Alterations in episodic memory in patients with systemic lupus erythematosus

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Abstract

The purpose of this paper was to examine memory performance in patients with SLE by studying the overall deterioration in memory, analyzing the differences and frequency of impairment in the variables from the visual and verbal memory tests, and studying the alterations in the memory. This study included 59 patients with a diagnosis of systemic lupus erythematosus (SLE) and 18 with a diagnosis of chronic discoid lupus (CDL), who were administered the Spanish complutense verbal learning test (TAVEC) and the Rey complex figure test (RCFT). Statistically significant differences were detected between the two groups on the immediate visual recall and delayed visual recall variables, with the mean of the SLE group being lower than that of the CDL group. The difference between the frequency of verbal and visual impairment could be explained by various factors, one of which would be a lateralization of memory impairment.

Keywords: Neuropsychological alterations; Systemic lupus erythematosus (SLE); Chronic discoid lupus (CDL); Verbal episodic memory; Visual episodic memory

1. Introduction

Systemic lupus erythematosus (SLE), prototype of the autoimmune diseases, is a systemic disease characterized by an alteration in the immunological response, with a production of antibodies directed toward mainly nuclear
antigens, thus affecting multiple organs and systems. The course of the disease includes a wide spectrum of clinical manifestations, different anatomopathological findings and a series of immunological abnormalities (Jiménez-Alonso & López-Gómez, 1991; Aula Acreditada, 2003).

The neuropsychiatric manifestations are present in SLE in 14–75% of the cases, and they make up what is called neuropsychiatric lupus (NPSLE) (ACR Ad Hoc Committee on Neuropsychiatric Lupus Nomenclature). Included are central nervous system syndromes, such as aseptic meningitis, cerebrovascular disorders, demyelination syndrome, headache (migraine and benign intracranial hypertension), movement disorders (including chorea), myelopathy, states of confusion, anxiety disorders, mood disorders, cognitive impairment and psychosis, as well as peripheral nervous system syndromes, such as Guillain–Barre, autonomic disorders, mononeuropathy, severe myasthenia, cranial neuropathy, plexopathy and polineuropathy.

Since 1999, the American College of Rheumatology (ACR) has included the neuropsychological alterations in the neuropsychiatric alterations of SLE; therefore, these alterations have become a sign of involvement of the nervous system in a disease where diverse organs, among them the brain, can be affected. Some recent studies show that the prevalence of psychiatric abnormalities present in SLE is 90% (Haupt, 2004), if the mild cognitive impairments are included.

The alterations in the nervous system and neuropsychological functioning in patients with systemic lupus erythematosus (SLE) have been the subject of numerous studies, with impairments found in diverse areas, among which memory, attention, verbal fluency, cognitive flexibility and visuomotor coordination are the most noteworthy, and with a prevalence of impairment of about 25% (Carbotte, Denburg, & Denburg, 1986; Denburg, Carbotte, & Denburg, 1987; Monastero et al., 2001; Sabbadini et al., 1999; Spangenberg, Möller, Hugo, Halland, & Whitelaw, 2000). The neuropsychological research on SLE is in a descriptive stage. The most important studies on the topic show the panorama of the general neuropsychological deterioration in this type of patients. However, the difficulty in finding patterns of neuropsychological impairment has not yet been resolved, as the literature refers to a great variability in the domains altered. The heterogeneity of the results obtained is, in part, due to the pathogenic processes of the disease themselves, which even today are not very well understood (Barr & Merchut, 1992), and, in part, to the methodological deficiencies of some of the studies (Skeel, Johnstone, Yangco, Walker, & Komatireddy, 2000).

