EXTENDED REPORT

Evoked potential studies in the antiphospholipid syndrome: differential diagnosis from multiple sclerosis

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Ann Rheum Dis 2006;**65**:525–528. doi: 10.1136/ard.2005.040352

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Accepted 15 August 2005
Published Online First
17 August 2005

Background: The CNS manifestations of the antiphospholipid syndrome (APS) can mimic multiple sclerosis both clinically and radiologically.

Objective: To compare evoked potential studies in APS patients and patients with multiple sclerosis with similar neurological disability.

Methods: 30 APS patients with CNS manifestations and 33 patients with definite multiple sclerosis and similar neurological disability underwent studies of visual evoked potentials (VEP), somatosensory evoked potentials (SSEP) in the upper and lower limbs (UL, LL), and sympathetic skin responses (SSR) in the upper and lower limbs.

Results: The neurological manifestations in the APS patients included stroke ($n=17$), transient ischaemic attacks ($n=10$), and severe headache with multiple white matter lesions on brain MRI ($n=3$). Abnormal SSEP (LL), and SSR (UL; LL) were seen in APS patients (37%, 27%, and 30%, respectively) but VEP and UL SSEP were rarely abnormal (10% and 6%, respectively in APS v 58% and 33% in multiple sclerosis; $p=0.0005$, $p=0.008$). Mean VEP latencies were more prolonged in multiple sclerosis (116 ms v 101 ms, $p<0.001$). Only one APS patient had abnormal findings in all three evoked potential studies, compared with seven patients in the multiple sclerosis group ($p=0.04$).

Conclusions: Abnormal VEPs are uncommon in APS in contrast to multiple sclerosis. Coexisting abnormalities in all other evoked potentials were similarly rare in APS. In patients with brain MRI findings compatible either with multiple sclerosis or APS, normal evoked potential tests, and especially a normal VEP, may support the diagnosis of APS.

The antiphospholipid syndrome (APS) is characterised by arterial or venous thrombosis, or both, recurrent fetal loss, and the presence of antiphospholipid antibodies (aPL).^{1,2} The diagnosis of APS is currently based on the Sapporo criteria.³ Clinical manifestations of APS are diverse and virtually any organ may be involved.² A broad spectrum of neurological manifestations has been described in association with APS, including transient ischaemic attacks (TIAs), strokes, chorea, seizures, impaired cognitive function, transverse myelitis, migraine headache, pseudotumor cerebri, cerebral venous thrombosis, and mononeuritis multiplex.^{2,4–9} Because of the diversity of the neurological manifestations, the differential diagnosis is wide and in the absence of previous vascular thrombosis or a typical obstetric history a diagnosis of neurological manifestations of APS may be difficult. This is further complicated by the fact that aPL are found in association with autoimmune diseases, especially systemic lupus erythematosus (SLE), and in 8–33% of patients with multiple sclerosis.^{10–13} APS may mimic multiple sclerosis both clinically and radiologically.⁹ Magnetic resonance imaging (MRI) of the brain in SLE patients, with and without aPL, and in patients with primary APS may show focal white matter brain lesions which can be difficult to distinguish from those found in multiple sclerosis.^{9,14}

As with APS, there is no definite diagnostic test for multiple sclerosis. The diagnosis is based on a combination of clinical and laboratory criteria and the exclusion of other diseases that could explain the neurological condition. Cerebrospinal fluid analysis and brain MRI may aid in the diagnosis.¹⁵ The relapsing forms of multiple sclerosis are

considered clinically definite when neurological dysfunction becomes disseminated in space and time. When there is diagnostic uncertainty, MRI studies and evoked potential studies may provide evidence that the lesions are disseminated in space.¹⁶ Visual or somatosensory evoked potentials (VEP, SSEP), or both, and assessment of central autonomic pathways by means of sympathetic skin responses (SSR) may provide support that there is dissemination in space even in the absence of clinical dysfunction.^{15,16} Evoked potential tests detect functional dysfunction such as slow conduction in various neural pathways, as in the optic nerves and the spinal cord. The evoked potentials reflect both the amount of demyelination and the extent of axonal loss, and are remarkably sensitive to clinically silent lesions.^{17,18}

Neurological symptoms, physical findings, laboratory tests, and MRI studies do not readily distinguish the CNS manifestations of APS from those of multiple sclerosis.⁹ Evoked potentials have, to the best of our knowledge, never been used before in the evaluation of patients with APS. We report here the results of electrophysiological studies done in APS patients with CNS manifestations and in cases of multiple sclerosis sharing a similar neurological disability.

