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CONCISE REPORT

# The role of antiphospholipid autoantibodies in the cognitive deficits of patients with systemic lupus erythematosus

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**Objective:** To analyze the role of the antiphospholipid autoantibodies (aPL) on the neuropsychological deficits in systemic lupus erythematosus (SLE) patients, comparing groups of patients with antiphospholipid syndrome (APS; $n=15$), SLE with aPL ($n=12$), and SLE without aPL ($n=27$), and a healthy control group ($n=31$). **Methods:** Patients fulfilled the American College of Rheumatology SLE classification criteria or the Sydney criteria for APS. All participants were woman, and groups were matched on age and education. A standardized cognitive examination classified patients as cognitively declined or impaired according to the American College of Rheumatology. **Results:** Differences between the groups were found in all of the studied variables, comprising attention and executive functions (sustained and selective attention, fluency, and inhibition), and memory (verbal and visual). Post-hoc analyses showed cognitive performance was equivalent between APS and SLE with aPL. Differences between SLE without aPL and control groups were found only in four of the 10 studied variables, while differences in all but two memory variables were found between SLE without aPL and control groups. Furthermore, cognitive deficit was three times more frequent in APS and SLE with aPL patients than for the control group (80%, 75%, and 16%, respectively), and two times more frequent compared to SLE patients without aPL (48%). **Conclusions:** Our results support the relationship between aPL and cognitive symptoms in SLE. Also, almost half of the patients with SLE and no aPL showed cognitive problems, pointing to the multifactorial causes of cognitive problems in SLE. Future research with larger sample size is guaranteed to replicate our results. *Lupus* (2015) **0,** 1–5.

**Key words:** Antiphospholipid syndrome; systemic lupus erythematosus; neuropsychiatric lupus

## Introduction

Neuropsychiatric systemic lupus erythematosus (SLE) has been frequently related to cognitive problems.[1] Nevertheless, the percentage of patients with SLE presenting cognitive deficits is very variable, with some studies pointing to 20% and others to 80%.[2] Studies using well-validated neuropsychological tests have reported cognitive deficits in patients with SLE in several cognitive domains such as attention, language, verbal and non-verbal fluency, learning and memory, working memory, speed processing, executive functions, spatial processing and motor dexterity, being attention and memory the most frequently reported on the literature.[1]

Etiopathogenesis of SLE remains unclear and is probably multifactorial. Regarding cognitive dysfunction, immune-mediating neuronal injury seems to play a key role.[3] Anti-neuronal, brain cross-reactive lymphocytotoxic antibodies, *N*-methyl-D-aspartate (NMDA), and receptor type NR2a or NR2b (anti-NR2) antibodies are some of the most commonly studied autoantibodies. However, antiphospholipid autoantibodies (aPL) are the most consistently associated with cognitive symptoms in SLE.[4] Nevertheless, this association remains controversial, with some studies finding differences on levels of aPL between SLE patients with and without cognitive deficits,[5,6] and others failing to do so.[3,7] Furthermore, the mechanism

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by which aPL may cause cognitive impairment is not clear, although current data suggest that it could be related to aPL promoting intravascular thrombosis.[8]

In order to elucidate the mechanisms of cognitive dysfunction in SLE, it has been stated the importance of studying cognitive parameters in patients with autoimmune disorders other than SLE.[3] Thus, the aim of the present study was to analyze the role of the aPL on the neuropsychological deficits in SLE patients, comparing groups of patients with antiphospholipid syndrome (APS), SLE with aPL, and SLE without aPL, and a healthy control group. We hypothesized that cognitive execution of patients with APS and SLE with aPL will be similar, but different of the patients with SLE without aPL and control participants.