In spite of all this, memory is one of the areas where impairments have systematically been found in the majority of the studies (Ainiala, Loukkola, Peltola, Korpela, & Hietaharju, 2001; Carbotte et al., 1986; Denburg et al., 1987; Hanly, 1992; Hay, 1992; Kutner, Busch, Mahnood, Racis, & Proebe, 1988; Monastero et al., 2001; Sabbadini et al., 1999; Spangenberg et al., 2000), although not in all of them (Ginsburg et al., 1992; Papero, Bluetime, White, & Lipnick, 1990; Wekking, Nossent, van Dam, & Swaak, 1991). This difference may be due to the use of small samples, non-standard tests, lack of a control group or the use of an inappropriate control group (Skeel et al., 2000). There has still not been enough research carried out to clarify which types of memory and processes are altered or intact. It can be hypothesized, based on the research that evaluates general neuropsychological deterioration, that the processes most frequently impaired are those of free recall, rather than those of recognition. However, there is a lot of controversy about the type of memory impaired, as some studies reveal damage in both verbal and visual memory (Ainiala et al., 2001; Carbotte et al., 1986; Denburg et al., 1987; Hanly, 1992; Hay, 1992; Kutner et al., 1988; Monastero et al., 2001; Spangenberg et al., 2000), and others only in visual memory (Hay, 1992; Ferstl, Niemann, Biehl, Hinrichsen, & Kirch, 1992).

On the other hand, these neuropsychological results obtained in other countries cannot be extrapolated to a Hispanic population. As the literature has shown, culture has an important effect on neuropsychological tests (Puente & Agranovich, 2004; Puente & Pérez-Garcia, 2000; Rosselli & Ardila, 2003). For this reason, it is important to use neuropsychological tests adapted to each population, in order to avoid any cultural effects (Puente & Pérez-Garcia, 2000), and to examine whether the results found in other populations are also found in the Spanish population.

Therefore, the purpose of this study is to investigate the memory alterations in patients with SLE, including frequency, type and processes in a Spanish population. The objective of specifying the type of process impaired is important in order to increase knowledge about the neuropsychological alterations of this autoimmune disease, to find out whether the pattern of memory deficits is similar to that of other types of patients and, finally, but not less important, to develop a specific intervention plan that is appropriate for the neuropsychological rehabilitation of these patients in this cognitive area.
2. Patients and methods

2.1. Patients

The participants in this study were 77 patients with a diagnosis of lupus. Fifty-nine patients with a diagnosis of SLE were recruited in the Systemic Autoimmune Disease Units of the Clinical Hospital San Cecilio and the University Hospital Virgen de las Nieves in Granada in the period between February 2000 and March 2005. As a control group, 18 patients (23.37% of the cases) with a diagnosis of chronic discoid lupus (CDL) were selected in the same services during the same period. This percentage is closely related to the percentage of patients with lupus diagnosed as CDL (http://www.medynet.com). This group of patients formed a very appropriate control group because CDL is a non-systemic autoimmune disease whose only affection is dermatological.

The criteria for inclusion were the following:

- age between 18 and 65 years.
- meet at least four American Rheumatology Association (ARA) criteria for the diagnosis of lupus (Tan et al., 1982).

The exclusion criteria were the following: (1) terminal renal insufficiency; (2) renal transplant; (3) patients with a high level of disease activity; (4) low cultural level (illiterate); (5) arteriosclerosis; (6) cardio-pathology; (7) cerebrovascular accidents; (8) pregnancy.

The patients’ most important clinical and demographic data are shown in Table 1.

2.2. Materials

The memory tests used for the evaluation of the patients were part of a broader neuropsychological battery, which includes measures of psychomotor performance, attention, verbal fluency and verbal and visual memory. We only refer to memory in this study, as this is a process that is systematically found to be impaired in the majority of the studies. The instruments used were the following:

(1) Initial exploratory interview about neuropsychological events, which provides a subjective view of the patient with regard to the different areas of cognitive functioning, such as memory, attention, concentration, processing speed, language, etc., in the patient’s daily life. The interview also explores mood, sleep problems, changes in personality and social and family relationships, as well as the medical history related to the disease.

