PAPER

# Detection of cerebral embolic signals in patients with systemic lupus erythematosus

**A Dahl, R Omdal, K Waterloo, O Joakimsen, E A Jacobsen, W Koldingsnes, S I Mellgren**

*J Neurol Neurosurg Psychiatry* 2006;**77**:774–779. doi: 10.1136/jnnp.2005.084285

See end of article for authors' affiliations

Correspondence to: Arve Dahl, Department of Neurology, Rikshospitalet University Hospital, Sognsvannsveien 20, 0027 Oslo, Norway; arve.dahl@rikshospitalet.no

Received 15 November 2005
Revised version received 10 February 2006
Accepted 15 February 2006
**Published Online First 24 February 2006**

**Background:** Involvement of the CNS in systemic lupus erythematosus (SLE) is caused by several pathogenic mechanisms including cerebral embolism.
**Aim:** To measure the frequency of microembolic signals (MES) by using transcranial Doppler (TCD) ultrasound and to assess their association with cerebral infarction, neuropsychological dysfunction, and biochemical, sonographic and clinical variables in an unselected group of patients with SLE.
**Methods:** A 1-h TCD recording from the middle cerebral artery was carried out in 55 patients with SLE having a mean age of 46 (SD 13) years. MRI of the brain, carotid artery ultrasonography with intima–media thickness and atherosclerotic plaque assessments were carried out in addition to a broad biochemical and clinical assessment. All patients underwent a neuropsychological assessment.
**Results:** Of the 55 patients, MES were detected in 5 (9%) and cerebral infarcts were found in 9 (18%). A significant association was found between MES and cerebral infarcts and considerably more neuropsychological deficits were found in MES-positive patients compared with the negative group. MES were not associated with other clinical, sonographic and biochemical factors believed to be associated with cerebral embolism.
**Conclusions:** Cerebral embolism may be one of the important mechanisms responsible for the high prevalence of cerebrovascular events and the neuropsychological deficits observed in patients with SLE. Although the number of MES-positive patients was small, the lack of a significant association between MES and other known risk factors for MES suggests a complex pathogenesis for the embolisation in these patients.

CNS symptoms and signs are common in systemic lupus erythematosus (SLE) and as many as 50% of patients with SLE may have neuropsychiatric involvement.[1 2] Well-known complications include psychosis, seizures, cerebrovascular accidents and cognitive dysfunction. Women with SLE, aged 18–44 years, are eight times as likely to be admitted to hospital because of stroke as controls.[3] The pathogenesis of CNS involvement in SLE has not been clarified, and multiple factors may be associated, such as microvascular damage, small-vessel vasculopathy, antibodies to nervous tissue and immunologically mediated thromboembolism. Postmortem examinations have shown microinfarcts and microhaemorrhages in cortical and subcortical regions. Several factors are associated with the increased risk of stroke in these patients. These include antiphospholipid antibodies, use of corticosteroids, cardiac involvement and other well-known risk factors for cerebrovascular disease.[2 4 5]

Transcranial Doppler (TCD) examination, a non-invasive technique, can detect cerebral embolisation in the major intracranial arteries.[6] Microembolic signals (MES) have been detected during cardiac surgery and carotid endarterectomy.[7 8] Long-term TCD monitoring of the intracranial arteries has shown abnormal signals, indicating clinically silent MES in patients with high-grade carotid stenosis, with prosthetic heart valves or after recent cerebrovascular events.[9–11] Cerebral microemboli may cause cognitive dysfunction if they enter the cerebral circulation in considerably large numbers. This has been studied in detail in patients who have had coronary artery bypass surgery.[12] Some instances showing a positive association between cerebral microemboli detected by TCD and postoperative neuropsychological outcome after cardiac surgery have been reported.[7 10]

Three studies[13–15] that used TCD for embolic detection in patients with SLE have showed conflicting results. It is therefore of interest to carry out further studies on the possible importance of cerebral microembolisation in SLE.

We measured the occurrence of MES in a group of patients with SLE and assessed the possible association with cerebral infarcts, neuropsychological function, risk factors for cerebrovascular disease, including carotid atherosclerosis, and biochemical variables associated with cerebrovascular disease.

