ORIGINAL INVESTIGATION

Cognitive Deficits in Patients With Antiphospholipid Syndrome

Association With Clinical, Laboratory, and Brain Magnetic Resonance Imaging Findings

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Background: Antiphospholipid syndrome (APS) is a multisystem disorder characterized by arterial and venous thromboses, pregnancy morbidity, and various neuropsychiatric manifestations. Cognitive dysfunction in APS has been poorly recognized. We examined for the first time, to our knowledge, the presence of cognitive dysfunction in patients with APS and its association with clinical, laboratory, and cerebral magnetic resonance imaging characteristics.

Methods: Sixty patients (39 with primary APS and 21 with systemic lupus erythematosus–related APS) and 60 healthy individuals matched for age, sex, and education were examined by means of a comprehensive 3-hour battery of neuropsychological tests. Twenty-three patients had a history of central nervous system involvement. Fifty-nine of 60 patients underwent brain magnetic resonance imaging at the time of neuropsychological assessment. A disease control group not fulfilling criteria for APS (15 patients with systemic lupus erythematosus and 10 with rheumatoid arthritis) was also included. The demographic, clinical, and laboratory characteristics of patients were recorded.

Results: Twenty-five (42%) of the 60 patients with APS had cognitive deficits compared with 11 (18%) healthy control subjects ($P=.005$). No patient was diagnosed as having dementia. The most commonly involved cognitive domains were complex attention and verbal fluency. No difference was found in cognitive performance between patients with primary APS and those with systemic lupus erythematosus–related APS. No relationship was detected between cognitive dysfunction and prior central nervous system disease. We noted a significant association between cognitive dysfunction and livedo reticularis ($P=.004$) as well as between cognitive dysfunction and the presence of white matter lesions on the findings of brain magnetic resonance imaging ($P=.01$). No difference was detected in cognitive performance between the disease control group and healthy individuals ($P=.86$).

Conclusions: Cognitive deficits may often be found among patients with APS, independent of any history of central nervous system involvement. Livedo reticularis and the presence of white matter lesions on brain magnetic resonance imaging are associated with an increased risk for cognitive dysfunction in APS.

Arch Intern Med. 2006;166:2278-2284

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THE ANTIPHOSPHOLIPID SYNdrome (APS) is a prothrombotic condition defined by the presence of arterial or venous thromboses and/or pregnancy morbidity in association with antiphospholipid (aPL) antibodies, namely anticardiolipin (aCL) antibodies and lupus anticoagulant (LA).[1] The APS may be primary or can be associated with other underlying disorders, especially systemic lupus erythematosus (SLE). Antiphospholipid antibodies can be detected in approximately 30% to 40% of patients with SLE; APS will develop in nearly one third of patients with SLE and aPL antibodies. Thrombosis in APS may occur at any vascular site and any organ system can be involved.

Central nervous system (CNS) involvement is one of the most common features of APS, including various neuropsychiatric manifestations such as stroke, transient ischemic attack, seizures, chorea, psychosis, retinal artery occlusion, amaurosis fugax, transverse myelitis, multiple sclerosis–like features, sensorineural hearing loss, migraine, and mood disorders.[2] However, cognitive dysfunction has been poorly recognized. Cognitive deficits in APS have been described in isolated cases or in small series, in the

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context of multi-infarct dementia or in the absence of CNS symptoms and neuroimaging findings.[3-8]

Involvement of the CNS in APS can be evaluated by a variety of radiological and neuropsychological procedures. Magnetic resonance imaging (MRI) represents one of the most sensitive methods for demonstrating cerebral structural abnormalities and circulatory disturbances. Abnormal MRI findings in APS include single or multiple infarcts, white matter lesions (WMLs), cortical atrophy, and focal hemorrhage.[9] Neuropsychological tests have been used to assess subclinical cerebral dysfunction by examining different areas of cognition such as memory, attention, concentration, language, and visuospatial abilities.[10]

The purposes of this study were to evaluate the presence of cognitive deficits by the application of comprehensive neuropsychological tests in patients with APS with or without a history of CNS involvement, and to examine any association between cognitive abnormalities and the clinical, laboratory, and brain MRI characteristics of these patients.

