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Impaired memory and learning abilities in patients with Systemic Lupus Erythematosus as measured by the Rey-Auditory Verbal Learning Test

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Abstract

Objective: To assess and characterize verbal memory impairment in SLE patients by the Rey-Auditory Verbal Learning Test (Rey-AVLT).

Methods: Forty consecutive, unselected SLE patients were evaluated with the Rey-AVLT, a clinical and research tool for the study of multiple learning and memory measures. All patients were assessed for disease activity, damage, presence of antiphospholipid antibodies and depression. Findings were compared to 40 healthy controls matched for age, sex and education.

Results: The study group included 40 SLE patients (F/M- 37/3), median age 33 yrs (range 20-59), median disease duration 8 yrs (range 0.3-32). Median disease activity measured by SLEDAI was 4 (range 0-16). Median damage measured by SLICC /ACR damage index score was 0 (range 0-4). Depression was detected in 16/40 patients. Several aspects of the memory domain, as measured by the Rey-AVLT were impaired in the SLE group, using Analysis of Variance with repeated measures. The learning curve of SLE patients was significantly less steep as compared to controls, \( p=0.036 \), the rate of words omitted from trial to trial was higher in the SLE group \( p=0.034 \) and retrieval was less efficient in SLE compared to controls \( p=0.004 \). The significance of these findings was maintained after omitting patients with stroke or depression.

Conclusion: Learning ability was impaired in SLE patients with a poor and inefficient learning strategy as reflected by an impaired learning curve, repeated omissions and impaired retrieval. This pattern of memory deficit resembles that seen in patients with frontal lobe damage and warrants further localizing brain studies.

Key words:
Systemic Lupus Erythematosus, Cognition, Memory.
**Introduction**

Central nervous system involvement in systemic lupus erythematosus is a common manifestation affecting 14-75% of SLE patients [1,2]. The nomenclature of the diverse neuropsychiatric syndromes described in SLE (NPSLE) has been revised repeatedly and has recently been standardized to include 19 defined neuropsychiatric syndromes [3]. Despite this standardization, NPSLE remains a diagnostic problem. No single laboratory marker or imaging modality serves as a gold standard and the diagnosis is primarily clinical [1, 4]. Moreover, the pathogenetic mechanisms leading to these diverse manifestations are not clear, leading to confusion regarding the choice of correct treatment. Nervous system involvement in SLE includes a wide variety of neurologic and psychiatric manifestations. Clinical syndromes of NPSLE range from overt neurologic dysfunction such as psychosis, seizure disorders, stroke and dementia to more subtle abnormalities of memory, concentration, and intellect, collectively termed cognitive dysfunction [3]. The reported prevalence of cognitive dysfunction in SLE ranges from 21 to 66% [5, 6, 7]. The etiology of cognitive dysfunction in SLE is unknown. Several studies have pointed to an association between cognitive abnormalities and other overt neuropsychiatric manifestations, but have not shown an association with active SLE, corticosteroid use or psychological stress [8, 9, 10].

Neuropsychological assessment examines the performance of individuals on a range of tests that evaluate different areas of cognition such as attention, memory and language function. The tests have been found to be sensitive in detecting mild cerebral dysfunction and have been widely applied in SLE [7, 11, 12]. A battery of such tests has been suggested by the ACR ad hoc committee on NPSLE nomenclature to facilitate and enhance clinical research and reporting [3]. The memory domain has been shown to be impaired frequently in SLE patients when using these tests [13-16]. Several studies have attempted to characterize the pattern or profile of cognitive impairment in SLE, aiming to better understand the pathogenesis of these deficits [17-21].

The goal of the present study was to assess and characterize the pattern of memory disabilities in a cohort of SLE patients by using the Rey AVLT which measures simultaneously a range of verbal memory processes (e.g., learning rate, retention over time, and retrieval efficiency) and correlate memory impairment with disease duration, disease activity, and damage as well as depression, medication and antiphospholipid antibodies.
Methods

Patients
Forty consecutive, unselected SLE patients who fulfilled the revised American College of Rheumatology criteria for the classification of SLE were evaluated after giving informed consent [22]. The study was approved by the institutional ethical committee. All patients underwent neuropsychological evaluation of the memory domain using the Rey Auditory Verbal Learning Test (RAVLT) [23] and evaluation for the presence of depression. Data was collected at the time of entry regarding disease activity as assessed by SLEDAI [24], disease damage as assessed by SLICC/ACR damage index score [25], presence of aPL (aCL, anti-β2 GPI, LAC), history of thrombosis/ pregnancy loss, history of NPSLE and current medication.