## PATIENTS AND METHODS

All records of inpatients and outpatients with a diagnosis of SLE seen at the University Hospital of Northern Norway, Tromsø, Norway, were reviewed. In all, 94 patients fulfilled the revised criteria (1982) of the American College of Rheumatology for SLE.[16] Seventeen patients were dead, three had moved to another part of the country and four were excluded from the study for various reasons. Of the remaining 70 patients, 14 did not want to participate in the present study. Thus, 56 patients, 49 (88%) women and 7 (12%) men (all Caucasians), were available for the TCD study. All studies were carried out during a 2-day stay at the Clinical Research Unit, University Hospital of North Norway, Tromsø, Norway, and each investigator was blinded to the assessments made by the other investigators. The mean age was 46.4 (SD 12.7, range 23–73) years and the disease duration was 14.3 (SD 9, range 2–36) years. Disease activity

**Abbreviations:** aCL, anticardiolipin antibodies; IMT, intima–media thickness; MES, microembolic signals; SLE, systemic lupus erythematosus; TCD, transcranial Doppler ultrasound

measured according to the Systemic Lupus Erythematosus Disease Activity Index[17] was 5.8 (SD 9.0). The Systemic Lupus Erythematosus Disease Activity Index is a weighted, cumulative index of disease activity in SLE. It is widely used and is a valid and reliable disease activity measure. The Regional Ethics Committee for medical research approved this study.

### TCD monitoring

Doppler examination of the left middle cerebral artery was carried out in all patients using a TCD2000S (Nicolet/EME, Nicolet Vascular, Madison, Wisconsin, USA) with a 2-MHz pulse wave transducer. Each monitoring period lasted for 60 min. A stable probe position was maintained by using a Müller and Mode fixation device (Nicolet/EME), at a depth of 45–56 mm and an angle giving the strongest Doppler signal from the middle cerebral artery. The sample volume was fixed at 10 mm and the sweep speed was kept constant and corresponded to a time window overlap between 50% and 65%. The filter was constant at 100 Hz. The audible Doppler shift and colour coded, fast-Fourier-transformed TCD spectra were continuously observed online. All Doppler findings were also recorded digitally on tape (Digital Audio Tape, DAT, Sony A8 Sony, Tokyo, Japan) for further offline analyses.

### MES

Two observers, blinded to clinical information, studied the digital audio tapes independently. Cerebral MES were counted using the guidelines given by an international consensus group.[18] The observers assessed the signals on the basis of their sound, duration and appearance on the monitor. The method of detection of emboli has been reported in detail previously.[6 10 11]

### Duplex ultrasound examination and intima–media thickness (IMT) measurements

Ultrasonography of both carotid arteries was carried out using a high-resolution ultrasound scanner (Acuson Xp10 128, ART-upgraded, Siemens Acuson, Mountain View, California, USA) equipped with a linear-array transducer. The common, internal and external carotid arteries were identified by combining B-mode and colour Doppler or pulsed-wave Doppler (5 MHz) ultrasound. We attempted to identify and record atherosclerotic plaques from six locations on the carotid artery: the near and far walls of the internal carotid artery, common carotid artery bifurcation segment and the common carotid artery from the bifurcation to the supraclavicular region. The maximum plaque thickness from each location was measured online on frozen B-mode images marked with electronic callipers with measurement read-outs in tenths of a millimetre. IMT measurements were taken from the near and far walls of the common carotid and the far wall of the bifurcation. This procedure is described in detail elsewhere.[19 20]

### MRI

MRI scans of the brain were carried out using a 0.5-T magnet (Gyroscan T5 II; Philips, Eindhoeven, The Netherlands). A sagittal T1-weighted sequence (520/20/2 (repetition time/echo time/excitations)) with 6 mm slice thickness and 0.6 mm interspace followed by an axial T2-weighted sequence (2000/20/90 (repetition time/echo time/excitations)) with 5 mm slice thickness and 0.5 mm interspace was carried out on the entire brain. A circular, transmit–receive head coil with a matrix of 256×256 and a field of view of 250 mm was used. One neuroradiologist, blinded to all clinical data, assessed the images. An infarct was defined as a region with low T1 or proton density and high T2 signal intensities, >15 mm.

### Neuropsychological assessment

The patients with SLE underwent a neuropsychological examination. A battery of standardised tests was applied to assess cognitive function. The description of the tests and cognitive domains is in agreement with the work by the American College of Rheumatology adhoc Committee on Neuropsychiatric Lupus Nomenclature.[21] The tests measure different categories of cognition such as memory, attention, language, visuospatial processing, psychomotor speed and executive function or cognitive flexibility. The patients were tested individually by an experienced test technician using the neuropsychological test battery in two sessions on the same day, each lasting up to 2 h and separated by a coffee break.