Abbreviations: aPL, antiphospholipid antibodies; APS, antiphospholipid syndrome; EDSS, Expanded Disability Status Scale; SSEP, somatosensory evoked potentials; SSR, sympathetic skin responses; VEP, visual evoked potentials

Table 1 Brain magnetic resonance imaging grading system

Size of lesion	Grade
Just seen (<2 mm)	1
Small (2.1–5.0 mm)	2
Medium (5.1–10 mm)	3
Large (>10 mm)	4
Patchy confluent	5
Number of lesions	
1	1
2–5	2
6–10	3
>10	4
Confluent	1–5

Total severity score = lesion size grade × lesion number grade.

Adapted from Cuadrado *et al.*⁹

METHODS

Patients

Thirty APS patients with CNS manifestations (20 with primary APS and 10 with APS secondary to SLE), all fulfilling the Sapporo criteria, and 33 definite cases of multiple sclerosis with a similar neurological disability underwent electrophysiological studies. These studies are done as part of our routine assessment in all patients with multiple sclerosis and all APS patients with CNS manifestations.

APS patients were recruited consecutively from the rheumatology and neuroimmunology clinics at the Tel-Aviv Sourasky Medical Centre. They were diagnosed as having APS on the basis of evidence of a stroke with a documented neurological deficit, evidence of a vascular thrombotic event outside the CNS, or a typical obstetric history, and the presence of aPL (anticardiolipin IgG, or anticardiolipin IgM, or lupus anticoagulant) on at least two occasions, at least six weeks apart. Anticardiolipin antibodies were measured in different laboratories in the outpatient clinics, using standard commercial enzyme linked immunosorbent assay (ELISA) kits. For each patient the tests were repeated in the same initial laboratory. Lupus anticoagulant was measured in all the patients in a single hospital based laboratory, using the activated partial thromboplastin time test (APTT) with a lupus anticoagulant sensitive thromboplastin, or the dilute Russell viper venom test (dRVVT).

Patients with clinically definite multiple sclerosis according to established clinical criteria (at least two exacerbations together with at least three typical lesions on MRI) were recruited from the neuroimmunology clinic at the Tel-Aviv Sourasky Medical Centre.

Neurological disability

All patients underwent a full neurological examination. The degree of neurological disability was scored according to the Expanded Disability Status Scale (EDSS) in both the multiple sclerosis and the APS groups.^{17, 19}

Table 2 Characteristics of the patients with antiphospholipid syndrome (APS) and multiple sclerosis (MS)

	APS	MS
Age (years)	48.3 (14.5)	36.8 (13.2)
F/M*	25/5	20/13
Neurological disability (EDSS)	1.4 (1.7)	2.0 (1.6)

Values are mean (SD) or *n.

EDSS, Expanded Disability Status Scale.

Electrophysiological studies

All patients underwent an extensive neurophysiological study using Nicolet Viking IV equipment (Madison, Wisconsin, USA). The evoked potentials examined were VEP, SSEP, and SSR.

Visual evoked potentials

VEP were elicited by a pattern reversal checkerboard of black and white squares of size 30 inches and a screen of 11°. Two or more sequences of at least 256 trials were averaged for each eye. Responses were recorded from electrode sites Oz, O₁, and O₂, using Fz as reference. The latency of the P100 peak and the amplitude of P100-N145 wave were measured. Responses were considered abnormal if absent, or if the P100 latencies exceeded 115 ms in at least one eye, or if there was an amplitude difference exceeding 50% between the better and worse eye.

Somatosensory evoked potentials

SSEP were elicited by square wave pulses of 0.1 ms duration, delivered percutaneously over the median nerves at the wrists and over the tibial nerves at the ankles. The stimulus of lowest intensity that caused a small twitch in the corresponding muscles was used. Two or more sequences of at least 512 trials in the arms and 1024 trials in the legs were averaged. Recording sites for arm stimulation were contralateral C3'/C4' and for leg stimulation Cz', both referenced to FPz. The measured variables were: in the upper limbs the cortical N20 latency to peak and baseline to peak amplitude; in the lower limbs the latency of the cortical P38 wave and its baseline to peak amplitude. Responses were considered abnormal if N20 or P38 was absent, or delayed to more than 21 ms for N20 or 46 ms for P38 in at least one limb, or if there was an amplitude difference of more than 50% between the better and worse side.

