Q J Med 2000; **93**:169–174

Risk factors for central nervous system involvement in systemic lupus erythematosus

F.B. KARASSA, J.P.A. IOANNIDIS[1], G. TOULOUMI[2], K.A. BOKI and H.M. MOUTSOPOULOS

From the Departments of Pathophysiology and [2]Hygiene and Epidemiology, School of Medicine, National University of Athens, Athens, Greece, and [1]Clinical and Molecular Epidemiology Unit, Department of Hygiene and Epidemiology, University of Ioannina School of Medicine, Ioannina, Greece, and Department of Medicine, Tufts University School of Medicine, Boston, USA

Received 19 November 1999

Summary

We investigated risk factors for central nervous system (CNS) involvement in systemic lupus erythematosus (SLE), in 32 such patients individually matched 1 : 3 to 96 control SLE patients without CNS events. Univariate analysis showed that CNS involvement was significantly associated with the antiphospholipid syndrome (APS) as well as its features: arterial thrombosis, recurrent fetal loss, livedo reticularis and IgG anticardiolipin (aCL) antibodies in high titres. Other potential associations included cutaneous vasculitic lesions, thrombocytopenia, positive ANA, anti-SS-B/La and low serum levels of C_3 and C_4 complement components, while articular manifestations and discoid rash were significantly less common in patients with neuropsychiatric (NP) disease. In multivariate modeling, CNS involvement was strongly associated with cutaneous vasculitic lesions OR 33, 95% CI 1.5–720) and arterial thromboses (OR 13, 95%CI 0.82–220), and negatively related to the presence of articular manifestations (OR 0.015, 95%CI 0.00–0.17) and discoid rash (OR 0.004, 95%CI 0.00–0.35). Associations with APS-related arterial thromboses and vasculitis point to the importance of arterial vascular pathophysiology in the pathogenesis of NP disease in SLE. Patients with articular manifestations and discoid rash are at very low risk of NP events. Patients with an adverse SLE disease profile may require closer observation and may be the target group for studying pre-emptive interventions.

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by multisystemic involvement and diverse manifestations. A large percentage of patients demonstrate severe psychiatric and/or neurological symptoms indicating central nervous system (CNS) involvement.[1,2] Such involvement constitutes a leading cause of morbidity in SLE, because patients with neuropsychiatric (NP) manifestations—especially those with focal symptoms—often do not reverse their deficits during therapy.[2] Neuropsychiatric systemic lupus erythematosus (NPSLE) also adversely affects survival in such patients: 7% to 13% of deaths in SLE have been attributed to CNS involvement.[3–6]

NPSLE may be seen in the context of antiphospholipid (aPL) antibodies[7–9] and/or in the presence of overarching antiphospholipid syndrome (APS). The syndrome encompasses a variety of clinical manifestations. These include recurrent pregnancy loss and vascular thrombosis, which are considered to be the key manifestations in the recently developed preliminary classification criteria for APS;[10] and others such as haemolytic anemia, thrombocytopenia, livedo reticularis, and NP manifestations, the

Address correspondence to Professor H.M. Moutsopoulos, Department of Pathophysiology, School of Medicine, National University of Athens, 75 M Asias St, 11527 Athens, Greece. e-mail: hmoutsop@dh.uoa.gr

exact relationship of which with APS still needs further investigation.[10–12] There is limited knowledge about which of these manifestations associate most strongly with NPSLE. It is also unknown whether additional laboratory and clinical manifestations of SLE are associated with the development of CNS involvement. Early reports emphasized relationships with thrombocytopenia, vasculitis and livedo reticularis.[13,14] The independent associations of such manifestations with NPSLE have been difficult to study, since it has been difficult to conduct studies with an adequate sample size.

Given the significant morbidity of NPSLE, it is important to determine risk factors for CNS involvement in SLE. Our study was designed to determine the independence of potential risk factors for CNS involvement in SLE, using an individually-matched nested case-control approach in patients from a large cohort of SLE patients.