The aspects of cognitive functioning examined and the tests given included the following:

- Complex attention: Seashore Rhythm Test.[22]
- Cognitive speed: Trail Making Test A.[21]
- Memory: Verbal and Visual Paired Associated immediate and 30 min delayed recall from Wechsler Memory Scale-Revised.[23]
- Language: Controlled Oral Word Association.[24]
- Cognitive flexibility or executive function: Trail Making Test B and a computer-administrated version of the Wisconsin Card Sorting Test.[25]

Furthermore, in evaluating intellectual functions, Similarities (verbal function) and Block Design (non-verbal function) subtests from Wechsler Adult Intelligence Scale[26] were used. Neuropsychological measures were treated as continuous variables and raw scores were therefore used for assessments.

### Laboratory tests

Urine analysis and haematological, biochemical and standard immunological tests were carried out. A commercial lupus anticoagulant-sensitive activated partial thromboplastin time reagent was used to test for the presence of lupus anticoagulant (PTT-LA; Diagnostica Stago, Asnieres, France). In cases when prolongation of the clotting time was ⩾6 s, confirmation assays were carried out as previously described.[27] Tests for anticardiolipin antibodies (aCL) of IgG and IgM isotypes were carried out using a commercial ELISA according to the manufacturer Shield (Dundee, UK). Values above 30 GPL and 30 MPL U/ml were considered positive. Anti-β2-glycoprotein-1 antibodies of IgG and IgM isotypes were detected by ELISA (IMTEC Immundiagnostica, Berlin, Germany). Values above 7 U/ml were considered to be positive according to the manufacturer's recommendations.

### Statistical analysis

Results are presented as means (SD). The unpaired t-test (two-tailed) was used for testing differences between two groups with respect to quantitative outcome variables. As the numbers of expected frequencies were small, Fisher's exact test was used for evaluating differences between proportions obtained from qualitative outcome variables. Forward stepwise regression and multiple regression analyses were used to test associations between single-outcome variables and several quantitative explanatory variables. Tests of differences and regression coefficients were considered to be significant if <5%.

## RESULTS

### Clinical findings

Table 1 shows the characteristics of the patients. Twenty four (48%) patients were current smokers; they smoked 12.3 (7.6) cigarettes daily, and had been smokers for 24.2 (8.5) years.

Two patients had had an ischaemic stroke. On the basis of clinical history and laboratory findings, 11 (20%) patients had (secondary) antiphospholipid antibody syndrome, with cerebral infarction in three of these.[28]

### Laboratory results

In all, 4 (7%) patients had a positive IgG aCL test, and 3 (5%) patients had a positive IgM aCL test; 33 (60%) patients were anti-β2 glycoprotein-1 IgG positive, and 13 (24%) anti-β2 glycoprotein-1 IgM positive; 3 (6%) had lupus anticoagulant. Total cholesterol was 5.6 (3.5) mmol/l (reference values for people>40 years, 4.1–8.7 mmol/l), high-density lipoprotein 1.4 (0.5) mmol/l (reference values for women, 1.0–2.2 mmol/l) and the mean concentration of homocysteine was 10.6 (3.5) μmol/l (reference values for women<50 years, 6–16 μmol/l).

### TCD monitoring

One patient had an insufficient acoustical window. Data from 55 patients were thus available for statistical calculations. MES were detected in 5 (9%) of the 55 patients. Four of these patients had 1 MES/h and one patient had 4 MES/h.

### MRI findings

Of the patients who underwent an MRI, 9 (18%) patients had one or more cerebral infarcts. The patients with cerebral infarcts were older than those without infarcts (58.4 *v* 43.4 years; $p<0.001$). We found no other remarkable differences regarding risk factors for stroke between the groups with and without cerebral infarcts.

### B-mode ultrasound

B-mode ultrasound of the carotid bifurcation with IMT measurements was carried out in 51 (95%) patients. In 26 (51%) patients, an atherosclerotic plaque was detected (table 2), whose average maximum plaque thickness was 1.87 (0.15) mm. IMT in the bifurcation far wall was 0.75 (0.26) mm and in the common carotid artery 0.59 (0.26) mm, as measured in 51 patients. Measurements from the bifurcation far wall were chosen for statistical analysis.

