

The use of anti-ribosomal P antibodies in the diagnosis of cerebral lupus—superiority of western blotting over enzyme-linked immunosorbent assay

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This study investigated the use of anti-ribosomal P antibodies in the diagnosis of cerebral complications of systemic lupus erythematosus using two different methods—western blotting and enzyme-linked immunosorbent assay. Anti-ribosomal P antibodies in patient serum were detected in both methods using a purified ribosomal P antigen substrate. Western blotting detected anti-ribosomal P antibodies with a 90% specificity for systemic lupus erythematosus in 56% of patients with the disease. The detection of anti-ribosomal P antibodies by western blotting in patients with systemic lupus erythematosus was significantly associated with psychosis and/or seizures; detection was positive in 90% of patients with these cerebral complications and in 41% of those without. Elevation of the level of anti-ribosomal P antibody, as measured by enzyme-linked immunosorbent assay, was 99% specific for systemic lupus erythematosus in 44% of patients with systemic lupus erythematosus that was not associated with cerebral involvement. We conclude that the measurement of anti-ribosomal P antibodies by western blotting is helpful in the diagnosis of cerebral lupus in selected patients.

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Introduction

The involvement of the central nervous system in systemic lupus erythematosus (SLE) remains a serious but poorly understood manifestation of the disease. Clinically, patients may present with affective disorders, strokes, psychosis, or seizures. The occurrence of psychosis, and/or seizures appears to be relatively rare in Hong Kong Chinese SLE patients, with reported incidences of 3% to 26%.^{1,2} The diagnosis of these complications may be difficult and other processes, which include metabolic encephalopathy, steroid-induced psychosis, or infection must be excluded. Various auto-antibodies have been linked to the pathogenesis of cerebral lupus, including anti-neuronal,^{3,5} anti-lymphocyte,⁶⁻⁸ anti-ribosomal P protein,^{9,10} and

anti-cardiolipin antibodies.¹¹ The clarification of these clinicoserological correlations would facilitate the management of cerebral lupus and lead to a better understanding of the disease. Anti-ribosomal P antibodies show a high degree of specificity for SLE^{12,13} but their association with cerebral complications have been more controversial. This topic has been reviewed recently.¹⁴ Although most studies have reported anti-ribosomal P antibodies to be associated with SLE psychosis,^{9,10,13,15} others have questioned this association.¹⁶⁻¹⁹ Furthermore, the prevalence of anti-ribosomal P antibodies in patients with SLE psychosis varies from 29% to 90%.^{9,10} Serum anti-ribosomal P antibodies in these reports have been mainly assayed by enzyme-linked immunosorbent assay (ELISA). The present study aims to re-examine the association between cerebral lupus and anti-ribosomal P antibodies as detected by western blotting and ELISA.

Subjects and methods

Patients and blood samples

All patients were ethnic Chinese and were under the care of the Department of Medicine, The University of Hong Kong. Patients were classified as having SLE

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according to the 1982 revised criteria of the American Rheumatism Association (ARA).²⁰ Cerebral lupus was defined as seizure, psychosis, or organic brain syndrome in the absence of offending drugs or known metabolic derangements such as uraemia, ketoacidosis, electrolyte imbalance, or infection. Ten patients with cerebral lupus were recruited. Of these, two were newly diagnosed as having SLE. The other eight were known to have SLE at presentation of their cerebral events. Six of the eight patients were taking an oral corticosteroid but none had a sudden change of steroid dose prior to the cerebral event. All patients presented with a high fever. Eight patients had magnetic resonance imaging changes that suggested the development of vasculitic infarcts; cerebral lupus in the remainder was diagnosed before magnetic resonance imaging was available. Patients with mild personality or behavioural changes were excluded from the cerebral lupus group. Disease activity was measured using the SLE disease activity index (SLEDAI),²¹ which combines clinical assessments and laboratory measurements. Antibodies against double-stranded DNA were measured using an in-house ELISA, and complements C3 and C4 were measured by nephelometry. Patients with an SLEDAI ≥ 8 were considered to have active disease; those with an SLEDAI < 4 and from 4 to 7 are categorised as having inactive disease and moderately active disease, respectively.