Methods

Patient selection and classification

SLE patients seen at the Department of the Pathophysiology were enrolled into this nested case-control study. All patients fulfilled four or more of the revised criteria for SLE.[15] The medical records of 324 consecutive SLE patients were reviewed, with particular attention to history of CNS manifestations and/or thrombotic events objectively documented with imaging or Doppler studies. Five patients with transient cognitive disorders not causing functional impairment ($n=2$), mild psychiatric manifestations ($n=1$) and anxiety disorders ($n=2$) were excluded from this study. From the remaining cohort, we found 32 patients who were hospitalized between August 1994 and July 1996 for definitive, severe NP events not attributed to any cause other than SLE. Their manifestations were classified according to the American College of Rheumatology (ACR) case definitions for NP lupus syndromes.[16] Patients without NP symptoms served as the source population for selecting the control group. NPSLE patients were individually matched 1 : 3 for sex, age (± 5 years) and disease duration (± 5 years) to controls.

Patients were also categorized according to whether at the time of evaluation they met at least one clinical and at least one laboratory criterion of the recently adopted classification criteria for APS.[10] The relevant exclusions for vascular thromboses, for those who had such events,[17] were also taken into account in this categorization.

Detection of autoantibodies

Serological studies

Sera were tested for the presence of antinuclear antibodies (ANA) by immunofluorescence (human epithelial cells [Hep-2] as substrate, positive titre $\geqslant 1/80$, Innova), C_3 and C_4 components of complement by nephelometry (Beckman), autoantibodies to cellular antigens (SS-A/Ro, SS-B/La, U_1 RNP and Sm) by counterimmunoelectrophoresis and antibodies to dsDNA by ELISA (as previously described).[18]

Lupus anticoagulant

Each patient with a prolonged partial thromboplastin time (PTT) underwent further studies to determine if a lupus anticoagulant (LA) was present. A LA was documented if the PTT was >5 s over the laboratory's normal upper limit, there was incomplete correction on 50 : 50 mixing with normal plasma and there was no other cause for the coagulopathy. The platelet neutralization test and/or dilute Russell's viper venom test were used for further confirmation.[19]

Anticardiolipin assay

Sera from all patients were tested for anticardiolipin (aCL) antibodies by an ELISA method, as previously described.[20] Negative aCL titre was defined when it had a value of <4 SD above the mean of 100 healthy subjects, low/moderate positive when levels were between $\geqslant 4$ SD and <7 SD of mean normal values and high positive when $\geqslant 7$ SD of reference values.[20]

Statistical analysis

The NPSLE group (cases) were compared with SLE patients without CNS involvement (controls) for several selected characteristics. To compare the two groups, univariate and multivariate conditional logistic regression models were applied based on maximization of conditional likelihood. Statistical analyses used the SPSS statistical package. All *p*-values are two-tailed.

Results

The study population consisted of 112 women and 16 men. Patients' mean age (SD) at SLE onset (evaluated from the first, well-described sign or symptom compatible with the disease) was 25.9 (11.6) years (range 5–60 years) and was similar in cases and controls: 26 (12) years vs. 26 (11) years, respectively ($p=0.9$). The mean (SD) time from SLE onset was 9.5 (8.4) years, and was also similar in cases and controls: 9.8 (9.1) years vs. 9.4 (8.2) years, respectively ($p=0.85$).

The most frequent NPSLE syndrome was cerebrovascular disease, affecting nine patients (28%). Seizures were seen in eight patients (25%) while acute confusional states occurred in six (19%) and psychosis in three (9%). Three more patients (9%)

Table 1 Selected clinical and laboratory characteristics of 32 NPSLE patients and 96 SLE patients without CNS involvement