### Positive MES—clinical and laboratory features

The two groups, with or without MES, were compared regarding risk factors for stroke or thromboembolism. We found no differences between patients with or without MES with regard to age, sex, disease duration, SLE Disease Activity Index, use of prednisolone, malaria drugs, cytotoxics, or taking or not taking any drugs for SLE. We observed no differences between patients with and without MES in the use of other drugs or with regard to miscarriages, thromboembolism, diastolic or systolic blood pressure, hypertension, valvular heart disease (n = 2), livedo reticularis, visual disturbances or other complications or concomitant diseases. Being a smoker, number of cigarettes smoked every day or number of years as a smoker was not markedly different between the two groups. B-mode ultrasound assessment of IMT measured in the far wall of the carotid bifurcation, the presence or absence of plaques and the maximum thickness of plaques did not differ between patients with or without MES.

**Table 1** Characteristics of the study population

| | |
|---|---|
| Age in years, mean (SD) | 46.4 (12.7) |
| Disease duration in years, mean (SD) | 14.3 (9.0) |
| Systemic Lupus Erythematosus Disease Activity Index, mean (SD) | 5.8 (9.0) |
| Smokers (current and previous) | 24 (48) |
| Hypertension* | 12 (22) |
| Coronary heart disease† | 5 (9) |
| Miscarriage | 9 (16) |
| Venous thrombosis | 8 (14) |
| Livedo reticularis | 10 (18) |
| Glomerulonephritis | 10 (18) |
| Valvular heart disease | 2 (4) |
| Lung fibrosis | 2 (4) |
| Osteonecrosis | 2 (4) |
| Diabetes mellitus | 2 (4) |
| Microembolic signals | 5 (9) |
| Cerebral infarcts | 9 (18) |
| **Medication for SLE (single drug or combination)** | |
| No drugs | 11 (20) |
| Prednisolone | 33 (60) |
| Malaria drugs | 24 (44) |
| Azathioprine | 12 (22) |
| Cyclophosphamide | 2 (4) |
| **Other medication** | |
| Non-steroidal anti-inflammatory drugs | 8 (14) |
| Hormone replacement therapy | 5 (9) |
| Acetylsalicylic acid | 5 (9) |
| β blocker | 4 (7) |
| Warfarin | 4 (7) |

Data are n (%) unless otherwise stated.
*Hypertension is defined as being treated with an antihypertensive agent, or blood pressure >140/90 mm Hg at repeated measurements.
†Four patients had angina pectoris (one had undergone coronary bypass) and one had myocardial infarction.
SLE, systemic lupus erythematosus.

Levels of haemoglobin, leucocytes, platelets, erythrocyte sedimentation rate, C reactive protein, rheumatoid factors, complement factors C3 and C4, antinuclear antibodies and their subspecificities did not differ between the two groups. Table 3 shows the lipid, homocysteine and smoking profiles of the patients. Tests for lupus anticoagulant, aCL, anti-β2 glycoprotein 1 also showed no differences between MES-positive and MES-negative patients. None of the 11 patients with antiphospholipid antibody syndrome had MES, although this did not reach significance ($p = 0.57$).

MRI showed a cerebral infarct in three of the five patients with MES as against an expected number of 0.9 ($\chi^2$ test). The remaining six patients with cerebral infarcts were normal on TCD monitoring. This difference reached significance ($p = 0.03$). A forward stepwise regression analysis was

**Table 2** Presence and thickness of plaques in 51 patients with systemic lupus erythematosus (SLE)

| Patients with SLE | | | Healthy subjects (Joakimsen *et al*[19]) | |
|---|---|---|---|---|
| Age intervals in years (n = 51 ) | Patients with plaques n (%) | Thickness in mm (SD) | % of women with plaques | Thickness of plaques in mm (n = 3404) |
| 23–34 (9) | 0 | 0 | 1.5 | 1.1 |
| 35–44 (12) | 3 (25) | 1.3 (0.3) | 10.8 | 1.5 |
| 45–54 (16) | 11 (69) | 1.6 (0.2) | 18.2 | 1.6 |
| 55–64 (9) | 8 (89) | 2.0 (0.5) | 40.3 | 1.9 |
| 65–73 (5) | 4 (80) | 2.8 (1.4) | 61.0 | 2.1 |

carried out with cerebral infarcts as the dependent variable and the following independent variables: maximum thickness of plaques, presence or absence of MES, age, disease duration, levels of homocysteine, total cholesterol and total years as a smoker. In this model, only MES was significantly associated with cerebral infarcts after one step ($R^2 = 0.30$, coefficient 0.83, F to remove 9.0, $p = 0.008$).

### Cognitive measures and TCD findings

We found no significant differences between patients with or without MES regarding Wechsler Adult Intelligence Scale verbal and non-verbal scores and no differences in intellectual functions. We found no pre-existing premorbid differences between the two groups.