Patients in the other disease groups and control subjects were age- and sex-matched. Rheumatoid arthritis was defined according to the 1987 revised criteria of the ARA.²² Other rheumatic diseases included discoid lupus erythematosus, systemic sclerosis, dermatomyositis, polymyositis, and primary Sjögren's syndrome. Lupus-related disease patients who had fewer than four of the 11 SLE criteria were classified as having other rheumatic diseases; antibody against SS-A/Ro (one of the extractable nuclear antigens) was commonly found in these patients. Serial serum samples were also obtained from eight cerebral lupus patients both before and after the cerebral events. For the other patient groups and controls, only single serum samples were analysed.

Enzyme-linked immunosorbent assay

Microtitre plates precoated with ribosomal P antigen (1 unit per well; Immunovision, Springdale, Arkansas, USA) were blocked with phosphate-buffered saline (PBS) containing 1% (w/v) bovine serum albumin (BSA) and 0.05% (v/v) Tween-20 and shaken for 1 hour at room temperature. After washing, the plates were exposed to human sera diluted 1:50 and shaken for 1 hour at room temperature. Plates were again

washed and exposed to alkaline phosphatase-conjugated goat anti-human IgG (Biosource, Camarillo, California, USA) diluted 1:1000 in PBS-Tween containing 1% BSA and shaken for 1 hour at room temperature. After washing, colour was developed with 1 mg/mL p-nitrophenol phosphate disodium (Sigma, St. Louis, Missouri, USA) in diethenolamine buffer and shaken for 10 to 15 minutes at 37°C. The optical density at 405 nm (OD_{405}) was related to a standard positive serum (Light Diagnostics, Temecula, California, USA). The OD_{405} reading corresponding to 1:100 dilution of this standard was arbitrarily assigned to be 100% and the standard curve was created by a four-fold serial dilution from 100% to 0.39%. Test sera were considered positive if the mean of triplicate samples was at least three standard deviations above the mean value obtained from 40 samples of normal sera.

Western blotting

Ribosomal P antigen was obtained from Immunovision at a concentration of 1 $\mu\text{g}/\mu\text{L}$. The antigen was mixed with an equal volume of sodium dodecyl sulphate (SDS) sample buffer (4% [w/v] SDS, 20% [v/v] glycerol, 10% [v/v] 2-mercaptoethanol, 0.12 mol/L Tris pH 6.8) and incubated in boiling water for 3 minutes. The mixture was applied to a 12% SDS-polyacrylamide gel and electrophoresed at 100 volts for 3 hours. Antigens were transferred to nitrocellulose membrane in carbonate buffer (10 mmol/L NaHCO_3 , 3 mmol/L Na_2CO_3 ; pH 9.9) in 20% (v/v) methanol at 30 mA for 1.5 hours. The membrane was cut into 3-mm-wide strips and stored at 4°C before use. Before incubation with sample sera, the strips were blocked with 5% non-fat milk in PBS for 1 hour at room temperature. Sample and standard sera were diluted 1:50 in PBS with 2% BSA and 0.1% Tween-20. The strips were immersed in sera, shaken at room temperature for 2 hours, and washed with PBS containing 0.05% (v/v) Nonidet P40. Rabbit anti-human IgG peroxidase conjugate (Dakopatts, Glostrup, Denmark), diluted 1:1000, was added and the strips shaken for 1 hour at room temperature before washing. The membrane was dried on filter paper and reacted with the enhanced chemiluminescence western blotting detection reagents (Amersham International Plc., Buckinghamshire, UK) for 1 minute. After drying, the membrane was exposed to X-ray film for about 10 seconds. The anti-ribosomal P antibodies standard (Light Diagnostics, Temecula, California, USA) reacted with three peptide bands from the substrate whose molecular weights were 39 kd (peptide P0), 20 kd (P1), and 18 kd (P2).

Statistical analysis

The Chi-squared test was used to determine the

Table 1. Detection of anti-ribosomal P antibodies by enzyme-linked immunosorbent assay or western blotting

Disease category	No. of patients	No. of patients with positive results (%)	
		ELISA	Western blotting
SLE* with cerebral complications	10	4 (40)	9 (90)
SLE without cerebral complications	22	10 (45)	9 (41)
Rheumatoid arthritis	38	0	2 (5)
Other rheumatic diseases	31	1 (3)	5 (16)
Control	40	1 (3)	0

*SLE systemic lupus erythematosus

significance of correlation between the occurrence of anti-ribosomal P antibodies and cerebral lupus.