Variables	NPSLE patients ($n=32$)	SLE patients ($n=96$)	p	Odds ratio*	95%CI
Clinical characteristics					
Antiphospholipid antibody syndrome	14 (44%)	13 (14%)	<0.001	5.1	2.32–11.6
Arthralgias/arthritis	4 (13%)	79 (82%)	<0.001	0.03	0.01–0.12
Discoid rash	1 (3%)	28 (29%)	<0.001	0.07	0.02–0.3
Cutaneous vasculitic lesions	14 (44%)	12 (13%)	<0.001	8.5	3.0–24
Livedo reticularis	13 (41%)	13 (14%)	0.002	4.3	2.0–9.2
Serositis	5 (16%)	28 (29%)	0.13	0.4	0.1–1.3
Arterial thrombosis	10 (31%)	5 (5%)	<0.001	9.3	2.8–31
Venus thrombosis	4 (13%)	14 (15%)	0.67	0.8	0.4–1.9
Pregnancy loss**	7 (22%)	6 (6%)	0.004	6.0	1.8–20
Renal disease	14 (44%)	51 (53%)	0.20	0.7	0.4–1.2
Laboratory data					
Haemolytic anaemia	4 (13%)	6 (6%)	0.12	2.5	0.8–8.0
Leukopenia ($<3500/mm^3$)	10 (31%)	16 (17%)	0.08	2.4	0.9–6.2
Thrombocytopenia ($<100.000/mm^3$)	7 (22%)	0	<0.001	–	–
Positive ANA	32 (100%)	81 (84%)	0.02	–	–
Positive anti-dsDNA	16 (50%)	57 (59%)	0.35	0.7	0.3–1.5
Positive anti-Sm	1 (3%)	10 (10%)	0.20	0.3	0.03–2.3
Positive anti-SS-A/Ro	12 (38%)	34 (35%)	0.83	1.1	0.5–2.7
Positive anti-SS-B/La	7 (22%)	8 (8%)	0.01	4.3	1.4–13
Positive anti-nRNP	2 (6%)	11 (11%)	0.40	0.5	0.11–2.5
Positive aCL IgM in high titre	5 (16%)	12 (13%)	0.56	1.3	0.6–2.7
Positive aCL IgG in high titre	12 (38%)	15 (16%)	0.001	4.5	1.9–10.9
Positive LA	6 (19%)	6 (6%)	0.29	1.8	0.6–5.4
$C_3<53$ mg%	8 (25%)	7 (7%)	0.003	3.8	1.6–9.4
$C_4<20$ mg%	16 (50%)	21 (22%)	<0.001	3.5	1.8–6.8

Data are numbers (percentages). * Derived from conditional logistic regression analysis. ** Results were similar regardless whether the analysis included all women (main analysis) or only women with a history of pregnancies. ACL, anticardiolipin; ANA, antinuclear antibodies; CI, confidence interval; CNS, central nervous system; LA, lupus anticoagulant; NPSLE, neuropsychiatric systemic lupus erythematosus; SLE, systemic lupus erythematosus.

met the diagnostic criteria for demyelinating syndrome, and three patients (9%) had cranial neuropathies. All three patients who developed isolated but significant deficits in cognitive functions had sAPS. Other NP manifestations (including myelopathy, chorea, major depressive episode, and Guillain-Barré syndrome) were less common. Twelve patients (38%) presented with a combination of two or more symptoms concurrently.

Table 1 shows the potential associations of CNS involvement with various clinical and laboratory characteristics in univariate relationships. APS was more common among patients who developed NP events. A history of arterial thrombosis and recurrent fetal loss, as well as the occurrence of IgG isotype aCL antibodies in high titres, were strongly associated with the risk of CNS involvement. Similarly livedo reticularis, another clinical feature often associated with APS, was a significant predictor of NPSLE. Cutaneous vasculitic lesions also correlated with CNS involvement whereas discoid rash, as well as musculoskeletal manifestations of arthralgias and arthritis, was significantly less common in patients with NP disorders. All NPSLE patients were positive for ANA, with titres above 1/160. None of the SLE control group had thrombocytopenia. There was also some evidence that anti-SS-B/La antibodies, as well as low serum levels of C_3 and C_4 complement components, were related to CNS involvement.

Factors associated with NP manifestations in the univariate analysis were entered stepwise into a multiple conditional logistic regression model. As shown in Table 2, articular manifestations and

Table 2 Independent prognostic factors of CNS involvement in systemic lupus erythematosus

Variable	Odds ratio	95%CI	p
Arthralgias/arthritis	0.015	0.00–0.17	<0.001
Arterial thromboses	13	0.82–220	0.069
Discoid rash	0.004	0.00–0.35	0.016
Cutaneous vasculitic lesions	33	1.5–720	0.028

CNS, central nervous system.

discoid rash remained as independent protective factors, while cutaneous vasculitic lesions and arterial thromboses were independent predictors of NPSLE. Articular manifestations reached the highest level of statistical significance, but the absolute magnitude of the associations for all these four predictors was very large. When APS was considered as a candidate predictor, instead of its individual laboratory and clinical components, it was selected as an independent predictor of CNS involvement in the multivariate model, and in addition, low C_4 complement level was an independent risk factor, while arthralgias/arthritis and discoid rash were independent protective factors with odds ratios of similar magnitude (not shown).