Several neuropsychological measures showed significant differences between patients with and without MES (table 4). Compared with patients without MES, those with MES performed more poorly on the Trail Making Tests A ($p = 0.02$) and B ($p = 0.008$), the Verbal Paired Associates and immediate recall ($p = 0.03$) from the Wechsler Memory Scale-Revised, and the total errors ($p = 0.03$), preservative responses ($p = 0.02$) and conceptual level ($p = 0.01$) from the Wisconsin Card Sorting Test. In multiple regression with cognitive performance as a dependent variable and MES and cerebral infarcts as independent variables, cerebral infarcts had a significant impact on Trail Making Tests A ($r = 17.94$; $p = 0.004$) and B ($r = 71.00$; $p<0.0001$). No other neuropsychological variables were significantly associated with cerebral infarcts or with MES. In addition, we found no associations between homocysteine level, the presence of antiphospholipid antibodies and cognitive function; the use of prednisolone did not influence cognition.

## DISCUSSION

In this study, we detected MES in 9% of an unselected group of patients with SLE during unilateral TCD monitoring. This frequency is similar to that found by Kron *et al*,[14] but is less than that in Kumral *et al's*[15] study. Both recorded an increased frequency of MES in patients with SLE compared with controls, by using bilateral TCD monitoring. Bilateral monitoring may therefore have detected more emboli in our patient group. Studies have shown that MES is a rare occurrence in healthy controls.[29] We found a marked association between MES-positive patients and cerebral infarcts diagnosed by MRI. A noticeable association between MES-positive patients and low test scores on several neuropsychological measures was also observed. These findings support the hypothesis that embolism may be an important pathogenic factor for cerebral infarcts and cognitive dysfunction in patients with SLE.

It is well documented that SLE is associated with an increased incidence of cardiovascular and cerebrovascular diseases.[30–32] In this study, we detected a cerebral lesion, by MRI, in 18% of the patients. Univariate analysis showed greater age to be associated with brain infarction. No other clinical or biochemical risk factors reached statistical significance. This was possibly because of the relatively small numbers of patients and the cut-off levels chosen for the aCL

**Table 3** Risk factors for cerebrovascular disease

| | MES positive | MES negative | |
|---|---|---|---|
| | n = 5 | n = 50 | p Value |
| Cholesterol, mmol/l | 4.6 (1.4) | 5.7 (1.6) | 0.09 |
| HDL cholesterol, mmol/l | 1.2 (0.3) | 1.4 (0.4) | 0.26 |
| Homocysteine, μmol/l | 10.9 (3.1) | 10.6 (3.6) | 0.89 |
| Current smokers | 3 (60%) | 21 (42%) | 0.66* |
| Patients with plaque | 2 (40%) | 24 (48%) | 0.67* |
| Plaque thickness, mm | 2.00 (0.28) | 1.86 (0.77) | 0.81 |
| IMT, mm | 0.78 (0.39) | 0.74 (0.25) | 0.74 |

Values are means (SD) unless otherwise stated.
*$\chi^2$, Fisher's exact p value.
HDL, high density lipoprotein; IMT, Intima–media thickness as measured in the bifurcation far wall; MES, microembolic signals.

**Table 4** Neuropsychological tests and results

| | Cerebral MES | | |
|---|---|---|---|
| Tests | Positive | Negative | p Value |
| Education in years | 10.8 (5.9) | 10.3 (2.7) 0.74 | |
| Intellectual function (WAIS) | | | |
| Verbal (Similarities) | 15.4 (6.6) | 16.1 (4.5) | 0.75 |
| Nonverbal (Block Design) | 34.8 (6.9) | 36.4 (8.3) | 0.67 |
| Neuropsychological and cognitive tests | | | |
| Trail Making Test A | 53.2 (33.7) | 35.3 (13.5) | 0.02 |
| Trail Making Test B | 145.2 (86.6) | 88.0 (38.4) | 0.008 |
| Seashore Rhythm Test | 21.6 (4.6) | 23.5 (3.79) | 0.30 |
| WMS-R, Verbal Paired Associates I | 12.4 (5.2) | 16.1 (3.5) | 0.03 |
| WMS-R, Verbal Paired Associates II | 5.2 (2.3) | 6.0 (1.4) | 0.25 |
| WMS-R, Visual Paired Associates I | 9.6 (4.5) | 11.9 (3.8) | 0.22 |
| WMS-R, Visual Paired Associates II | 3.8 (1.8) | 4.8 (1.5) | 0.15 |
| COWA (FAS) | 25.2 (19.1) | 32.0 (11.6) | 0.24 |
| WCST, total errors | 38.0 (2.3) | 46.9 (8.9) | 0.03 |
| WCST, perseverative responses | 39.4 (6.6) | 50.8 (11.1) | 0.03 |
| WCST, perseverative errors | 38.6 (6.9) | 49.7 (10.4) | 0.02 |