(2) Spanish complutense verbal learning test (TA VEC) for the evaluation of episodic verbal memory, which consists of a list of words that are presented to the subject five times with the purpose of evaluating different memory processes, such as immediate recall, learning curve and information storage 20 min after the last presentation of the list (Benedet & Alejandre, 1998).

(3) Rey complex figure test (RCFT) for evaluating episodic visual memory, which consists of a complex figure that the subject has to copy, immediately recall (3 min), and recall again after 30 min, both freely and by recognizing the parts that make it up (Meyers & Meyers, 1995).

(4) The Ruff 2&7 selective attention test for evaluating attention consists of 20 trials. Within each trial, 30 target stimuli (2 and 7) are intermingled among three rows of alphabetic or numeric distracters. The 20 sections are quasi-randomly ordered, with 10 automatic detection trials and 10 controlled search trials. The total administration time of the test is 5 min (15 s for each of the 20 trials) (Ruff & Allen, 1996).

(5) The Ruff fluency test (RFFT) is a measure of nonverbal fluency analogous to the verbal fluency test. The RFFT is a timed test and consists of 5 trials. The purpose of the test is to make as many patterns (or figures) as possible, but each pattern has to be

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### Table 1

Statistical descriptive of age, educational level, disease activity index (SLEDAI), mean duration of illness

<table>
<thead>
<tr>
<th>Variable</th>
<th>SLE (Mean ± S.D.)</th>
<th>CDL (Mean ± S.D.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>40.8 ± 11.16</td>
<td>43 ± 10.8</td>
</tr>
<tr>
<td>Educational level</td>
<td>10.01 ± 4.1</td>
<td>9.7 ± 4.3</td>
</tr>
<tr>
<td>SLEDAI</td>
<td>1.35 ± 2.1</td>
<td></td>
</tr>
<tr>
<td>Mean duration of illness</td>
<td>5.5 ± 4.6</td>
<td>3.4 ± 2.6</td>
</tr>
</tbody>
</table>

S.D.: statistical deviation. Note: The group CDL have not got any punctuations of SLEDAI because it is not part of the protocol of medical evaluation.
different in some way from all the others. The total administration time of the test is 5 min (1 min for each of the 5 trials) (Ruff, 1996).

(6) Stroop color and word test and finger tapping test. These tests are described in detail in Lezak (1995) and Spreen and Strauss (1998).

2.3. Procedure

The patients were given an appointment in the clinic, where the study was explained to them. If they agreed to participate, they were given an appointment in the nuclear medicine service. Once there, they were told what the evaluation would consist of, they were given an informed consent form to sign, and the evaluation was carried out, which lasted about an hour. At the end of the evaluation, they were offered the possibility of being informed directly about the results, and they were promised that a report would be filled out that would become part of their medical history.

2.4. Variables and statistical analyses

The type of lupus variable (SLE and CDL) was used as the independent variable (IV).

As dependent variables (DVs), various scores were selected from the tests of episodic visual and verbal memory:

(1) For verbal memory, the following variables were obtained from the Spanish complutense verbal auditory test (TAVEC):
   - Immediate recall on the first trial with verbal material (RIA1)
   - Total immediate recall with verbal material (RIAT)
   - Short-term free recall with verbal material (RLCP)
   - Long-term free recall with verbal material (RLLP)
   - Recognition with verbal material (RCN)

(2) For visual memory, the following variables were obtained from the Rey figure test:
   - Copy of the figure (CO)
   - Immediate recall with visual material (RINM)
   - Delayed recall with visual material (RDEM)
   - Recognition with visual material (RCNT)

In the first place, descriptive analyses were carried out of the dependent variables in the study.

In order to verify that there were no statistically significant differences in the demographic variables between the two groups of subjects, a univariate ANOVA was performed between subjects.