METHODS

In this cross-sectional study, we included 60 patients with definite APS (39 with primary APS and 21 with SLE-related APS [SLE-APS]) who had regular follow-up in the Department of Pathophysiology, National University of Athens, and 60 healthy volunteers matched individually to each patient for age, sex, and education. Definite APS was diagnosed according to the Sapporo criteria.[1] The patients were divided between those who had a history of CNS involvement and those who had never experienced neuropsychiatric events. A disease control group matched for age, sex, and education was also included in this study and consisted of 25 patients with other autoimmune diseases (15 patients with SLE and 10 with rheumatoid arthritis); none of these patients fulfilled the clinical or laboratory criteria for APS. Subjects with active CNS involvement (neuropsychiatric symptoms present at the time of neuropsychological assessment or resolved within the previous 4 weeks) and those lacking fluency with the local language were excluded from the study. Healthy individuals with a history of neuropsychiatric disease were also excluded from the study. The protocol was approved by the regional ethics committee, and informed written consent was obtained from all participants.

The baseline examination included a detailed medical and neuropsychiatric history, a physical examination, and the Mini-Mental State Examination for the diagnosis of dementia.[10] All of the participants (N=120) were examined by a clinical psychologist (N.V.) using comprehensive neuropsychological tests. Fifty-nine of the 60 patients with APS underwent cerebral MRI at the time of neuropsychological assessment; the remaining patient was claustrophobic.

The following clinical and laboratory variables were examined at the time of the neuropsychological assessment: APS duration (the period from the first APS manifestation to the neuropsychological assessment), arterial or venous thrombosis, pregnancy morbidity as defined by the Sapporo criteria, CNS involvement, pulmonary embolism, livedo reticularis, thrombocytopenia (platelet count, $<100 \times 10^3$ cells/μL), autoimmune hemolytic anemia, systemic hypertension (systolic blood pressure, >140 mm Hg; diastolic blood pressure, >90 mm Hg), nephrotic syndrome (urine protein level, >3 g in 24 hours), diabetes mellitus, hyperlipidemia, obesity, smoking, alcohol abuse, and the presence of LA and IgG aCL, IgM aCL, and anti–β_2 glycoprotein I (anti-β2GPI) antibodies. Treatment with aspirin, oral anticoagulants, corticosteroids, and immunomodulatory and psychiatric drugs was also recorded.

LABORATORY EXAMINATIONS

Levels of complement and antinuclear, anti-DNA, and anti–extractable nuclear antigen antibodies were measured according to standard methods. We determined IgG and IgM aCL and anti-β2GPI antibody levels by enzyme-linked immunosorbent assay as previously described.[11] We measured LA levels by activated thromboplastin time, kaolin clotting time, and diluted Russell viper venom time.

NEUROPSYCHOLOGICAL TESTS

A clinical psychologist (N.V.) who was unaware of the subject's medical status applied a comprehensive 3-hour, noncomputerized battery consisting of 9 neuropsychological tests that were specifically selected to cover a wide range of cognitive functions (**Table 1**). Four of the 9 neuropsychological tests included more than 1 subtest; therefore, a total of 14 measurements were performed for each participant (Table 1). At the beginning of neuropsychological assessment, the general mental ability of each subject was estimated by a vocabulary test, which is included in the Wechsler Adult Intelligence Scale battery.[10] A more detailed description and normative data for each test can be found in Lezak et al.[10] These neuropsychological tests examined the following cognitive domains: verbal memory (Auditory Verbal Learning Test Trials I and VII), learning (Auditory Verbal Learning Test Trials I-V), complex attention (Wechsler Adult Intelligence Scale digit span, Wechsler Adult Intelligence Scale digit symbol, Stroop Color-Word Interference Test, and Trail-Making Test Part A), visuospatial perception and organization (Wechsler Adult Intelligence Scale block design), verbal fluency (Controlled Oral Word Association Test), abstract behavior (Wisconsin Card Sorting Test and Trail-Making Test Part B), visuospatial constructional ability (Rey Complex Figure Test copy phase), and visuospatial memory (Rey Complex Figure Test recall phase).[10]

To have a direct comparison between tests, raw scores from the neuropsychological tests were transformed into T scores, scaled scores, or *z* scores (means [SDs] were 50 [10], 10 [3], and 0 [1], respectively) using published normative data for specific tests. The score of each measurement was considered low when it was at least 1 SD below the mean value of published normative data for this measurement. The number of measurements with low scores was further calculated for each patient or healthy individual. Subjects were considered to have cognitive deficits when the number of measurements with low scores was at least 1 SD above the mean number of low-ranked measurements observed in the control group.