Values are means (SD).
COWA, Controlled Oral Word Association; MES, microembolic signals; TCD, transcranial Doppler; WAIS, Wechsler Adult Intelligence Scale; WCST, Wisconsin Card Sorting Test; WMS-R, Wechsler Memory Scale-Revised.

and lupus anticoagulant tests. On the other hand, anti-β2 glycoprotein-1 tests, which displayed a rather high positive prevalence, were not associated with cerebral infarcts. This was valid both in the univariate and multiple regression tests, with age included as a co-independent variable. We found an association only between MES and cerebral infarcts, which supports an association between asymptomatic emboli and cerebral infarcts.

The association between MES and prognosis has been assessed in prospective studies on patients with symptomatic and asymptomatic carotid stenosis, and antiplatelet treatment has been shown to reduce MES.[33 34] Several studies have proposed that TCD monitoring with MES detection gives useful prognostic information in patients at high risk of cerebral infarction. As the increased risk of cerebral infarctions is well established in patients with SLE and the mechanism is poorly understood, we believe that embolic detection by TCD monitoring is a relevant examination and research tool.

We could not find any difference between MES-positive and MES-negative patients with regard to risk factors. Rademacher *et al*[13] and Kumral *et al*[15] found that MES was associated with antiphospholipid antibodies, but we could not reproduce their findings. A similar negative observation was also reported by Kron *et al*.[14] An explanation for the lack of association may be that the increased numbers of MES are caused by multiple mechanisms or that our study did not have sufficient statistical power to detect these factors.

IMT assessments of the carotid arteries did not detect increased thickness compared with age-matched people,[19] but showed an increased amount of carotid atherosclerosis when assessing the number of patients with plaques. This finding confirms that patients with SLE have an increased amount of early atherosclerosis, as observed by Roman *et al*.[30] The reason for the accelerated atherosclerosis is incompletely understood, but use of corticosteroids and an increased level of conventional risk factors for atherosclerosis have been suggested.[32 35] Recent studies have observed an association between atherosclerosis and the activity of the disease and a negative association with cyclophosphamide treatment.[30] This suggests that inflammatory mechanisms promote the atherosclerotic process—for example, that the vasculopathy associated with SLE causes endothelial dysfunction that predisposes people to atherosclerosis. In this study, however, we could not find any relation between carotid lesions and MES or brain infarcts. An increased homocysteine level has been associated with increased arteriosclerosis and thromboembolism in patients with SLE.[36 37] The exact mechanism behind this association is unknown, but several factors may be involved and different mechanisms have been postulated. Our observations of no association with homocysteine levels with regard to both the MRI and MES findings do not support the importance of homocysteine.

Patients with SLE and MES had several cognitive dysfunctions: cognitive speed, complex attention, short-term verbal memory, and cognitive flexibility or executive function. The difference observed when comparing the MES-positive and MES-negative groups had a closer association with cerebral infarct for two of the domains. The cognitive dysfunction observed in patients with MES in this study is similar to the observation reported by Kumral *et al*,[15] who found MES to be associated with an increased amount of neuropsychiatric disturbances. Earlier studies on cerebral microemboli and cognition have assessed patients with coronary artery bypass surgery and artificial heart valves. This study is the first to show that cerebral microemboli influence cognitive function in patients with SLE. Associations between cognitive dysfunction and both symptomatic and asymptomatic carotid atherosclerosis are reported,[38] but the mechanisms have not been clarified. In general, silent brain infarcts in healthy elderly people are associated with cognitive decline when compared with those in people without such lesions, and silent infarcts are commonly observed in patients with atherosclerosis on neuroimaging.[39] Silent infarcts due to cerebral microemboli may thus be a cause of the cognitive decline in some of our patients with SLE, but it is also possible that cerebral microembolisation by itself contributes to the cognitive dysfunction so often observed in patients with SLE.

A limitation of our study is the relatively small number of patients. Several factors influence the formation of microemboli and clinical infarcts, both of which do not attain statistical significance because of lack of power. Our observations, however, suggest a complex pathogenic mechanism behind asymptomatic embolic signals and cerebral infarcts in SLE, consistent with several factors being active in these patients.