Sympathetic skin responses

SSR were recorded synchronously from both palms and soles following a single supramaximal square wave electrical stimulus of the right median nerve at the wrist.¹⁶ Latency to the first peak and peak to peak amplitude were measured for all four limbs. Responses were defined as abnormal if absent in any one limb, or if having an amplitude less than 50% of the contralateral side.

Brain MRI

MRI studies, which were available for review in 23 patients with APS and 30 with multiple sclerosis, were done in several institutions, on different types of machine, and were technically variable. All studies included fast spin echo (FSE) T2 weighted sequences, which were the primary source of information. When available, proton density weighted and FLAIR sequences were used to increase

Table 3 Percentage of abnormal evoked potentials in patients with antiphospholipid syndrome (APS) and multiple sclerosis (MS)

Evoked potential	APS	MS	p Value
VEP	10%	58%	0.0005
UL SSEP	6%	33%	0.008
LL SSEP	37%	45%	NS
UL SSR	27%	27%	NS
LL SSR	30%	35%	NS

LL SSEP, lower limb somatosensory evoked potential; LL SSR, lower limb sympathetic skin response; UL SSEP, upper limb somatosensory evoked potential; UL SSR, upper limb sympathetic skin response; VEP, visual evoked potential.

observation confidence. Lesion load was scored on the basis of a scoring system previously described by Cuadrado *et al.*⁹ Foci and areas of high signal intensity (mostly white matter lesions) were graded according to size and number. The severity score for each focus or area was obtained by multiplying the lesion size grade by the lesion number grade. The sum of these scores comprised the total MRI severity score (table 1).

All MR images were interpreted by a single observer (YS) in a retrospective and blinded fashion. The degree of brain atrophy was assessed on an arbitrary scale of 0–3 (0, no atrophy; 1, mild; 2, moderate; 3, severe).

Statistical analysis

Differences between the groups were determined using Fisher's exact test and the *t* test, as appropriate. Subanalyses stratifying for neurological disability and MRI lesion burden were planned before data collection.

RESULTS

The mean (SD) age of the APS patients recruited to the study was 48.3 (14.5) years. They were mainly female (25/30). Neurological disability, as measured by the EDSS, was mild to moderate, ranging from 0 to 5 (mean 1.4 (1.7)). The corresponding data for the multiple sclerosis patients are given in table 2.

The CNS manifestations in the APS patients included stroke in 17, TIAs with multiple white matter lesions on brain MRI in 10, and severe headache with multiple white matter lesions on brain MRI in three. The latter three patients had a history of recurrent pregnancy loss (2) or a thrombotic event outside the central nervous system (arterial thrombosis of hand) (1). Other APS related events in the APS patients included superficial vein thrombosis in one patient, deep vein thrombosis in four, arterial thrombosis in two (in one patient involving the femoral artery and leading to a below knee amputation), central retinal vein occlusion in one patient, and recurrent pregnancy loss in six cases, including intrauterine death in the third trimester in one.

We compared the results of the APS patients with those seen in multiple sclerosis. The percentages of abnormal VEP, upper and lower limb SSEP, and upper and lower limb SSR tests in the multiple sclerosis group (58%, 33%, 45%, 27%, and 35%, respectively) were higher than in the APS group (10%, 6%, 37%, 27%, and 30%). This difference was statistically significant for the VEP and upper limb SSEP tests ($p = 0.0005$ and $p = 0.008$, respectively, Fisher's exact test) (table 3).

Exclusion of the three APS patients whose CNS manifestation was severe headache did not change the significance of the results (data not shown). Mean VEP latencies were significantly prolonged in the multiple sclerosis patients compared with the APS patients (mean (SD): 116 (18) ms *v* 101 (9) ms, $p < 0.001$). VEP amplitudes, SSEP latencies and amplitudes, and SSR latencies and amplitudes did not show any reliable trend. Only one APS patient had abnormal findings in all three evoked potential tests, compared with seven in the multiple sclerosis group ($p = 0.04$, Fisher's exact test).