A screening examination for depression was performed using the Zung test.[12] The rating scale of the test is as follows: scores of 50 to 59 indicate mild depression; scores of 60 to 69, moderate to marked depression; and scores of 70 or higher, severe to extreme major depression.

MRI TECHNIQUE

The scanning protocol included sagittal and axial spin-echo T1-weighted images, axial spin-density, T2-weighted images, and proton density–fluid-attenuated inversion recovery images on a 1.5-T MRI device. Gadolinium contrast was applied. The MRI findings were independently evaluated by a radiologist (G.K.)

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Table 1. Description of Neuropsychological Tests and Examined Cognitive Functions

Name of the Test	Function Examined	Short Description of Test
WAIS digit span	Attention	Repeating random number sequences forward and backward
Rey AVLT		
Trial I	Immediate word span	Immediate recall trial after 5 oral presentations of a 15-word list
Sum of Trials I-V	Learning ability	
Trial VII	Retrieval efficiency	Delayed recall trial after 30 min
RCFT		
Copy phase	Visuospatial constructional ability	Copying a complex figure
Immediate recall phase	Visuospatial memory	Recall the drawing after 3 min
WAIS digit symbol	Psychomotor speed	Filling in blank spaces with symbols that are paired to numbers, as quickly as possible for 90 s
SCWT	Concentration effectiveness	Naming the color rather than reading words printed in different colors
TMT		
Part A	Scanning and visuomotor tracking	Drawing lines to connect consecutively numbered circles on a work sheet
Part B	Cognitive flexibility	Connecting consecutively numbered and lettered circles on another work sheet by alternating between the 2 sequences
WAIS block design	Visuospatial perception and organization	Using 4 or 9 blocks (each block has 2 red, 2 white, and 2 red-white sides) to construct replicas of designs printed in smaller scale
COWAT	Verbal fluency	Oral production of spoken words beginning with a designated letter, as quickly as possible for 60 s
WCST		
Number of categories completed	Abstract reasoning	Placing cards one by one under 4 stimulus cards, according to a principle that the participant must deduce from the pattern of the examiner's responses to the participant's placement of the card
Perseverative responses, %	Conceptual flexibility	

Abbreviations: AVLT, Auditory Verbal Learning Test; COWAT, Controlled Oral Word Association Test; RCFT, Rey Complex Figure Test; SCWT, Stroop Color-Word Interference Test; TMT, Trail-Making Test; WAIS, Wechsler Adult Intelligence Scale; WCST, Wisconsin Card Sorting Test.

who was unaware of the patient's clinical and neuropsychological data.

Brain MRI abnormalities were categorized as infarcts, WMLs, cortical atrophy, and hemorrhages. Infarcts were defined as focal lesions with increased signal intensity on T2-weighted images and reduced signal intensity on T1-weighted images. They were classified according to their location into parietal, frontal, occipital, temporal, brainstem, and cerebellar lesions. White matter lesions on MRI were identified as ill-defined hyperintensities on T2-weighted and proton density–fluid-attenuated inversion recovery images without prominent hypointensity on T1-weighted images. We classified WMLs according to their location into subcortical, periventricular, and deep white matter changes, and we graded them according to their size as punctate, beginning confluent, or confluent.[13] Cortical atrophy was also graded as absent, mild, moderate, or severe on the basis of sulcal and ventricular enlargement.[13]

STATISTICAL ANALYSIS

We compared the neuropsychological measurements between cases and controls using parametric paired *t* test or nonparametric (Wilcoxon) signed rank test as appropriate. We based further comparisons on the χ^2 test or the Fisher exact test in the case of categorical variables and on the Mann-Whitney test in the case of continuous variables. The association of cognitive dysfunction in patients with APS and potential prognostic factors was initially explored by applying univariate logistic regression models, and the effect of each factor was expressed as an odds ratio. Multiple logistic regression models were further applied to adjust for potential confounders.