In conclusion, the observation of an increased number of asymptomatic cerebral emboli in our study supports the hypothesis that multiple small or large emboli may explain some of the neuropsychiatric phenomena and cerebral infarcts in patients with SLE. The association between MES and neuropsychological findings also suggests that microemboli may be a cause of cognitive dysfunction commonly found in this patient group. In this study, conventional risk factors for cerebrovascular disease and factors commonly associated to thromboembolism in SLE were not associated with asymptomatic cerebral emboli.

## ACKNOWLEDGEMENTS

RO was supported as a post-doctoral research fellow by the Norwegian Research Council for Science and Humanities and the Norwegian Foundation for Health Rehabilitation.

**Authors' affiliations**

**A Dahl,** Department of Neurology, Rikshospitalet University Hospital, Oslo, Norway
**R Omdal,** Clinical Immunology Unit, Department of Internal Medicine, Stavanger University Hospital, Stavanger, Norway
**K Waterloo, O Joakimsen, S I Mellgren,** Department of Neurology, University Hospital of North Norway, Tromsø, Norway
**E A Jacobsen,** Department of Radiology, Rikshospitalet University Hospital
**W Koldingsnes,** Department of Rheumatology, University Hospital of North Norway

Competing interests: None declared.

## REFERENCES

1 **Hanley JG**, Walsh NMG, Sanalang V. Brain pathology in systemic lupus erythematosus. *J Rheumatol* 1992;**19**:732–41.
2 **Omdal R**. Some controversies of neuropsychiatric systemic lupus erythematosus. *Scand J Rheumatol* 2002;**31**:192–7.
3 **Ward MM**. Premature morbidity from cardiovascular diseases in women with systemic lupus erythematosus. *Arthritis Rheum* 1999;**42**:338–46.
4 **Tam L-S**, Fan B, Li EK, *et al*. Patients with systemic lupus erythematosus show increased platelet activation and endothelial dysfunction induced by acute hyperhomocysteinemia. *J Rheumatol* 2003;**30**:1479–84.
5 **Devinsky O**, Petito CK, Alonso DR. Clinical and neuropathological findings in systemic lupus erythematosus; the role of vasculitis, heart emboli and thrombotic thrombocytopenic purpura. *Ann Neurol* 1988;**23**:380–4.
6 **Russell D**, Madden KP, Clark WM, *et al*. Detection of arterial emboli using Doppler ultrasound in rabbits. *Stroke* 1991;**22**:253–8.
7 **Stump D**, Rogers A, Hammon J, *et al*. Cerebral emboli and cognitive outcome after cardiac surgery. *J Cardiothorac Vasc Anesth* 1996;**10**:113–9.
8 **Spencer MP**, Thomas GI, Nicholls SC. Detection of middle cerebral artery emboli during carotid endarterectomy using transcranial Doppler ultrasonography. *Stroke* 1990;**21**:415–23.
9 **Siebler M**, Kleinschmidt A, Sitzer M, *et al*. Cerebral microembolism in symptomatic and asymptomatic high-grade internal carotid artery stenosis. *Neurology* 1994;**44**:615–8.
10 **Brækken SK**, Reinvang I, Russell D, *et al*. Association between intraoperative cerebral microembolic signals and postoperative neuropsychological deficit: comparison between patients with cardiac valve replacement and patients