Results

Incidence of cerebral lupus

During the study period (1 July 1993 to 30 June 1996), a total of 153 patients with SLE were followed up. Cerebral lupus was diagnosed in eight of the patients during this time. In addition, two patients with a past history of cerebral lupus (one in 1983 and the other in 1985) were identified by reviewing the clinical records. This gave a prevalence of cerebral lupus with psychosis and/or seizures of 6.5% in Chinese SLE patients. Anti-ribosomal P antibodies were tested in all 10 patients who had cerebral lupus and in 22 lupus patients without cerebral complications. The two groups of patients had similar age and sex distributions.

Detection of anti-ribosomal P antibodies by enzyme-linked immunosorbent assay

Anti-ribosomal P antibody levels measured by ELISA were increased in 44% (14/32) of the SLE patients, none of the 38 rheumatoid arthritis (RA) patients, 3% (1/31) of the patients with other rheumatic diseases, and 3% (1/40) of the control subjects (Table 1). The only patient with a raised anti-ribosomal P antibody level in the 'other rheumatic diseases' group was suffering from a lupus-related disorder. This indicated a high specificity (99%) but a medium sensitivity (44%) in measuring anti-ribosomal P antibodies for the diagnosis of SLE. Of the 10 SLE patients with cerebral lupus, four (40%) had a raised level of anti-ribosomal P antibody; this was similar

to the patients without cerebral lupus (10/22; 45%). Measuring the anti-ribosomal P antibody level by ELISA was thus neither sensitive (40%) nor specific (55%) for the diagnosis of cerebral lupus.

Detection of anti-ribosomal P antibodies by western blotting

Antibodies reacted with the P0, P1, and P2, or P1 and P2 peptides of the ribosomal P antigen in 56% (18/32) of SLE patients, 5% (2/38) of RA patients, 16% (5/31) of patients with other rheumatic diseases, and none of the 40 control subjects (Tables 1 and 2). Of the five patients with other rheumatic diseases who had anti-ribosomal P antibodies, two had a lupus-related disorder, two had Sjögren's syndrome, and one had discoid lupus erythematosus. Cerebral complications were not found in these five patients. The sensitivity and specificity of western blotting in detecting anti-ribosomal P antibodies to diagnose SLE were thus comparable to the sensitivity and specificity of ELISA (56% and 90%, respectively). A significantly greater proportion of cerebral lupus patients had detectable anti-ribosomal P antibodies than non-cerebral lupus patients (90% versus 41%, respectively; $P < 0.05$). Hence, western blotting had a good sensitivity (90%) but moderate specificity (59%) for the diagnosis of cerebral lupus. Of the 18 SLE patients with anti-ribosomal P antibodies, 13 showed reactions to all three peptides while the remainder were reactive with P1 and P2 peptides only. Reaction with only P1 and P2 peptides was more common in cerebral SLE patients (4/9) than in non-cerebral SLE patients (1/9), but the difference was not statistically significant (Table 2).

Table 2. Detection of antibodies against the three ribosomal P peptides by western blotting

Disease category	No. of patients	No. of patients positive for:		No. of patients negative
		P0, P1, and P2	P1 and P2 only	
SLE* with cerebral complications	10	5	4	1
SLE without cerebral complications	22	8	1	13
Rheumatoid arthritis	38	1	1	36
Other rheumatic diseases	31	3	2	26
Control	40	0	0	40

*SLE systemic lupus erythematosus

Table 3. Correlation between the presence of anti-ribosomal P antibodies and lupus disease activity

Detection method	Cerebral lupus patients No. (%)		Non-cerebral lupus patients No. (%)		
	Active disease (SLEDAI* \geq 8), n=10	Inactive disease (SLEDAI <4), n=0	Active disease (SLEDAI \geq 8), n=6	Moderately active (SLEDAI, 4-7) n=4	Inactive disease (SLEDAI <4), n=12
ELISA	4 (40)	0	3 (50)	2 (50)	5 (42)
Western blotting	9 (90)	0	2 (33)	2 (50)	5 (42)

*SLEDAI systemic lupus erythematosus disease activity index

Correlation between the presence of anti-ribosomal P antibodies and the systemic lupus erythematosus disease activity index