RESULTS

All subjects included in the study (92 women and 28 men) were white. The mean (SD) ages of the patient and control groups were 41.1 (11.5) and 40.6 (11.1) years, respectively (P=.82). The mean (SD) education levels of the groups were 12.7 (3.0) and 13.1 (2.9) years, respectively (P=.48). The clinical and laboratory characteristics of the patients are summarized in **Table 2**. The MRI features of patients with APS, with or without a history of CNS involvement, are presented in **Table 3**.

The Mini-Mental State Examination scores showed that no patient or healthy individual fulfilled the criteria for dementia. No difference was found between patients, disease controls, and healthy controls in the vocabulary test. Comparisons of scores between the patients with APS and the controls for each measurement of the neuropsychological tests are presented in **Table 4**. After correction for multiple comparisons, significant differences were found in 3 of the 14 measurements examining the domains of complex attention and verbal fluency. The mean (SD) number of measurements with low scores observed in the patient and control groups were 4.5 (3.1) and 2.8 (1.9), respectively (P=.003). The subjects in this study were considered to have cognitive deficits when they had at least 5 measurements with low scores, according to our definition (≥1 SD above the mean number of measurements with low scores observed in the control group). Using this definition, 25 (42%) of the 60 patients with APS had cognitive deficits compared with 11 (18%) of the 60 healthy controls (P=.005). In addition, 4 (16%) of the 25 patients in the disease control group had cognitive abnormalities; all of them had SLE. No difference was found in cognitive performance between the disease control group and healthy control group (P=.86). The patients with APS more often had cognitive deficits than did the disease control group (P=.02).

The associations between cognitive deficits and several clinical, laboratory, and radiological characteris-

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Table 2. Clinical and Laboratory Characteristics of Patients With Primary APS and SLE-APS*

Characteristic	Patient Groups: Primary APS (n = 39)	Patient Groups: SLE-APS (n = 21)	*P* Value
APS duration, mean (SD), y	7.1 (5.5)	9.3 (5.5)	.06
CNS involvement	16 (41)	7 (33)	.56
Stroke	9 (23)	4 (19)	>.99
Transient ischemic attack	5 (13)	3 (14)	>.99
Seizures	3 (8)	2 (10)	>.99
Transverse myelitis	1 (3)	1 (5)	>.99
Optic neuropathy	1 (3)	2 (10)	.28
Arterial thrombosis	6 (15)	2 (10)	.70
Venous thrombosis	19 (49)	10 (48)	.94
Pregnancy morbidity	8 (28.6)	4 (22.2)	.74
Pulmonary embolism	4 (10)	1 (5)	.65
Livedo reticularis	16 (41)	9 (43)	.89
Thrombocytopenia	11 (28)	6 (29)	.98
Autoimmune hemolytic anemia	5 (13)	3 (14)	>.99
Hypertension	8 (21)	8 (38)	.14
Nephrotic syndrome	1 (3)	1 (5)	>.99
Hyperlipidemia	11 (28)	8 (38)	.43
Diabetes	0	0	
Obesity	2 (5)	0	.54
Smoking	14 (36)	3 (14)	.08
Alcohol abuse	1 (3)	0	>.99
aCL IgG antibodies	35 (90)	18 (86)	.64
aCL IgM antibodies	19 (49)	9 (43)	.66
LA	29 (74)	10 (48)	.04
Anti-β2GPI antibodies	21 (54)	11 (52)	.92
Treatment			
Corticosteroids	6 (15)	21 (100)	<.001
Corticosteroid dose, mean (SD), mg	2.5 (0.6)	10.2 (1.6)	<.001
Immunomodulatory drugs	7 (18)	18 (86)	<.001
Psychiatric drugs	0	0	
Depression			.19
Mild	6 (15)	3 (14)	
Moderate	2 (5)	5 (24)	
Severe	2 (5)	0	

Abbreviations: aCL, anticardiolipin; anti-β2GPI, anti-β_2 glycoprotein I; APS, antiphospholipid syndrome; CNS, central nervous system; LA, lupus anticoagulant; SLE-APS, systemic lupus erythematosus–related APS.
*Unless otherwise indicated, data are expressed as number (percentage) of patients.