with coronary artery bypass grafting. *J Neurol Neurosurg Psychiatry* 1998;**65**:573–6.
11 **Lund C**, Rygh J, Stensrød B, *et al*. Cerebral microembolus detection in an unselected acute ischemic stroke population. *Cerebrovasc Dis* 2000;**10**:403–8.
12 **Lund C**, Hol PK, Lundblad R, *et al*. Comparison of cerebral embolization during off-pump and on-pump coronary artery bypass surgery. *Ann Thorac Surg* 2003;**76**:765–70.
13 **Rademacher J**, Söhngen D, Specker C, *et al*. Cerebral microembolism, a disease marker for ischemic cerebrovascular events in the antiphospholipid syndrome of systemic lupus erythematosus? *Acta Neurol Scand* 1999;**99**:356–61.
14 **Kron J**, Hamper UM, Petri M. Prevalence of cerebral microemboli in systemic lupus erythematosus: transcranial Doppler. *J Rheumatol* 2001;**28**:2222–5.
15 **Kumral E**, Evyapan D, Keser G, *et al*. Detection of microembolic signals in patients with neuropsychiatric lupus erythematosus. *Eur Neurol* 2002;**47**:131–5.
16 **Tan EM**, Cohen AS, Fries JF, *et al*. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982;**25**:1271–2.
17 **Bombardier C**, Gladman DD, Urowitz MB, *et al*. Derivation of the SLEDAI: a disease activity index for lupus patients. *Arthritis Rheum* 1992;**35**:630–40.
18 **Ringelstein EB**, Droste DW, Babikian VL, *et al*. International consensus group on microembolus detection. Consensus on microembolus detection by TCD. *Stroke* 1998;**29**:725–9.
19 **Joakimsen O**, Bønaa KH, Stensland-Bugge E, *et al*. Age and sex differences in the distribution and ultrasound morphology of carotid atherosclerosis. The Tromsø study. *Arterioscler Thromb Vasc Biol* 1999;**19**:3007–13.
20 **Stensland-Bugge E**, Bønaa KH, Joakimsen O. Reproducibility of ultrasonographically determined intima-media thickness is dependent on arterial wall thickness. The Tromsø study. *Stroke* 1997;**28**:1972–80.
21 **ACR Adhoc Committee on Neuropsychiatric Lupus Nomenclature**. The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. *Arthritis Rheum* 1999;**42**:599–608.
22 **Reitan RM**, Davidson LA. *Clinical neuropsychology*. New York: Hemisphere, 1974.
23 **Wechsler D**. *Wechsler Memory Scale-Revised. Manual*. New York: The Psychological Corporation, 1987.
24 **Spreen O**, Strauss E. *A compendium of neuropsychological tests*, 2nd edn. New York: Oxford University Press, 1998.
25 **Heaton RK**. *Wisconsin Card Sorting Test: computer version-2*. Odessa: Psychological Assessment Resources, 1993.
26 **Wechsler, D**. *Wechsler Adult Intelligence Scale*. New York: The Psychological Corporation, 1955.
27 **Schetlein R**, Sletnes KE, Wisloff E. A quantitative, semi-automated and computer-assisted test for lupus anticoagulant. *Thromb Res* 1993;**69**:239–50.
28 **Wilson WA**, Gharavi AE, Koike T, *et al*. International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome. *Arthritis Rheum* 1999;**42**:1309–11.
29 **Eicke BM**, von Lorentz J, Paulus W. Embolus detection in different degrees of carotid disease. *Neurol Res* 1995;**17**:181–4.
30 **Roman MJ**, Shanker B-A, Davis A, *et al*. Prevalence and correlates of accelerated atherosclerosis in systemic lupus erythematosus. *N Engl J Med* 2003;**349**:2399–406.
31 **Bessant R**, Hingorani A, Patel L, *et al*. Risk of coronary heart disease and stroke in a large British cohort of patients with systemic lupus erythematosus. *Rheumatology* 2004;**43**:924–9.
32 **Manzi S**, Selzer F, Sutton-Tyrrell K, *et al*. Prevalence and risk factors of carotid plaque in women with systemic lupus erythematosus. *Arthritis Rheum* 1999;**42**:51–60.
33 **Markus HS**, MacKinnon A. Asymptomatic embolization detected by Doppler ultrasound predicts stroke risk in symptomatic carotid artery stenosis. *Stroke* 2005;**36**:971–5.
34 **Goertler M**, Blaser T, Krueger S, *et al*. Cessation of embolic signals after antithrombotic prevention is related to reduced risk of recurrent arterioembolic transient ischemic attack and stroke. *J Neurol Neurosurg Psychiatry* 2002;**72**:338–42.
35 **Petri M**, Perez-Gutthann S, Spense D, *et al*. Risk factors for coronary artery disease in patients with systemic lupus erythematosus. *Am J Med* 1992;**93**:513–9.
36 **Fijnheer R**, Roest M, Haas FJLM, *et al*. Homocysteine, methylenetetrahydrofolate reductase polymorphism, antiphospholipid antibodies, and thromboembolic events in systemic lupus erythematosus. A retrospective cohort study. *J Rheumatol* 1998;**25**:1737–42.
37 **Refai TMK**, Al-Salem IH, Nkansa-Dwamena D, *et al*. Hyperhomocysteinaemia at risk of thrombosis in systemic lupus erythematosus patients. *Clin Rheumatol* 2002;**21**:457–61.
38 **Mathiesen EB**, Waterloo K, Joakimsen O, *et al*. Reduced neuropsychological test performance in asymptomatic carotid stenosis. The Tromsø study. *Neurology* 2004;**62**:695–701.
39 **Vermeer SE**, Prins ND, den Heijer T, *et al*. Silent brain infarcts and the risk of dementia and cognitive decline. *N Engl J Med* 2003;**348**:1215–22.