## Patients and methods

### *Participants*

Four groups of women ($N = 85$) were included in the present study: 31 healthy controls, 15 patients with APS, 12 SLE patients with aPL, and 27 SLE patients without aPL. The three clinical groups were consecutive patients recruited at the Systemic Autoimmune Disease Units of the Hospital Universitario Virgen de las Nieves in Granada (Spain) during a five-year period. Healthy controls were recruited between the patients' family members or companions to the hospital appointment. SLE patients had at least four of the criteria for the lupus diagnostic according to the American College of Rheumatology, and were distributed to the subgroups (with or without aPL) by their doctor according to the criteria of having persistent high aPL on at least two different occasions repeatedly over time. Systemic Lupus International Collaborating Clinics (SLICC) damage index was between 0 and 8 (mean = 1; SD = 1.77), Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) was between 0 and 4 (mean = 0.38; SD = 0.96), and mean years of evolution of the disease were 4 (SD = 3.8). Participants with APS were selected attending to the Sydney criteria for APS. Inclusion criteria included age between 18 and 65 years. Exclusion criteria considered illiteracy, terminal renal insufficiency or renal transplant, arteriosclerosis, cardio-pathology, cerebrovascular accidents, and pregnancy. These criteria were explored by clinical interview and by the review of the clinical history of the patients. All participants were volunteers and received no monetary compensation. See Table 1 for demographic variables.

### *Materials*

Considering ethical problems related to fatigue of the patients, five tests were selected to focus on the main cognitive problems related to SLE (memory and attention/executive functions).[1] The battery included four of the tests proposed by the American College of Rheumatology that are available for Spanish population:

- TAVEC: This is the Spanish version of the California learning verbal test,[9] and measures verbal episodic memory. The list of 16 words is read to the participants over five trials. The test provides information about immediate and delayed recall, learning curve, or recognition.
- Rey–Osterrieth complex figure test (ROCFT), Spanish adaptation: This test measures visual memory.[10] Participants are required to copy a complex figure, and after a delay (immediate – 3 minutes; delayed – 30 minutes) they are asked to draw what they remember of the figure.
- Stroop color and word test, Spanish version: This test is a measure of inhibition.[11] It includes three cards: the first with the reading condition, the second with the color-naming condition, and the third with the interference condition (the participants are asked to name the color of the ink and not to read the word).
- Verbal phonemic fluency (FAS) and semantic fluency (animals), Spanish adaptation: Participants are instructed to name as many words starting with letters F, A, and S within one minute.[12] Also, participants should name as many animals as possible within one minute.

Also, the battery included the next attentional task:

- Ruff 2&7 selective attention test: This test consists of a series of 20 trials of a visual search and

**Table 1** Demographic variables for the groups of the study

| *Variable* | *SLE− mean (SD)* | *SLE+ mean (SD)* | *APS mean (SD)* | *Control mean (SD)* |
|---|---|---|---|---|
| Age | 39.8 (12.7) | 44.6 (14.4) | 46.1 (11.5) | 44.22 (13.32) |
| Education | 1.7 (1.2) | 1.1 (0.9) | 1.4 (1.1) | 1.03 (1.2) |

Note: Education: 0 = no studies; 1 = basic studies; 2 = high school; 3 = university; SLE− = systemic lupus erythematosus without antiphospholipid antibodies group; SLE+ = systemic lupus erythematosus with antiphospholipid antibodies group; APS = antiphospholipid syndrome group.

cancellation task in which participants should cross out the two target digits: 2 and 7.[13]

### *Procedure*

Patients with SLE and APS were recruited from the Hospital Clínico San Cecilio in Granada during three consecutive years. Healthy controls were recruited between the family members or companions that walk with patients to the Hospital. When participants decided to volunteer it was set a day for the individual neuropsychological assessment. The Ethical Committee of the Hospital approved the study and all of the participants provided informed consent after receiving the information about the objectives and characteristics of the study.

### *Statistical analyses*

To determine whether there was a difference in age and educational levels across the four groups, one analysis of variance (ANOVA) and one chi-squared were conducted. Considering that variances of the variables were not homogeneous, non-parametric analyses were conducted (Kruskal–Wallis) to probe if there were differences on the cognitive measures between the groups. Level of significance was fixed at 0.05 and confidence interval (CI) at 95%. When statistical differences appeared between the groups, post-hoc non-parametric analyses were conducted. Finally, to study if percentages of patients with severe, moderate, and mild/no cognitive deficits differed between the groups, we run chi-squared analyses. Data were analyzed using SPSS Version 20.