Brain MRI scores ranged from 0 to 65 in the APS patients, with an average of 17.5 (14.3), and in the multiple sclerosis patients from 4 to 65, with an average of 30.7 (16.6) ($p < 0.01$, *t* test). Scores for brain atrophy ranged from 0 to 3 in the APS patients, with an average of 1.1 (1.0), and from 0 to 2.5 in the multiple sclerosis patients, with an average of 1.0 (0.9) (NS). When stratifying for neurological disability, multiple sclerosis patients with more severe neurological disability (EDSS ≥ 2 , $n = 14$) had more abnormal VEP ($p = 0.001$), SSEP ($p = 0.04$), and SSR tests ($p = 0.04$) than APS patients with

an EDSS of ≥ 2 ($n = 13$). There were no significant differences between the less disabled patients in either group. In patients matched for high lesion burden (MRI severity score ≥ 20 ; 20 with multiple sclerosis, seven with APS) there were more abnormal VEP ($p = 0.04$), SSEP ($p = 0.02$), and SSR ($p = 0.02$) tests in the multiple sclerosis group. In patients with low lesion burden (MRI severity score < 20 ; 10 with multiple sclerosis, 16 with APS) only abnormal VEP tests were significantly more common in the multiple sclerosis patients ($p = 0.02$).

DISCUSSION

Our study is the first systematic study of evoked potentials in APS patients. The results show that abnormal VEP and upper limb SSEP are quite rare in APS patients. Indeed the optic nerves and spinal cord seem not to be commonly affected in APS (as opposed to multiple sclerosis). Coexisting abnormalities in all evoked potential tests performed were similarly rare in the APS patients. Ten APS cases had completely normal electrophysiological results and in those with abnormal findings an abnormality was demonstrated in a single test in 13 cases, in two tests in five cases, and in three tests in only one case.

Our APS patients had a similar neurological disability to the multiple sclerosis patients; thus it was interesting to compare their electrophysiological results. Multiple sclerosis and APS are autoimmune conditions which affect similar age groups (age 20 to 50) and may have similar neurological manifestations.^{2, 9, 15} There are no definitive diagnostic tests for either condition, and the diagnosis relies on a combination of clinical manifestations, laboratory tests, imaging, and the exclusion of other conditions. Moreover, brain MRI interpretation by a radiologist as compatible with the diagnosis of multiple sclerosis may mislead the clinician. Additional methods may not be helpful in the differential diagnosis. Analysis of cerebrospinal fluid for oligoclonal bands is not specific for multiple sclerosis, neither is the presence of aPL, which may be found in 8–33% of cases of multiple sclerosis, specific for APS.^{13, 20} Two large studies tested patients with multiple sclerosis for aPL antibodies and clinical manifestations. They found aPL antibodies in 2% and 15% of the patients, respectively, and no predominance of any clinical manifestation.^{21, 22} These results do not support the hypothesis suggested by Karussis *et al* that multiple sclerosis with aPL antibodies represents a new subdivision of the disease.²³ In the latter study, atypical clinical manifestations such as persistent headache were more suggestive of a vascular aetiology.²³ As there is still controversy over the specificity of headache as a manifestation of APS,^{8, 24} we reanalysed our data excluding the three cases whose CNS manifestation was severe headache. Exclusion of these patients did not change the significance of the results.

Although the clinical neurological disability—as demonstrated by EDSS scores—was similar in both groups of patients, those with multiple sclerosis had more extensive abnormalities of their evoked potentials. By using clinical and MRI stratification it was possible to show that these differences were more pronounced in patients with more severe neurological disability and a higher white matter lesion load on brain MRI. This finding is compatible with more severe and widespread involvement of myelin in multiple sclerosis, which is unlike the punctate vascular lesions expected in APS.

The APS patients we recruited were older than the multiple sclerosis group, with a 12 year difference in mean age between the two groups. Although this was not our intent, this age difference may further support the significance of our observations, as one might expect more abnormal electrophysiological tests in the older age group, while we

were able to show a smaller percentage of abnormal tests in this group.

