainous headaches were frequent. She was maintained on a combination of low dose prednisolone (5–10 mg) and hydroxychloroquine (200 mg) daily. When seen in 1982 she was found to be hypertensive, with marked livedo reticularis. Fluorescein angiography showed a choroiditis.

In 1983 she suffered a stroke, and the lupus anticoagulant was found to be positive. Several months later she noticed deterioration in her vision with grossly diminished visual acuity, and marked restriction of the visual fields was present on ophthalmological examination.

CT scanning demonstrated a right parieto-occipital infarct (Fig. 3) in addition to a left sided occipital infarction several months later.

The hypertension was treated and she was also placed on dipyridamole (100 mg three times a day) and paediatric aspirin (75 mg daily). Dicoumarol was added several months later after a third cerebral infarction.

The lupus anticoagulant remained strongly positive as did aCL antibodies. DNA binding was persistently raised accompanied by low complement levels (C4, C3, and decreased CH<sub>50</sub>), thrombocytopenia ( $74 \times 10^9/l$ ), and raised ESRs during periods of lupus activity. The VDRL was positive at 1/2 (TPHA negative).

When seen in 1984 she was found to have a left homonymous hemianopia. Mentation had become slow and recall poor. She was intermittently confused.

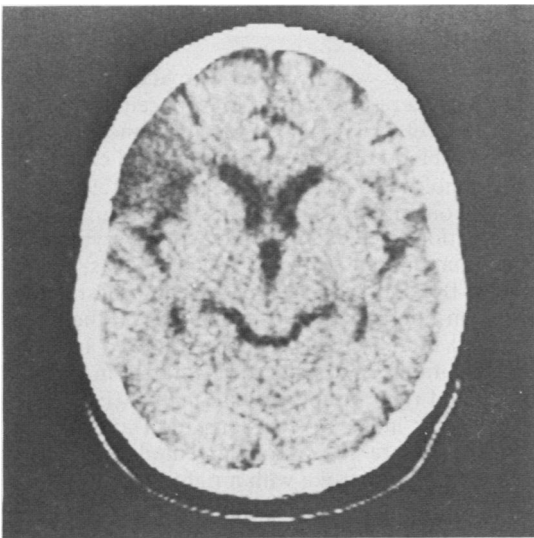


Fig. 2 Unenhanced axial CT scan showing a low attenuation area in the left frontoparietal cortex adjacent to the frontal horn of the left lateral ventricle. This did not enhance. The appearance is of a focal cortical infarct. Other scans at different levels obtained at the same time showed further infarcts in the right frontal and right occipital cortices and a lacunar infarct in the right thalamus.

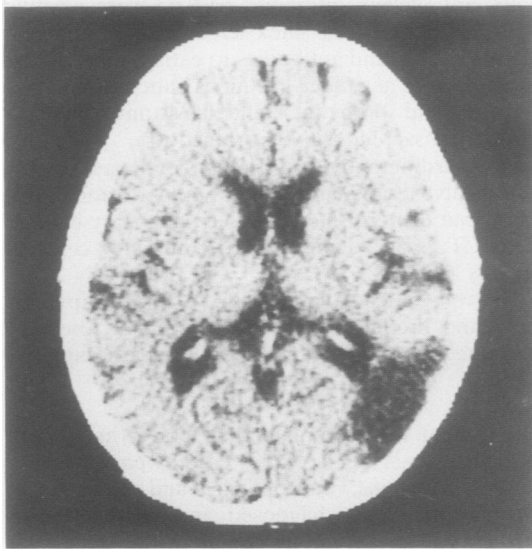


Fig. 3 Unenhanced axial CT scan showing a low attenuation area in the right parieto-occipital cortex adjacent to the occipital horn of the right lateral ventricle. This did not enhance. The appearance is of a focal cortical infarct. A further scan at a different level obtained at the same time showed an additional area of infarction in the left occipital cortex.