## Results

Preliminary results did not reveal significant differences for age or years of education between the groups.

### *Differences between the groups on the neuropsychological tests*

Results showed statistical differences between the groups in all of the variables: attention and executive functions (RFFT Accuracy $p = .012$; Stroop interference $p = .045$; verbal fluency $p = .004$), verbal memory (TAVEC number of words on the first trial $p = .051$; total words $p = .002$; immediate recall $p < .001$; delayed recall $p = .001$), and visual memory (ROCFT immediate recall $p = .002$; delayed recall $p = .001$; recognition $p < .001$). Post-hoc analyses showed statistical differences in all variables between the APS and control groups, and no differences between APS and SLE with aPL groups or between SLE with and without aPL. Differences between SLE without aPL and APS were restricted to immediate and delayed verbal recall. Differences between SLE without aPL and control groups were found in half of the studied variables. Finally, differences in all but two neuropsychological variables from the TAVEC (number of words recalled on the first trial and delayed recall) were found between SLE without aPL and control groups (see Table 2).

### *Cognitive deficits on the different groups*

Participants were classified as cognitive decline or impairment with scores 1.5 or more SD below the

**Table 2** Non-parametric analyses on the scores of the neuropsychological variables (T scores) on the groups of the study and post-hoc analyses

| *Tests* | *Variables* | *SLE−* *Mean (SD)* | *SLE+* *Mean (SD)* | *APS* *Mean (SD)* | *Control* *Mean (SD)* | p | *Post-hoc* p | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | *1vs2* | *1vs3* | *1vs4* | *2vs3* | *2vs4* | *3vs4* |
| Ruff 2&7 | Accuracy | 45.73 (9.38) | 44.50 (10.11) | 41.22 (10.23) | 51.00 (5.75) | **.012** | .891 | .265 | **.012** | .437 | .063 | **.008** |
| TAVEC | Words first trial | 43.70 (9.22) | 40.91 (7.90) | 38.80 (8.08) | 45.41 (8.60) | **.051** | .368 | .078 | .779 | .405 | .119 | **.004** |
| | Total words | 41.40 (10.50) | 41.83 (11.16) | 36.13 (10.56) | 48.00 (6.96) | **.002** | .891 | .131 | **.008** | .222 | .056 | **.001** |
| | Immediate recall | 46.66 (9.50) | 40.08 (9.60) | 37.66 (10.35) | 49.74 (5.42) | **<.001** | .090 | **.006** | .172 | .479 | **.001** | **<.001** |
| | Delayed recall | 44.92 (10.45) | 41.33 (9.83) | 38.00 (11.12) | 49.51 (5.48) | **.001** | .492 | **.038** | **.047** | .353 | **.011** | **<.001** |
| ROCFT | Immediate recall | 43.51 (13.51) | 41.08 (12.39) | 38.33 (9.89) | 51.35 (9.63) | **.002** | .455 | .176 | **.042** | .751 | .055 | **.001** |
| | Delayed recall | 42.07 (13.91) | 40.08 (11.21) | 36.26 (11.18) | 51.00 (9.41) | **.001** | .532 | .198 | **.021** | .420 | **.004** | **<.001** |
| | Recognition | 41.81 (11.52) | 44.25 (11.11) | 44.80 (13.26) | 54.83 (7.09) | **<.001** | .393 | .581 | **<.001** | .961 | **.007** | **.009** |
| Stroop | Interference | 46.88 (6.35) | 46.18 (7.66) | 45.23 (4.72) | 50.00 (5.95) | **.045** | .973 | .641 | **.037** | .638 | .145 | **.009** |
| Verbal fluency | FAS + animals | 52.29 (12.41) | 43.60 (21.31) | 51.20 (10.09) | 41.63 (6.59) | **.004** | .416 | .835 | **.002** | .705 | .152 | **.003** |

Note: SLE− = systemic lupus erythematosus without antiphospholipid syndrome; SLE+ = systemic lupus erythematosus with antiphospholipid syndrome; APS = Antiphospholipid syndrome; SD = standard deviation; TAVEC = Test de aprendizaje verbal España-Complutense; ROCFT = Rey–Osterrieth complex figure test. Statistical differences in bold.