Table 3. MRI Findings of 59 Patients With APS With and Without a History of CNS Involvement

MRI Findings	No. (%) of Patients*: CNS Involvement (n = 23)	No. (%) of Patients*: No CNS Involvement (n = 36)
Infarcts	13 (57)	0
Parietal	8 (62)	0
Frontal	2 (15)	0
Brainstem	2 (15)	0
Cerebellar	2 (15)	0
WMLs	12 (52)	8 (22)
Location		
Periventricular	12 (100)	7 (88)
Subcortical	4 (33)	2 (25)
Deep white matter	1 (8)	1 (12)
Size		
Punctate	8 (67)	6 (75)
Beginning confluent	4 (33)	2 (25)
Confluent	0	0
No. of lesions		
1	0	1 (12)
2	2 (17)	2 (25)
3	1 (8)	0
Multiple	9 (75)	5 (62)
Cortical atrophy	2 (9)	1 (3)
Hemorrhages	0	0

Abbreviations: APS, antiphospholipid syndrome; CNS, central nervous system; MRI, magnetic resonance imaging; WMLs, white matter lesions.
*Percentages have been rounded and might not total 100.

tics of the patients with APS are shown in **Table 5**. No difference was detected in cognitive performance between the patients with primary APS and those with SLE-APS. A significant association was noted between cognitive dysfunction and livedo reticularis (P=.004). No relationship was found with a history of CNS involvement and the other clinical, laboratory, or treatment variables examined in our study (described in the "Methods" section). In addition, we detected no association between cognitive deficits and mild, moderate, or severe depression.

No association was found between cognitive deficits and brain infarcts noted on brain MRI (P=.76). However, a significant association was demonstrated between cognitive deficits and the presence of WMLs (P=.01), especially in patients with no history of CNS involvement. More specifically, in the subgroup of patients with no prior CNS symptoms, cognitive deficits were found in 7 (88%) of the 8 patients with WMLs on MRI compared with only 6 (21%) of the 28 patients without WMLs (P=.001). Among the 7 patients with WMLs and no CNS involvement, 6 had punctate lesions and 1 had beginning confluent lesions. In addition, a significant association was found between the presence of WMLs on MRI and livedo reticularis (P=.049).

The effect of WMLs and livedo reticularis on cognitive dysfunction in the patients with APS was further investigated in a multivariate analysis, where the roles of potential confounders such as age, APS type (primary or SLE-APS), CNS involvement, depression, corticosteroid use, hypertension, and the presence of LA and anti-β2GPI, aCL IgG, and aCL IgM antibodies were evaluated. Our small sample size did not allow the simultaneous evaluation of all of these factors in the same multivariate model. We applied a multistep approach with small models, including no more than 1 or 2 confounders in the model at once. The effect of WMLs and livedo reticularis did not change substantially in the presence of other factors. In addition, none of these confounders was found to be significant in the multivariate evaluation.

In an attempt to use more stringent criteria for the definition of cognitive dysfunction, we reanalyzed our data, setting as a cutoff point the presence of 6 measurements with low scores, which corresponds to the 90th

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Table 4. Comparison of Neuropsychological Test Scores Between Patients With APS and Control Subjects

Neuropsychological Test	Mean (SD) Score: Patients With APS	Mean (SD) Score: Controls	*P* Value
WAIS digit span, scaled score*	9.0 (2.2)	9.6 (2.2)	.61
AVLT, *z* score†			
Trial I	−0.8 (1.1)	−0.3 (1.2)	.35
Trials I-V	−0.3 (1.0)	0.1 (1.1)	.63
Trial VII	0 (1.0)	0.6 (0.9)	.11
RCFT			
Copy phase, raw score‡	33.1 (3.2)	33.8 (2.8)	.92
Immediate recall phase, T score§	42.6 (14.3)	42.5 (13.0)	>.99
WAIS, scaled score*			
Digit symbol	10.9 (3.0)	12.8 (2.6)	.01
SCWT, T score§	45.4 (9.0)	48.5 (8.2)	.18
TMT, *z* score†			
Part A	−0.4 (1.9)	0.4 (0.9)	.03
Part B	−1.3 (2.3)	−0.4 (1.6)	.77
WAIS block design			
Scaled scores*	9.7 (2.5)	10.8 (2.2)	.41
COWAT, raw score‖	35.8 (9.8)	43.2 (11.4)	.01
WCST			
No. of categories completed, raw score¶	4.2 (1.7)	4.5 (2.0)	.71
% of perseverations, T score§	40.2 (12.0)	45.3 (14.1)	.46