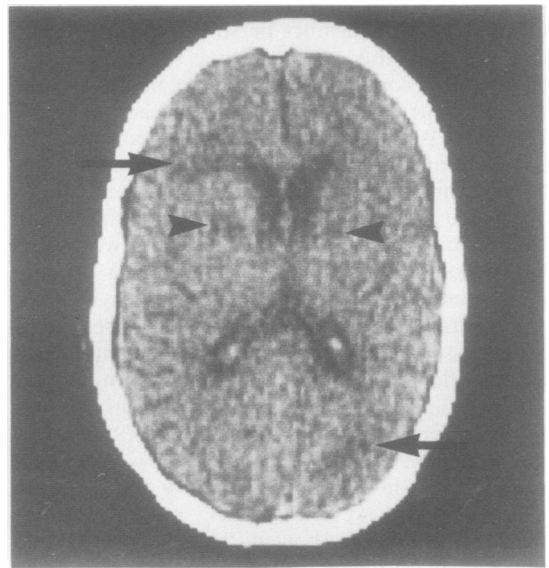


Fig. 4 Unenhanced axial CT scan showing two areas of focal low attenuation bilaterally in the basal ganglia (arrowheads). These did not enhance. The appearances are of lacunar infarcts. Further areas of ill defined low attenuation are present in the left frontal and right occipital white matter (arrows). These also failed to enhance and have the appearance of subcortical infarcts (Binswanger's disease).

In late 1984 she suffered a further massive stroke, which was followed by aphasia and gross right sided weakness. She was admitted to a home for the chronically sick and died there one year after admission in 1985.

#### CASE 4

A 43 year old female college lecturer with a previous history of lupus nephritis and hypertension presented with an 18 month history of deteriorating mental function, personality change, and visual impairment. She had previously had two spontaneous first trimester abortions, an episode of superficial thrombophlebitis, and frequent attacks of migraine. Her intellect and vision had continued to deteriorate despite good control of her blood pressure and there had been no improvement with prednisolone (20 mg daily) and azathioprine (100 mg daily) treatment. Formal psychometric testing confirmed an impairment of higher mental function with a verbal IQ of 93 and a performance IQ of 64, consistent with organic brain disease. Her blood pressure varied within the range 120/80 to 160/110 mmHg. Serological investigations showed a positive ANA titre (1/80), but no antibodies to DNA. Anticardiolipin antibodies of the IgG class were present in high titre, while clotting tests were normal

and the VDRL was negative. Circulating immune complexes were detected in low concentration and the C4 level was reduced. Renal function tests showed a blood urea of 11.1 mmol/l and creatinine of 124  $\mu$ mol/l with creatinine clearance of 39 ml/min and 24 hour urinary protein loss of 0.7 g. Normal investigations included full blood count, erythrocyte sedimentation rate, thyroid function tests, serum vitamin B<sub>12</sub> and red cell folate levels, chest x ray, electrocardiogram, and examination of the cerebrospinal fluid. A CT brain scan showed bilateral lacunar infarcts and subcortical infarcts in the left frontal and right occipital white matter (Fig. 4). A decision was made to start long term anticoagulation, but before it was implemented the patient suffered a major stroke with a right lower quadrantanopia, dysphasia, and a monoplegia of her right upper limb.

#### Discussion

Dementia has a vascular basis in 20–30% of patients; the commonest cause, however, is Alzheimer's disease.<sup>5</sup> Vascular or 'multi-infarct' dementia is usually accompanied by focal neurological signs,

and most patients will have had a number of strokes.<sup>6</sup> Multiple thrombotic disease of the cerebral arteries in SLE is well described, but presentation as dementia or the association with progressive intellectual impairment or mood alterations is unusual.

In this report we describe four patients with recurrent cerebral thrombotic disease, leading to dementia in SLE and lupus-like disease.

Although three out of four of our cases suffered recurrent TIAs or strokes, the fourth patient presented with progressive dementia and only subsequently suffered a major stroke 18 months later.

All four patients had features of the recently described 'anticardiolipin syndrome',<sup>7</sup> including atypical lupus serology (frequently normal anti-DNA titres), peripheral thrombosis, livedo reticularis, migraines, and labile hypertension (Tables 1 and 2).

Guillain-Barré syndrome,<sup>8,9</sup> optic neuritis,<sup>10</sup> chorea,<sup>11-13</sup> pulmonary hypertension,<sup>14-18</sup> and recurrent fetal loss<sup>19-22</sup> appear to be particularly common in this subset of patients, while peripheral large vessel arterial occlusions have been recorded, often with the occurrence of gangrene.<sup>23</sup> The cerebral vasculature is the commonest site of arterial involvement and the frequent occurrence of migraines and TIAs in these patients has been

stressed,<sup>24-26</sup> though statistical evidence of this association is lacking.