Discussion

Central nervous system involvement remains a major cause of morbidity and mortality in SLE.[2–6] Nevertheless, the overall prevalence of major NP disorders varies among series.[2,14] This is mainly due to the difficulty in defining psychiatric abnormalities and cognitive dysfunction in this disease. In some cases it is difficult to determine whether occasional NP manifestations reflect organic damage caused by SLE, or are simply psychological reactions to the stress of having a major chronic systemic illness. In an effort to provide more accurate results, we chose to exclude poorly-defined cognitive dysfunction, anxiety disorders and subtle psychiatric manifestations from our study for the purposes of defining CNS disease as rigorously as possible.

Early observations suggested that vasculitis and thrombocytopenia are significantly and strikingly correlated with NP involvement in SLE patients.[14] Our study confirms these observations. The presence of cutaneous vasculitic lesions was significantly associated with NPSLE in our best-fit multivariate model, and thrombocytopenia also was a significant risk factor for such involvement, at least in univariate analysis.

The most common neuropathological finding in autopsy studies of NPSLE is a small-vessel non-inflammatory proliferative vasculopathy characterized by hyalinization, occasionally associated with occlusion, pericapillary microglia, microinfarcts and microhemorrhages.[21–23] These findings differ from those seen in chronic cutaneous lupus erythematosus, such as discoid lesions, where a perivascular mononuclear inflammatory infiltrate from activated T cells predominates.[24] Different tissue pathology may reflect different pathophysiological mechanisms, and this could explain the strong negative correlation between NPSLE manifestations and the presence of discoid lesions. Furthermore, this association may also indicate that SLE patients with discoid lesions have a more benign disease course overall.

Although articular manifestations are frequent in SLE patients, in our study those patients with NP manifestations had significantly less arthralgia or acute symmetric arthritis than patients without CNS involvement. Recall bias stemming from the retrospective design of the study could possibly affect the strength of this association. Nevertheless, this negative correlation agrees with the results of another study in Greek SLE patients, in which articular manifestations tended to accompany rashes or constitutional symptoms, but not CNS involvement, during flares of the disease.[25] Toubi *et al.* reported no significant difference in the prevalence of skin manifestations and arthritis between NPSLE and SLE control patients.[7] This study was conducted in a different continent, and Black patients represented 20% of the total NPSLE group. Moreover, no exact figures were provided, so it is unknown whether any tendency for a difference might have been present. On the other hand, West *et al.* showed a trend toward a smaller prevalence of articular manifestations in NPSLE group compared with that of SLE control patients.[26] Thus, small sample sizes, patient selection, racial and genetic heterogeneity or differences in environmental factors which may influence disease expression, could explain discrepancies between studies in this field.

Previous studies have tried to determine diagnostic laboratory markers to define or detect active NPSLE, but these have yielded conflicting data, and have generally failed to establish clearly defined pathogenic factors.[27–29] Elevated antibody titres to dsDNA have been proposed as helpful in identifying NPSLE patients,[28] but CNS involvement can occur in the presence of normal values of anti-dsDNA antibodies.[27,29] Controversy also exists regarding the association of anti-Sm antibody with NPSLE manifestations.[28,29] Increased antibody titres to dsDNA, as well as anti-Sm antibody, were not correlated with NP manifestations in our study. On the contrary, low serum levels of C_3, and particularly of C_4 complement components, were seemingly strongly associated with NPSLE. This association probably implies an underlying relation to common pathogenic mechanisms, such as local deposition of immune complexes in blood vessel walls with subsequent complement activation, resulting in vasculitis. Vasculitis of the brain vessels has been documented in 7–15% of NPSLE autopsy cases.[21–23]