In a clinical setting it is often important to make a definitive diagnosis early on as treatment is fundamentally different in these two conditions, and assigning incorrect treatment may be dangerous. For example, β interferon treatment in SLE and other autoimmune diseases may lead to severe exacerbations²⁵; and lifelong anticoagulation, commonly used in APS, entails the risk of haemorrhage, while withholding anticoagulation in APS carries a high risk of recurrent thromboses, which may be fatal.^{2 26}

Evoked potential testing offers simple, inexpensive, objective, and quantitative data on the distribution of functional systems affected, and may detect involvement of systems poorly visualised by neuroimaging. In multiple sclerosis it is now well established that apart from the lesions clearly seen on T2 weighted images there is also diffuse white matter disease, demonstrated by magnetic resonance spectroscopy or by more modern diffusion magnetic resonance techniques such as high-b value diffusion.^{27 28} The use of such techniques in the differentiation of multiple sclerosis from APS is currently under investigation by several groups.²⁹ Physiologically, the present results indicate that multiple sclerosis is a diffuse white matter disease while APS seems to affect the brain in a more restricted and focal manner. Our findings may indicate qualitative as well as quantitative differences between multiple sclerosis, which mainly affects the sensory tracts, and APS, which mainly affects the cortex and motor tracts. This observation may be relevant to the pathogenesis of the autoimmune damage to the brain in the two disorders. A myelin directed reaction seems central to multiple sclerosis, while APS is more likely to involve vascular and neurone specific mechanisms.³⁰

We suggest that in patients with central nervous system findings as the sole clinical manifestation, and in whom brain MRI findings are compatible with either multiple sclerosis or APS, normal evoked potential tests—and especially a normal VEP—support the diagnosis of APS. Our results are based on the study of patients with a clear cut clinical diagnosis. It remains to be seen whether electrophysiological studies can help in making a correct diagnosis in more complicated cases or early in the course of the disease.