To study the overall memory impairment in SLE and CDL patients, contingency analyses were carried out relating the type of lupus variable (SLE and CDL) and the type of memory impairment. For this purpose, a global score was obtained for memory impairment, both for verbal and visual memory, based on the $T$ scores: a score equal to or less than 35 was considered pathological (Heaton, Robert, Grant, & Matthews, 1991); a score greater than or equal to 36 was considered normal or with slight impairment.

To analyze the differences between the two groups of patients on the variables from the tests of episodic visual and verbal memory, univariate ANOVAs were performed (5 for verbal memory and three for visual), with the type of lupus (SLE vs. CDL) as the IV and the scores on the test variables as the DVs (RIA1, RIAT, RLCP, RLLP, RCN, RINM, RDEM and RCNT).

For all the analyses, a level of significance of 0.05 was adopted.

3. Results

In the first place, an examination was made of whether the two groups (SLE and CDL) were statistically equal on the main demographic variables like age and schooling. For this purpose, two univariate ANOVAs were performed for a between-group design, with the group (SLE and CDL) as the factor and age and years of schooling of the patients as the dependent variables. The results showed that there were no statistically significant differences between the two groups on these variables.

Next, the prevalence of the memory impairment, according to the type of lupus, was studied. For this purpose, 2 contingency analyses were carried out, one for verbal memory and another for visual memory, relating the type of lupus variable (SLE and CDL) and the memory deterioration. The results showed that the frequency of the visual memory impairment was statistically greater for the systemic lupus group (SLE = 43.1% vs. CDL = 11.8%) [Chi-square (1) = 5.49; $p < 0.01$]. All of the patients showed a normal performance on the copying, so that no statistical analyses were required to see whether there were differences on this variable. This result guarantees that a performance below
the mean on the memory variables is not due to other problems (visual, dispraxia, etc.), but rather to memory problems. In the case of verbal memory, no statistically significant differences were detected (Fig. 1).

Finally, the question of whether group differences existed on the neuropsychological memory test variables was studied. For this purpose, 8 univariate ANOVAs were carried out (5 for verbal memory and 3 for visual), with the type of lupus (SLE vs. CDL) as the IV and the scores on the test variables as the DVs (RIA1, RIAT, RLCP, RLLP, RCN, RINM, RDEM, and RCNT). The results showed that there were statistically significant differences between the two groups on the immediate visual recall variable \( F(1.75) = 5.13; p < 0.05 \), with the performance of the SLE group being worse than that of the CDL group (mean SLE = 40.28 vs. mean CDL = 49.22), and the delayed visual recall variable \( F(1.75) = 5.67; p < 0.05 \), with the mean of the SLE group being lower than that of the CDL group (39.79 vs. 49.33). There were no statistically significant differences for the rest of the variables (Table 2).

### 4. Discussion

The purpose of this study was to examine the neuropsychological impairment in patients with SLE in a Spanish population, focusing specifically on memory, given that few studies have focused exclusively on this function, in spite of the fact that it is one of the most frequently deteriorated functions in these patients (Ainiala et al., 2001; Carbotte et al., 1986; Denburg et al., 1987; Fersd et al., 1992; Hanly, 1992; Hay, 1992; Kutner et al., 1988; Loukkola et al., 2003; Monastero et al., 2001; Sabbadini et al., 1999; Spangenberg et al., 2000). The results show that the patients with SLE demonstrated worse performance than the control subjects on visual memory tests.
The difference between the frequency of verbal and visual impairment may be explained by various factors. In the first place, we cannot rule out the possibility that this effect is dependent on the sample, due to the reduced number of patients with CDL in our study. However, our results have also been found in other studies with larger sample sizes (Hay, 1992; Ferstl et al., 1992), although in still others damage has been found on both verbal and visual memory (Ainiala et al., 2001; Carbotte et al., 1986; Denburg et al., 1987; Hanly, 1992; Kutner et al., 1988; Monastero et al., 2001; Spangenberg et al., 2000).