**Table 3** Percentages of participants in each group with severe, mild/moderate, or no cognitive deficit

| *Cognitive deficit* | *SLE−* | *SLE+* | *APS* | *Control group* | p |
|---|---|---|---|---|---|
| No deficit | 51.9% | 25% | 20% | 83% | <.001 |
| Mild/moderate deficit | 25.9% | 41.7% | 20% | 16.1% | <.001 |
| Severe deficit | 22.2% | 33.3% | 60% | 0% | <.001 |

Note: SLE− = systemic lupus Erythematosus without antiphospholipid antibodies group; SLE+ = systemic lupus erythematosus with antiphospholipid antibodies group; APS = antiphospholipid syndrome group.

mean (T scores inferior to 35) according to the Ad Hoc Committee on Lupus Response Criteria: Cognition Sub-Committee.[1]

As can be checked in Table 3, APS and SLE with aPL groups present similar percentages of normal cognitive execution (20% vs. 25%), while 83% of the control group and 52% of the SLE without aPL showed no deficits. On the other hand, 80% of the APS patients and 78% of the SLE patients with aPL showed cognitive deficits, as did 48% of the SLE without aPL and only 16% of the control group (see Table 2).

## Discussion

This is the first study to compare a group of APS patients with groups of SLE patients with and without aPL and a control group on several neuropsychological tests. Cognitive performance in attention, memory and executive functioning was equivalent between APS and SLE with aPL groups, consistent with the only previous study comparing both groups.[14] Furthermore, cognitive deficit was three times more frequent in APS and SLE with aPL patients than for the control group, and two times more frequent compared to SLE patients without aPL. This last finding is consistent with Denburg et al.[7] Thus, our results support the relationship between aPL antibodies and cognitive symptoms found in prior studies.[4]

Both longitudinal and cross-sectional studies have related aPL and cognitive deficits.[4–7] Moreover, those cognitive deficits tend to disappear when aPL are eliminated with ultraviolet irradiation.[14] Furthermore, prolonged exposure of aPL generates cognitive damage in animal models.[15] Our results support all those studies by finding a relation between aPL and memory and attentional problems, and sum to the literature supporting aPL as an important causal role for the neuropsychological deficits in SLE patients, probably linked to microvascular thrombosis or direct effects of aPL antibodies on brain tissue.[8,16–18]

Nevertheless, our hypothesis was only partially achieved, since no differences appear between SLE patients with aPL and the groups of SLE without aPL and control, despite the means obtained on the neuropsychological measures were smaller than the ones for the other two groups. Thus, absence of significant differences could be due to the small sample size. It is also noteworthy that almost half of the patients with SLE and no aPL showed cognitive problems, pointing to the multifactorial causes of cognitive problems in SLE.[16]

Some of the main limitations of the present study are the previously mentioned small sample size, and consequently the small neuropsychological battery used to allow for the statistical analyses. Thus, future studies with more patients and the inclusion of the full battery recommended by the American College of Rheumatology are recommended to replicate and improve our results. Furthermore, the inclusion and exclusion criteria may have biased the sample; first, the selection of ambulatory patients may have excluded the most severe cases. This could explain the mild cognitive deficits showed by the mean scores of the groups. Also, exclusion of illiterate people may have excluded the lowest socioeconomic status and patients with less cognitive reserve. Nevertheless, groups were matched on years of education. Further, antibodies were not tested in the control group (that included 7 out of 31 first or second degree patients' family members), but an initial clinical interview was carried out to discard symptoms related to the disorders of the study.

In conclusion, our results support the importance of the aPL antibodies to explain the cognitive deficits on SLE patients. A particular strength of the present study is the selection of groups, including a rigorous control group and a group of APS as recently recommended by Kozora et al.[3]

## Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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