Correlations between anti-ribosomal P antibodies and the SLEDAI of the cerebral lupus and non-cerebral lupus patients at the time of study are shown in Table 3. All cerebral lupus patients had an SLEDAI \geq 8 which by definition indicated active disease. 40% (4/10) of the patients tested positive for anti-ribosomal P antibodies by ELISA; and 90% (9/10) of patients tested positive by western blotting. For eight of the cerebral lupus patients, serial blood samples were obtained before and after the cerebral event and when their disease was inactive (SLEDAI <4). Anti-ribosomal P antibodies were detectable by western blotting both before (up to 3 months) and after (up to 3 years) the cerebral episode. Except in one patient, anti-ribosomal P antibodies remained detectable after the cerebral disease had subsided. For anti-ribosomal P antibodies measured by ELISA, serial measurements showed an increase in antibody level during the cerebral episode in two of the eight patients (Fig). Thus, in most patients there was no correlation between the anti-ribosomal P antibody level and cerebral disease.

Among non-cerebral lupus patients, there were 6, 4, and 12 patients with active (SLEDAI >7), moderately active (SLEDAI from 4 to 7), and inactive (SLEDAI <4) disease, respectively, at the time of study. When measured by ELISA, anti-ribosomal P antibodies were found to be present in 50% (3/6), 50% (2/4), and 42% (5/12) of patients with active, moderately active, and inactive disease, respectively. When measured by western blotting, anti-ribosomal P antibodies were present in 67% (2/3), 50% (2/4), and 42% (5/12) of patients with active, moderately active, and inactive disease, respectively.

Discussion

Auto-antibodies that react with eukaryotic 60S ribosomal phosphoproteins have been identified by western blotting as three distinct bands—namely, P0 (38 kd), P1 (18 kd), and P2 (17 kd).²³ The three proteins share a common linear epitope within the carboxyl-terminal 22 amino acids of each protein.²⁴ These auto-antibodies have been reported to occur in sera from 10% to 20% of patients with SLE.^{10,13,23,25,26} A higher occurrence of these antibodies was found in the present study (44% by ELISA and 56% by western blotting),

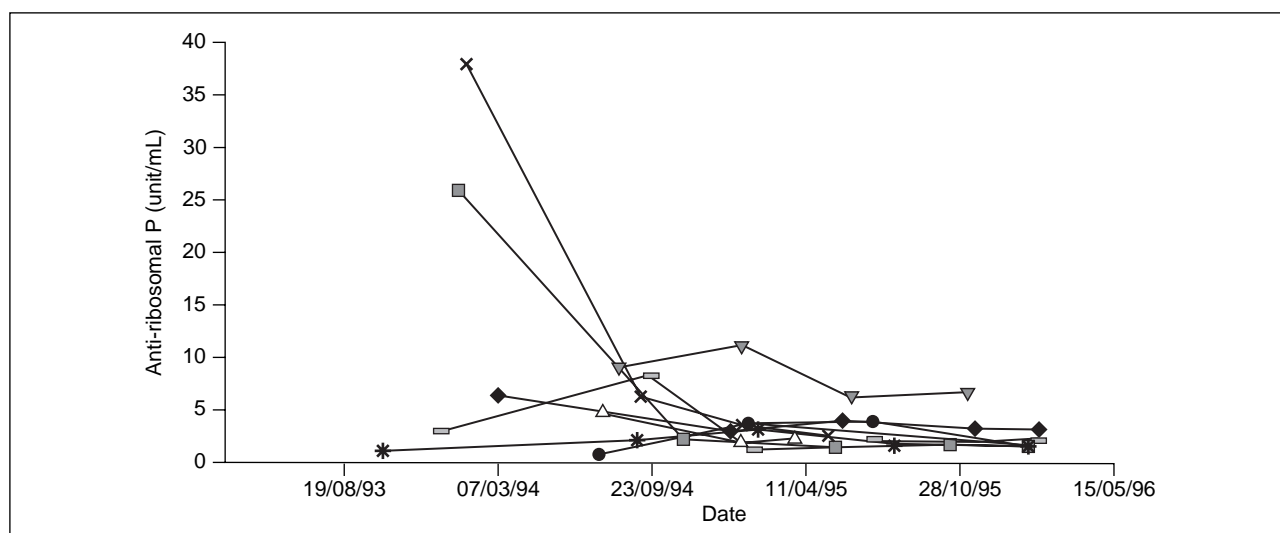


Fig. Serial measurements of anti-ribosomal P antibody level by enzyme-linked immunosorbent assay in eight patients with cerebral lupus