Another possible reason for our findings would be that these patients present a preferential deterioration in one of the cerebral hemispheres. As neuropsychological research has shown, especially related to temporal neurosurgery for epilepsy, the memory has a distributed representation in the temporal lobes, so that the left temporal lobe is more specifically involved in memorizing verbal material, and the right temporal lobe in memorizing visual material (Campo, León-Carrión, Domínguez-Roldán, Revuelta, & Murrillo-Cabezas, 1998; Gleibner, Helmstaedter, & Elger, 1998; Szabó et al., 1998). A more affected right temporal lobe in the patients with SLE would explain the greater impairment in visual memory (Meyers & Meyers, 1995). This hypothesis is supported by Sabbadini et al. (1999), who report on right parietal hypoperfusions correlated with performance on the Rey complex figure test (RCFT), which evaluates visual memory. Other studies using cerebral imaging techniques corroborate the hypothesis of the lateralization of the damage, such as the study by Carbotte, Denburg, Denburg, Nahmias, and Garnett (1992). Using PET, these authors found alterations in the right temporal and parietal lobes, coinciding with visuospatial and memory impairments.

Another recent study (Glanz, Schur, Lew, & Khoshbin, 2005) also found a lateralization of the damage in the left hemisphere, with impairments in verbal memory, among others. The authors attribute this lateralization in the patients to effects of immune mediators in specific areas of the brain (Felten & Felten, 1987), stating that the lateralized dysfunction in the lupus may indicate a relationship between the development of cerebral asymmetries and a resultant vulnerability of certain types of cells to the immune influence (Glanz et al., 2005).

However, there is no evidence that makes it possible to state a preference of cerebrovascular conditions for one hemisphere or the other. The brain damage in the lupus may be due to cerebral ischaemia phenomena with various causes (Jennekens & Kater, 2002), among which the presence of antiphospholipid antibodies could play an important role (Horbach, Van Oort, Donders, Derksen, & De Groot, 1996; Omdal et al., 2005). Evidence supporting the relationship between the antiphospholipid antibodies and cognitive function is extensive (Brey et al., 2002; Denburg et al., 1987; Hanly, Hong, Smith, & Fisk, 1999; Menon et al., 1999; Sastre-Garriga & Montalban, 2003; Whitelaw, Spangerberg, Rickman, Hugo, & Roberts, 1999). Furthermore, the presence of antcardiolipin antibodies (ACA), both IgG and IgM, as well as lupus anticoagulant (LA), has been associated with diverse neuropsychological conditions, such as focal ischaemia and thrombosis (Levine & Welch, 1987), these being related, at the same time, to micro-thrombotic events or vasculopathies (Hughes, 1994). Therefore, the antiphospholipid antibodies could be producing silent damage in the cerebral microcirculation and affecting cognitive function. Furthermore, findings using neuroimaging techniques reveal cerebral vasculitis with multiple intracerebral lesions, both in gray matter as well as white. Significant relationships have also been shown between the findings when these techniques (MRI) are used and neuropsychological impairments, except when these impairments are slight (Wolf, Niedermaier, Bergner, & Lowitzsch, 2001). Likewise, a relationship has been found between the presence of positive antiphospholipid, neuropsychological alterations and alterations on cerebral imaging tests, specifically ischaemic and focal changes (Spangenberg et al., 2000). The evidence from these tests supports the hypothesis of a more subcortical rather than cortical damage, with SLE having been associated with small vessel vasculopathy and mini-strokes extended especially in parietotemporal zones (Bosma et al., 2002; Carbotte et al., 1992; Kodama et al., 1995), areas that are involved in memory.

In conclusion, our study has found alterations in visual memory in SLE patients in a Spanish population. These findings may be limited by the reduced size of the control group. Therefore, it is necessary to continue to investigate each of the cognitive domains usually impaired, the processes involved and the possible causes. Increasing the research in this direction will make it possible to find out more about the neuropsychological alterations of SLE and study possible therapeutic approaches to these alterations.

Acknowledgement

To patients with lupus.