Abbreviations: See Table 1.
*Mean ± SD = 10 ± 3.
†Mean ± SD = 0 ± 1.
‡Range, 0-36.
§Mean ± SD = 50 ± 10.
‖Indicates number of words.
¶Range, 0-6.

percentile of the controls' performance distribution. The higher frequency of cognitive deficits in patients with APS compared with controls (35% vs 12%; $P=.003$) and the association between cognitive deficits and the presence of WMLs on MRI was preserved (odds ratio, 3.54; $P=.03$).

COMMENT

Our findings suggested that mild to more severe cognitive deficits, but not dementia, can be frequently found among patients with APS, independent of any history of CNS involvement. The most commonly involved cognitive domains were complex attention and verbal fluency. We detected a significant association with livedo reticularis and the presence of WMLs on MRI. Comparison with a small group of patients with SLE and patients with rheumatoid arthritis showed that patients with APS more often had cognitive abnormalities.

Neuropsychological tests have been used to assess subtle cognitive abnormalities, providing a sensitive tool for the evaluation of CNS involvement. Previous studies examining cognitive deficits in patients with autoimmune disorders, especially SLE, have used a variety of computerized or noncomputerized neuropsychological tests and diverse definition criteria for cognitive impairment. In our study, we selected a comprehensive 3-hour battery of neuropsychological tests to cover a wide range of cognitive functions and a noncomputerized method, given the varying familiarity of the population with computers. We also used a control group that was strictly matched for age, sex, and education, factors that have been associated with cognitive deficits. The evaluation of cognitive deficits on the basis of published normative data for specific tests and the performance of our control group increased the strength of our study.We also used a disease control group matched for age, sex, and education to examine the presence of cognitive deficits in other autoimmune diseases. The additional use of this group further increased the strength of the study. The purpose of this study was to evaluate the presence of mild to more severe cognitive deficits; therefore, we avoided the use of very strict definition criteria for cognitive dysfunction that would exclude patients with subtle cognitive abnormalities. On the other hand, when we reanalyzed our data and applied more stringent criteria, similar results were demonstrated.

Our study had some limitations. The sample size of patients with APS was quite small and, unavoidably, our study could not have had enough power to detect modest differences. Moreover, given that all of our patients were white, the results may not have generalizability. Multicenter studies of patients of mixed ethnicity are probably needed.

Antiphospholipid syndrome is a multisystem disorder with a wide range of neurological manifestations. However, cognitive dysfunction in APS has been only partially elucidated, despite the increased interest in this area in recent years. A number of studies of patients with SLE and healthy individuals have shown an association between positive aPL antibody findings and cognitive dysfunction, although most of the subjects with positive aPL antibody findings did not fulfil the criteria for APS.[14-17] Among studies that have included patients with definite APS, Asherson et al[3] described 4 patients with APS in 1987 who also had recurrent stroke and progressive multi-infarct dementia. Recently, Gomez-Puerta et al[4] reviewed the clinical and radiological characteristics of 30 published cases of APS with dementia and reported that 14 of them (47%) had silent infarcts. A high frequency of dementia has been reported in 2 small studies of patients with primary APS.[5,6] In one of them, greater age and the presence of LA were detected as risk factors for dementia. Computed tomographic findings were abnormal in all of the demented patients, showing focal lesions and generalized atrophy.[6] In a multicenter study including 1000 patients with APS, a prevalence of 2.5% was reported for multi-infarct dementia, but no data were provided on subtle forms of cognitive dysfunction.[18] Most of these studies of patients with APS have focused on dementia; however, the presence of less severe forms of cognitive dysfunction in APS remains unknown. Aharon-Peretz et al[7] used neuropsychological tests to examine 20 patients with APS (14 with CNS involvement) and 10 healthy individuals; 13 of 14 patients with CNS disease

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Table 5. Associations Between Cognitive Deficits and Several Clinical, Laboratory, and Radiological Characteristics of Patients With APS