Clinical and experimental evidence indicates that aPL antibodies are significantly associated with, and may have a causative role in, vascular thromboses and pregnancy losses.[8,11,30–33] These antibodies have also been implicated as a risk factor for CNS involvement in SLE,[7,9] especially for manifestations

of vascular origin.[8,30] Toubi *et al.* reported that 55% of their CNS/SLE patients had aPL antibodies, compared with 20% in the SLE control group.[7] In that report, SLE patients with thromboembolic manifestations were excluded from the control group. Therefore, certain patients who might have had aPL antibodies were rejected from that study. In our study, we also found that the likelihood of developing CNS events is enhanced in SLE patients by the presence of APS, and that the occurrence of IgG isotype aCL antibodies in high titres was strongly associated with NPSLE. Patients with a history of thromboses in several anatomical sites of arterial circulation, affecting mostly large or medium arteries but also occasionally small vessels, were more likely to have NPSLE. This finding supports previous studies which have shown that recurrent events in patients with aCL antibodies cluster to either the arterial or the venous circulation,[34] and patients tend to have recurrent events of the same type.[35] Factors influencing arterial and venous thrombosis may differ. We also noted that women with a history of two or more spontaneous abortions were six times more likely to have CNS events than those without any recurrent abortions and that livedo reticularis, a minor feature of APS, was a significant predictor for NP disease in a univariate analysis.

The pathogenetic mechanism underlying the association with aPL antibodies is still uncertain. Some studies suggest that it involves interactions between antibodies to anionic phospholipid-protein complexes and antigen targets on platelets,[36] endothelial cells[37,38] or components of the coagulation cascade.[39,40] The possibility that aPL may react with complex brain lipids such as cephalin or sphingomyelin has also been suggested.[41] A genetic component, at least partially mediated through HLA associations,[42] may also explain diversity in studies of different populations.

In summary, CNS involvement in SLE was most strongly associated with the presence of APS features, in particular with arterial thrombosis, and with cutaneous vasculitic lesions. It was negatively related to the presence of articular manifestations and discoid rash. The definition of a group of SLE patients with adverse predictors for NP disease may be important for therapeutic or preventive purposes. Although pulsed cyclophosphamide treatment[43] can achieve favourable responses during NP events, other therapeutic options for NPSLE patients are currently limited. Therefore, pre-emptive interventions may need to be studied in high-risk patients defined by the presence of adverse predictors.

References

1. Bluestein HG. The central nervous system in systemic lupus erythematosus. In: Lahita RG, ed. *Systemic Lupus Erythematosus*, 2nd edn. New York, Churchill Livingstone, 1992.
2. West SG. Neuropsychiatric lupus. *Rheum Dis Clin North Am* 1994; **20**:129–58.
3. Estes D, Christian CL. The natural history of systemic lupus erythematosus by prospective analysis. *Medicine (Baltimore)* 1971; **50**:85–95.
4. Feng PH, Cheah PS, Lee YK. Mortality in systemic lupus erythematosus. A 10-year review. *Br Med J* 1973; **4**:772–4.
5. Ginzler EM, Diamond HS, Weiner M, Schlesinger M, Fries JF, Wasner C, Medsger TA Jr, Ziegler G, Klippel JH, Hadler NM, Albert DA, Hess EV, Spencer-Green G, Grayzel A, Worth D, Hahn BH, Barnett EV. A multicenter study of outcome in systemic lupus erythematosus. Entry variables as predictors of prognosis. *Arthritis Rheum* 1982; **25**:606–11.
6. Rosner S, Ginzler EM, Diamond HS, Weiner M, Schlesinger M, Fries JF, Wasner C, Medsger TA Jr, Ziegler G, Klippel JH, Hadler NM, Albert DA, Hess EV, Spencer-Green G, Grayzel A, Worth D, Hahn BH, Barnett EV. A multicenter study of outcome in systemic lupus. I. Causes of death. *Arthritis Rheum* 1982; **25**:612–17.
7. Toubi E, Khamashta MA, Panarra A, Hughes GRV. Association of antiphospholipid antibodies with central nervous system disease in systemic lupus erythematosus. *Am J Med* 1995; **99**:397–401.
8. Asherson RA, Khamashta MA, Gil A, Vasquez JJ, Chan O, Baguley E, Hughes GRV. Cerebrovascular disease and antiphospholipid antibodies in SLE, lupus-like disease and the primary antiphospholipid syndrome. *Am J Med* 1989; **86**:391–9.
9. Herranz MT, Rivier G, Khamashta MA, Blaser KU, Hughes GRV. Association between antiphospholipid antibodies and epilepsy in patients with systemic lupus erythematosus. *Arthritis Rheum* 1994; **37**:568–71.
10. Wilson WA, Gharavi AE, Koike T, Lockshin MD, Branch DW, Piette JC, Brey R, Derksen R, Harris EN, Hughes GRV, Tripplett DA, Khamashta MA. International consensus statement on preliminary classification criteria for definitive antiphospholipid syndrome. *Arthritis Rheum* 1999; **42**:1309–11.
11. Alarcon-Segovia D, Deleze M, Oria CV, Sanchez-Guerrero J, Gomez-Pachero L, Cabiedes J, Fernandez L, Ponce de Leon S. Anti-phospholipid antibodies and the antiphospholipid syndrome in systemic lupus erythematosus. *Medicine (Baltimore)* 1989; **68**:353–65.
12. Deleze M, Alarcon-Segovia D, Oria CV. Hemocytopenia in systemic lupus erythematosus: relationship to antiphospholipid antibodies. *J Rheumatol* 1989; **16**:926–30.
13. Sneddon JB. Cerebrovascular lesions in livedo reticularis. *Br J Dermatol* 1967; **14**:259–62.
14. Feinglass EJ, Arnett FC, Dorsh CA, Zizic TM, Stevens MB. Neuropsychiatric manifestations of systemic lupus erythematosus: diagnosis, clinical spectrum and relationships to other features of the disease. *Medicine (Baltimore)* 1976; **55**:323–39.
15. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, Schaller JG, Talal N, Winchester RJ. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982; **25**:1271–7.
16. ACR Ad Hoc Committee on Neuropsychiatric Lupus Nomenclature. Case definitions for neuropsychiatric syndromes in systemic lupus erythematosus. *Arthritis Rheum* 1999; **42**:599–608.
17. Harris EN. Antiphospholipid syndrome. In: Klippel JH,