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REFERENCES

- Hughes GRV, Harris EN, Gharavi AE. The anticardiolipin syndrome. *J Rheumatol* 1986;**13**:486–9.
- Levine JS, Branch W, Rauch J. The antiphospholipid syndrome. *N Engl J Med* 2002;**346**:752–63.
- Wilson WA, Gharavi AE, Koike T, et al. International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome: report of an international workshop. *Arthritis Rheum* 1999;**42**:1309–1311.
- Levine SR, Brey RL, Sawaya KL, Salowich-Palm L, Kokkinos J, Kostrzema B, et al. Recurrent stroke and thrombo-occlusive events in the antiphospholipid syndrome. *Ann Neurol* 1995;**38**:119–24.
- Cervera R, Asherson RA, Font J, Tikly M, Pallares L, Chamorro A, et al. Chorea in the antiphospholipid syndrome. Clinical, radiologic, and immunologic characteristics of 50 patients from our clinics and the recent literature. *Medicine* 1997;**76**:203–12.
- Verrot D, San-Marco M, Dravet C, Genton P, Disdier P, Bolla G, et al. Prevalence and significance of antinuclear and anticardiolipin antibodies in patients with epilepsy. *Am J Med* 1997;**103**:33–7.
- Menon S, Janeson-Shotall E, Newman SP, Hall-Craggs MR, Chinn R, Isenberg DA. A longitudinal study of anticardiolipin antibody levels and cognitive functioning in systemic lupus erythematosus. *Arthritis Rheum* 1999;**42**:728–34.
- Brey RL, Gharavi AE, Lockshin MD. Neurologic complications of antiphospholipid antibodies. *Rheum Dis Clin North Am* 1993;**4**:833–50.
- Cuadrado MJ, Khamashta MA, Ballesteros A, Godfrey T, Simon MJ, Hughes GR. Can neurologic manifestations of Hughes (antiphospholipid) syndrome be distinguished from multiple sclerosis? Analysis of 27 patients and review of the literature. *Medicine* 2000;**79**:57–68.
- Petri M. Epidemiology of the antiphospholipid antibody syndrome. *J Autoimmun* 2000;**15**:145–51.
- Cervera R, Khamashta MA, Font J, Sebastiani GD, Gil A, Lavilla P, et al. Systemic lupus erythematosus: clinical and immunologic patterns of disease expression in a cohort of 1000 patients. *Medicine* 1993;**72**:113–24.
- Love PE, Santoro SA. Antiphospholipid antibodies: anticardiolipin and the lupus anticoagulant in systemic lupus erythematosus (SLE) and in non-SLE disorders: prevalence and clinical significance. *Ann Intern Med* 1990;**112**:682–98.
- Roussel V, Yi F, Jauberteau MO, Couderc C, Lacombe C, Michelet V, et al. Prevalence and clinical significance of antiphospholipid antibodies in multiple sclerosis: a study of 89 patients. *J Autoimmun* 2000;**14**:259–65.
- Molad Y, Sidi Y, Gornish M, Lerner M, Pinkhas J, Weinberger A. Lupus anticoagulant: correlation with magnetic resonance imaging of brain lesions. *J Rheumatol* 1992;**19**:556–61.
- Noseworthy JH, Lucchinetti C, Rodriguez M, Weinshenker BG. Multiple sclerosis. *N Engl J Med* 2000;**343**:938–52.
- Aminoff MJ, Davis SL, Panitch HS. Serial evoked potentials studies in patients with definite multiple sclerosis. Clinical relevance. *Arch Neurol* 1984;**41**:1197–202.
- Weinshenker BG, Rice GP, Noseworthy JH, Carriere W, Baskerville J, Ebers GC. The natural history of multiple sclerosis: a geographically based study. Applications to planning and interpretation of clinical therapeutic trials. *Brain*, 1991;**114**:1057–67.
- Drory VE, Nisipeanu P, Korczyn AD. Tests of autonomic dysfunction in patients with multiple sclerosis. *Acta Neurol Scand* 1995;**92**:356–60.
- Kurtzke JF. Rating neurological impairment in multiple sclerosis: an Expanded Disability Status Scale (EDSS). *Neurology* 1983;**33**:1444–52.
- Ijdo JW, Conti-Kelly AM, Greco P, Abedi M, Amos M, Provenzale JM, et al. Antiphospholipid antibodies in patients with multiple sclerosis and MS-like illnesses. *Lupus* 1999;**8**:109–15.
- Sastre-Garriga J, Reverter JC, Font J, Tintore M, Espinosa G, Montalban X. Anticardiolipin antibodies are not a useful screening tool in a non-selected large group of patients with multiple sclerosis. *Ann Neurol* 2001;**49**:408–11.
- Heinzle O, Weill B, Johanet C, Szadovitch V, Caillat-Zucman S, Tournier-Lasserre E, et al. Anticardiolipin antibodies in patients with multiple sclerosis do not represent a subgroup of patients according to clinical, familial, and biological characteristics. *J Neurol Neurosurg Psychiatry* 2002;**72**:647–9.
- Karussis D, Leker RR, Ashkenazi A, Abramsky O. A subgroup of multiple sclerosis patients with anticardiolipin antibodies and unusual clinical manifestations: do they represent a new nosological entity? *Ann Neurol* 1998;**44**:629–34.
- Sanna G, Bertolaccini ML, Cuadrado MJ, Khamashta MA, Hughes GR. Central nervous system involvement in the antiphospholipid (Hughes) syndrome. *Rheumatology* 2003;**42**:200–13.
- Vial T, Descotes J. Immune-mediated side-effects of cytokines in humans. *Toxicology* 1995;**105**:31–57.
- Khamashta MA, Cuadrado MJ, Mujic F, Taub NA, Hunt BJ, Hughes GR. The management of thrombosis in the antiphospholipid-antibody syndrome. *N Engl J Med* 1995;**332**:993–7.
- Leary SM, Davie CA, Parker GJ, Stevenson VL, Wang L, Barker GJ, et al. 1H Magnetic resonance spectroscopy of normal appearing white matter in primary progressive multiple sclerosis. *J Neurol* 1999;**246**:1023–6.
- Assaf Y, Ben-Bashat D, Chapman J, Peled S, Biton IE, Kafri M, et al. High b-value q-space analyzed diffusion-weighted MRI: application to multiple sclerosis. *Magn Reson Med* 2002;**47**:115–26.
- Rovaris M, Viti B, Ciboddo G, Gerevini S, Capra R, Iannucci G, et al. Brain involvement in systemic immune mediated diseases: magnetic resonance and magnetisation transfer imaging study. *J Neurol Neurosurg Psychiatry* 2000;**68**:170–7.
- Chapman J, Cohen-Armon M, Shoenfeld Y, Korczyn AD. Antiphospholipid antibodies permeabilize and depolarize brain synaptosomes. *Lupus* 1999;**8**:127–33.