Thrombotic cerebral occlusive disease in SLE is infrequently due to vasculitis,<sup>27,28</sup> and other pathogenetic factors may be important. Cases recorded in the 1960s and 1970s may well have been associated with antiphospholipid antibodies. For example, Bennett *et al* described a patient in 1972 with a false positive Wassermann reaction and circulating anticoagulants who had recurrent strokes and a left retinal artery thrombosis.<sup>29</sup> Similarly Silverstein, 10 years earlier, had reported two patients with positive Wassermann tests in his series of five patients with cerebrovascular accidents as the initial manifestation of SLE.<sup>30</sup> The definitive association of antiphospholipid antibodies with cerebral vascular occlusions was first reported by Landi *et al* in 1983.<sup>31</sup> Further reports of this association have appeared since then,<sup>32,33</sup> and other series also show a high frequency of cerebral artery involvement. Lechner and Pabinger-Fasching report its prevalence in 25% of their own patients and also analysed 80 cases reported by others and found a similar incidence.<sup>34</sup> Vermynen *et al* in their review also stress this association,<sup>35</sup> while Derksen *et al* recently studied 20 patients with SLE and CNS manifestations and demonstrated the lupus anti-

Table 1 Clinical features of the four patients with recurrent stroke and multi-infarct dementia

Patient No	Age	Blood pressure	Livedo reticularis	Valve lesions	Sjögren's syndrome	Deep venous thromboses	Migraines	Other CNS features
1	52	↑	++	+(MI)	+	+(2)	++	—
2	33	↑	++	+(MI)	+/-	+	++	GBS, TIAs
3	40	↑ ↓ (labile)	++	—	—	+	++	Choroiditis
4	43	N	++	—	—	+	++	—

CNS=central nervous system; MI=mitral incompetence. GBS=Guillain-Barré syndrome. TIAs=transient ischaemic attacks.

Table 2 Laboratory features of the four patients with recurrent stroke and multi-infarct dementia

Patient No	DNA	ENA	ANA	VDRL	PI	Haemolytic anaemia	Antiphospholipid antibodies	
							aCL	LA
1	-(3%)	-ve	+	+	Normal	+	IgG = 320 U IgM = -ve	+
2	-(19%)	-ve	+(1/640)	ND	Normal	+	IgG = 10.7 U IgM = 3.6 U	+
3	+(72%)	+(Ro,La)	+	+	↓ (74 × 10 <sup>9</sup> /l)	-	IgG = 80 U IgM = -ve	+
4	-(9%)	+(Ro)	+(1/80)	-	Normal	-	IgG = 75 U IgM = -ve	+

DNA = dsDNA binding (Farr assay) (normal <30%); ENA = antibodies to extractable nuclear antigens; ANA = antinuclear antibodies; VDRL = Venereal Disease Research Laboratory test; PI = platelet count; aCL = anticardiolipin antibodies, APL units (normal IgG <5.0 U; IgM <3.2 U); LA = lupus anticoagulant; ND = not done.

coagulant in eight (40%), four of whom had a history of cerebral infarction.<sup>36</sup> Hart *et al* in 1984 reviewed the cases of seven young adults (<40 years) with cerebral infarction and the lupus anticoagulant, only four of whom only had SLE.<sup>37</sup> Three of the seven had multiple cerebral infarctions and two had other large vessel arterial occlusions. Livedo reticularis was remarked upon particularly in one patient and this preceded the stroke by six months.

A similarity exists among all cases reported. Predominantly large intracranial arteries are usually involved and recurrent infarction is not only common but is often preceded by migrainous headaches or TIAs, or both.

The association of livedo reticularis was first described as occurring in SLE by Golden,<sup>38</sup> and its association with antibodies to phospholipid was first commented upon by Hughes.<sup>39</sup>

Livedo reticularis was present in all of our patients. The association of livedo reticularis and stroke was first recorded by Sneddon in 1965<sup>40</sup> and, since then, many others reports have appeared.<sup>41-52</sup> Recently its association with antiphospholipid antibodies (phosphatidylethanolamine) was reported by Jonas *et al*,<sup>52</sup> and the high incidence of CNS complications in patients with SLE with livedo and anticardiolipin antibodies confirmed by Asherson *et al*<sup>53</sup> and Weinstein *et al*.<sup>54</sup>

Recent reports have commented on the high incidence of valvular lesions (aortic and mitral predominantly) in this group of patients,<sup>55</sup> and a 'thrombotic' endocarditis should always be excluded in patients demonstrating antiphospholipid antibodies, heart valve lesions, and recurrent cerebral episodes.<sup>56</sup>

Although routine echocardiography was not performed in our patients, recurrent cerebral occlusions from embolic cardiac sources should always be considered in patients with SLE and multiple strokes who demonstrate antiphospholipid antibodies.

This group of patients appears to represent a unique subgroup with anticardiolipin syndrome, in whom early treatment with anticoagulants, when recognised, may well forestall the catastrophic consequences of recurrent multiple cerebral infarctions.

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