Dieppe PA, eds. *Rheumatology*. Philadelphia, Mosby-Year Book Europe, 1994: section 6, 32.1–32.6.

18. Tzioufas AG, Manoussakis MN, Drosos AA, Silis G, Charavi AE, Moutsopoulos HM. Enzyme immunoassays for the detection of IgG and IgM anti-ds-DNA antibodies: Clinical significance and specificity. *Clin Exp Rheumatol* 1987; **5**:247–53.
19. Thiagarajan P, Pengo V, Shapiro SS. The use of the dilute Russell viper venom time for the diagnosis of lupus anticoagulants. *Blood* 1986; **68**:869–74.
20. Manoussakis MN, Charavi AE, Drosos AA, Kitridou RC, Moutsopoulos HM. Anticardiolipin antibodies in unselected autoimmune rheumatic disease patients. *Clin Immunol Immunopath* 1987; **44**:297–307.
21. Johnson RT, Richardson EP. The neurologic manifestations of systemic lupus erythematosus, a clinical-pathological study of 24 cases and review of the literature. *Medicine (Baltimore)* 1968; **47**:337–69.
22. Ellis SG, Verity MA. Central nervous system involvement in systemic lupus erythematosus: a review of neuropathologic findings in 57 cases, 1955–1977. *Semin Arthritis Rheum* 1979; **8**:212–21.
23. 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.
24. Laman SD, Provost TT. Cutaneous manifestations of lupus erythematosus. *Rheum Dis Clin North Am* 1994; **20**:195–212.
25. Vlachoyiannopoulos PG, Karassa FB, Karakostas KX, Drosos AA, Moutsopoulos HM. Systemic lupus erythematosus in Greece. Clinical features, evolution and outcome: a descriptive analysis of 292 patients. *Lupus* 1993; **2**:303–12.
26. West SG, Emlen W, Werner MH, Kotzin BL. Neuropsychiatric lupus erythematosus: a 10-year prospective study on the value of diagnostic tests. *Am J Med* 1995; **99**:153–63.
27. Swaak AJ, Huysen V, Nossent JC, Smeenk RJ. Antinuclear antibody profiles in relation to specific disease manifestations of systemic lupus erythematosus. *Clin Rheumatol* 1990; **9**:82–94.
28. Winn DM, Wolfe JF, Lindberg DA, Fristoe FH, Kingsland L, Sharp GC. Identification of a clinical subset of systemic lupus erythematosus by antibodies to the Sm antigen. *Arthritis Rheum* 1979; **22**:1334–7.
29. Winfield JB, Brunner CM, Koffler D. Serologic studies in patients with systemic lupus erythematosus and central nervous system dysfunction. *Arthritis Rheum* 1978; **21**:289–93.
30. Love PE, Santoro SA. Antiphospholipid antibodies: Anticardiolipin and the lupus anticoagulant in systemic lupus (SLE) erythematosus and non-SLE disorders. *Am Intern Med* 1990; **112**:682–98.
31. Lockshin MD, Druzin ML, Goei S, Qamar T, Magid MS, Jovanovic L, Ferenc M. Antibody to cardiolipin as a predictor of fetal distress or death in pregnant patients with systemic lupus erythematosus. *N Engl J Med* 1985; **313**:152–6.