The earliest sample from each patient was obtained during the acute cerebral episode

which could be due to a genetic difference in patient populations. A higher occurrence of anti-ribosomal P in the Chinese population has been reported previously.^{15,19,27} Similarly, a higher incidence of anti-Ro and a lower incidence of anti-Sm antibodies have also been found in local Chinese SLE patients.^{1,2} Technical differences in assay methods is a less likely explanation because two standard methods have been used in the current study and both showed a high prevalence of anti-ribosomal P antibodies in our population.

A pathogenic role for anti-ribosomal P antibodies has been suggested by studies that show an association with cerebral disease in SLE patients,^{9,10,13,15} although this has not been confirmed by other studies.¹⁶⁻¹⁹ The controversy might be due to different definitions of cerebral complications in different studies. Using the 1982 revised ARA criteria for SLE, the present study confirms the association of psychosis and/or seizures in SLE patients with the occurrence of anti-ribosomal P antibodies when detected by western blotting. No association was found if antibodies were assayed by ELISA. This discrepancy may be explained by the difference in the two methodologies. Although ELISA is generally considered to have a higher analytical sensitivity than western blotting, two different detecting antibodies were used in this study. The two assays were therefore not directly comparable. Another disadvantage of ELISA is that non-specific reactions may be measured if the antigen used is not pure. The antigen used in this study consistently formed several other reaction bands with patient and normal sera in western blotting. These bands were considered non-specific because their positions were not those of the three standard ribosomal P peptides. By the nature of ELISA, these non-specific reactions were not distinguishable and would be considered as part of the positive reaction. Western blotting was thus more specific in defining antibody specificities. Another problem in our study is the relatively small number of patients with cerebral disease and the prevalence of cerebral complications among the SLE patients was low (6.5%). This could be improved by performing a multicentre study.

It remains unknown whether auto-antibody production against intracellular antigens in SLE is a cause or an effect of the disease process. The presence of anti-ribosomal P antibodies does not appear to be related to the overall disease activity, as shown in our study. In addition, this and other studies have shown that about 50% of SLE patients without cerebral complications have detectable anti-ribosomal P antibodies. The pathogenic role of anti-ribosomal P antibodies is thus doubtful.^{9,14} Small vessel infarcts

have frequently been found in the brain of patients with cerebral lupus.²⁸ Neuronal degeneration in these lesions may predispose to anti-ribosomal P antibody production, because neurons are rich in ribosomes. On the other hand, anti-ribosomal P antibodies have not been detected in a variety of infections and neoplasms of the central nervous system.²⁹ In our study, anti-ribosomal P antibodies were detected both before and after the cerebral events. These findings may argue against the theory that anti-ribosomal P antibodies might be produced as a result of neuronal damage.

If anti-ribosomal P antibodies have a pathogenic role in cerebral lupus, the exact mechanism of specific organ dysfunction is unknown. The antibodies inhibit protein synthesis during in vitro protein synthesis and when microinjected into cultured human fibroblasts.³⁰ Several studies have failed to detect anti-ribosomal P antibodies in cerebrospinal fluid, which suggests the possibility of their sequestration by brain antigens.^{10,16} Though ribosomal P is a cytoplasmic protein, anti-ribosomal P antibodies have been shown to react with a plasma membrane protein located on the surface of human neuronal cells.^{31,32} However, matching for a cross-reactive brain membrane antigen using a computer search has been unsuccessful.¹⁰

Regardless of the pathogenic role of anti-ribosomal P antibodies, measuring these antibodies in the serum from patients with SLE may be clinically useful in the evaluation of cerebral disease. Of the numerous tests proposed to detect cerebral lupus, none has consistently had sufficient diagnostic sensitivity and specificity. The diagnosis of cerebral lupus is often based on clinical features and imaging techniques. Our study shows that assaying anti-ribosomal P antibodies by western blotting has a high sensitivity and is helpful in excluding cerebral lupus if the test is negative. A positive result, however, is not diagnostic: 41% of lupus patients tested positive, despite having no cerebral involvement. Our results also show that ELISA is much less useful. This may be due to the difficulty in obtaining a purified ELISA antigen.

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