	Cognitive Deficits, No. (%)			
	No (n = 35)	Yes (n = 25)	OR* (95% CI)	*P* Value*
SLE-APS	11 (52)	10 (48)	1.45 (0.50-4.25)	.49
Arterial thrombosis	6 (75)	2 (25)	0.42 (0.08-2.28)	.32
Venous thrombosis	18 (62)	11 (38)	0.74 (0.26-2.08)	.57
Pregnancy morbidity	7 (58)	5 (42)	0.80 (0.21-3.04)	.75
CNS involvement	11 (48)	12 (52)	0.20 (0.70-5.82)	.20
Livedo reticularis	9 (36)	16 (64)	5.14 (1.69-15.65)	.004
Depression, Zung score ≥50	10 (56)	8 (44)	1.18 (0.39-3.59)	.78
aCL IgG antibodies	30 (57)	23 (43)	1.92 (0.34-10.78)	.46
aCL IgM antibodies	18 (64)	10 (36)	0.63 (0.22-1.78)	.38
LA	20 (51)	19 (49)	2.38 (0.76-7.40)	.14
Anti-β2GPI antibodies	16 (50)	16 (50)	2.11 (0.74-6.05)	.16
MRI findings				
Infarcts	7 (54)	6 (46)	1.22 (0.35-4.20)	.76
WMLs	7 (35)	13 (65)	4.18 (1.33-13.11)	.01

Abbreviations: aCL, anticardiolipin; anti-β2GPI, anti-β_2 glycoprotein I; APS, antiphospholipid syndrome; CI, confidence interval; CNS, central nervous system; LA, lupus anticoagulant; MRI, magnetic resonance imaging; OR, odds ratio; SLE-APS, systemic lupus erythematosus–related APS; WMLs, white matter lesions.
*Calculated from results of univariate logistic regression.

had mild cognitive deficits. Mikdashi and Kay[8] described 4 patients with APS who had deficits in visual attention, executive function abilities, and verbal and nonverbal memory skills. None of them had a history of CNS involvement.

The pathogenesis of cognitive impairment in APS has not been clearly understood. Suggested mechanisms include aPL antibody–related microvascular thrombosis[14] or a direct effect of aPL antibodies on brain tissue.[19] Recent studies have shown that animals immunized with aCL or anti-β2GPI antibodies developed behavioral changes and cognitive impairment.[19]

A significant association between cognitive deficits and livedo reticularis was detected in this study. Livedo reticularis represents the most frequent dermatologic manifestation in APS, characterized by diminished blood flow in arterioles and dilatation of venules and capillaries. In a recent study by Francès et al,[20] livedo reticularis was found to be strongly associated with arterial events in APS, and it was suggested to be a strong marker of the arterial-arteriolar APS subset.

The absence of any association between cognitive abnormalities and a history of CNS involvement is of particular interest. Cognitive dysfunction in patients who had never experienced neuropsychiatric events may reflect subclinical CNS compromise. Results of the MRI evaluation in patients with no CNS involvement in our study showed a significant correlation between cognitive impairment and small periventricular and subcortical WMLs. An association between cognitive changes and WMLs has also been documented in previous studies that included demented patients and healthy elderly and middle-aged individuals.[21] The pathogenesis of WMLs remains unknown, but it is generally thought that WMLs are related to vascular disease in the long penetrating arteries of the brain. White matter lesions have been associated with age and the presence of vascular risk factors such as hypertension, stroke, diabetes, hyperlipidemia, and smoking.[22] It has also been suggested that WMLs in patients with SLE or APS could be due to small vessel thrombi.[23] The white matter of the brain is much more vulnerable than the gray matter to hypoxemia and ischemia because of widely spaced linear arterioles, few anastomoses, and sparse collateralization.

The association between cognitive deficits and the presence of livedo reticularis and WMLs on MRI supports the view that cerebral microvasculopathy could be an underlying mechanism for cognitive dysfunction. Thrombotic microangiopathy has been considered the hallmark histopathologic finding for a variety of other APS manifestations in the skin, lungs, kidneys, heart, bones, and brain.[24,25] Additional multicenter studies are needed to further examine our findings regarding cognitive dysfunction in APS and its associations.

In summary, cognitive dysfunction may represent an additional clinical feature of APS occurring independently of prior CNS disease. Cognitive deficits are associated with the presence of livedo reticularis and WMLs on MRI.

Accepted for Publication: July 24, 2006.
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Financial Disclosure: None reported.

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