32. Hamsten A, Norberg R, Bjorkholm M, De Faire V, Holm G. Antibodies to cardiolipin in young survivors of myocardial infarction: an association with recurrent cardiovascular events. *Lancet* 1986; **1**:113–16.
33. Pierangeli SS, Liu XW, Anderson G, Barker JH, Harris EN. Thrombogenic properties of murine anti-cardiolipin antibodies induced by β_2-glycoprotein 1 and human IgG antiphospholipid syndrome. *Circulation* 1996; **94**:1746–51.
34. Rosove MH, Brewer PMC. Antiphospholipid thrombosis: clinical course after the first event in 70 patients. *Ann Intern Med* 1992; **117**:303–8.
35. Tektonidou M, Ioannidis JPA, Boki KA, Vlachoyiannopoulos PG, Moutsopoulos HM. Predictive factors for serious clinical outcomes in patients with antiphospholipid syndrome. In: *Abstracts of EULAR 2000, Annual European Congress of Rheumatology*. Nice, 2000.
36. Campbeli AL, Pierangeli SS, Wellhausen S, Harris EN. Comparison of the effect of anticardiolipin antibodies from patients with the antiphospholipid syndrome and with syphilis on platelet activation and aggregation. *Thromb Haemostasis* 1995; **73**:529–34.
37. Oosting JD, Derksen RHWM, Blokzijl L, Sixma JJ, Degroot PG. Antiphospholipid antibody positive sera enhance endothelial cell procoagulant activity: Studies in a thrombosis model. *Thromb Haemostasis* 1992; **68**:278–84.
38. Simantov R, Lo SK, Charavi A, Sammaritano LR, Salmon HE, Silverstein RL. Antiphospholipid antibodies activate vascular endothelial cells. *Lupus* 1996; **5**:440–1.
39. Cariou R, Tobelin G, Belluci S, Soria J, Soria C, Maclouf J, Caen J. Effect of the lupus anticoagulant on antithrombogenic properties of endothelial cells-inhibition of thrombomodulin dependent protein C activation. *Thromb Haemostasis* 1988; **60**:54–8.
40. Malia RG, Kitchen S, Greaves M, Preston FE. Inhibition of activated protein C and its cofactor protein S by antiphospholipid antibodies. *Br J Haematol* 1990; **76**:101–7.
41. Harris EN, Gharavi AE, Boey ML, Patel BM, Mackworth-Young CG, Loizou S, Hughes GRV. Anticardiolipin antibodies: detection by radioimmunoassay and association with thrombosis in systemic lupus erythematosus. *Lancet* 1983; **2**:1211–14.
42. Ioannidis JPA, Tektonidou MG, Vlachoyiannopoulos PG, Stavropoulos-Giokas C, Spiropoulou M, Reveille J, Arnett FC, Moutsopoulos HM. HLA associations of anti-beta2 glycoprotein response in a Greek cohort with antiphospholipid syndrome and meta-analysis of four ethnic groups. *Human Immunology* 1999; **60**:1274–80.
43. Boumpas DT, Yamada H, Patronas NJ, Scott D, Klippel JH, Balow JE. Pulse cyclophosphamide for severe neuropsychiatric lupus. *Q J Med* 1991; **81**:975–84.