Control subjects
Forty healthy control subjects were selected from the Israeli standardization sample [23] to match the patient group for gender, age by years, and education by years.

Rey Auditory Verbal Learning test (Rey -AVLT)
The memory domain was assessed using the recommended Rey Auditory Verbal Learning test (Rey -AVLT) as part of the battery of tests suggested by the ACR ad hoc committee on neuropsychaitric lupus nomenclature [3]. Rey-AVLT is a widely used clinical and research tool for the study of multiple learning and memory measures [26]. Many measures can be extracted from this tool including immediate and delayed recall, learning rate, recognition, proactive and retroactive interference and primacy and recency effects [26, 27]. The assessment of multiple memory components enhances the tests sensitivity as a diagnostic tool. The Rey AVLT is differentially affected by age, intelligence and population type [27, 28].
The Hebrew version of the Rey Auditory Verbal Learning Test (AVLT) was administered by 2 certified psychologists in standard fashion [23]. The test consists of 15 common nouns that are read to the participants on five consecutive trials (trials 1 to 5); participants are asked to remember as many words as possible. Each trial is then followed by free recall. In trial 6, an interference list of 15 new common nouns is presented, followed by free recall of these new nouns. In trial 7, participants are asked again to recall the first list. Twenty minutes later participants are again asked to recall the first list (trial 8). They are then asked to identify the 15 words from the first list, out of 50 words presented verbally (including the 15 words in the second list and 20 new common nouns) (trial 9) (Table 1).
Table 1.

The Rey Auditory Verbal learning Tests consists of 9 trials which assess the ability to learn and remember lists of nouns with interfering measures:

<table>
<thead>
<tr>
<th>Trial</th>
<th>Definition of task</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial 1-5</td>
<td>Learning curve: List A: 15 common nouns are read to the patient 5 times</td>
</tr>
<tr>
<td></td>
<td>- free recall of nouns requested after each trial</td>
</tr>
<tr>
<td></td>
<td>- number of recalled words recorded at each trial</td>
</tr>
<tr>
<td></td>
<td>- the exact recalled words are listed</td>
</tr>
<tr>
<td>Trial 6</td>
<td>Interference: List B: interference list of 15 other nouns are read once</td>
</tr>
<tr>
<td></td>
<td>- free recall of nouns requested</td>
</tr>
<tr>
<td></td>
<td>- number of recalled words recorded</td>
</tr>
<tr>
<td>Trial 7</td>
<td>- requested to recall list A without additional reading</td>
</tr>
<tr>
<td>Trial 8</td>
<td>Delayed recall:</td>
</tr>
<tr>
<td></td>
<td>- requested to recall list A after 20 minutes</td>
</tr>
<tr>
<td>Trial 9</td>
<td>Recognition:</td>
</tr>
<tr>
<td></td>
<td>- list of 50 words are read (15 from list A, 15 from list B, 20 new nouns)</td>
</tr>
<tr>
<td></td>
<td>- requested to identify 15 words of list A</td>
</tr>
</tbody>
</table>

*Retrieval = Delayed recall – Recognition*

**Depression assessment**

The presence of depression at the time of entry was assessed by the Beck Depression Inventory [29]. A score of ≥12 was considered evidence of depression.

**Statistical Analysis**

A mixed design ANOVA (SPSS, version 15 for Windows) was conducted to analyze the effects of group (SLE vs. control), and the various Rey-AVLT trials. The former is a between-subjects factor, and the latter is a within-subjects factor. In addition the Pearson's product-moment correlation (2 tailed) was used to analyze the relations between the different memory measures and disease measures including disease duration, disease activity (SLEDAI), disease damage (SLICC /ACR damage index score), medications and depression (BDI).
Results
The demographic and disease characteristics of the SLE patients are presented in table 2. The patients' age ranged from 20 to 59 years (median-33 years), and their education ranged from 9 to 18 years of education (median-14 years). The control group's age ranged from 21 to 58 years (median-31 years) and their education ranged from 8 to 17 years (median-14 years). In the patient group, disease duration ranged from 0.3-32 years (median-8 yrs). The disease activity was mild to moderate in most patients (median SLEDAI: 4, range 0-16) and median damage according to SLICC/ACR damage index score was 0 (range 0-4). Corticosteroid treatment was prevalent (57.5%) but the majority (37.5%), were on a low dose of prednisone (5-10mg/d, median-5mg/d, range 0-60mg/d).

Table 2.
Demographic and disease characteristics of the SLE patients

<table>
<thead>
<tr>
<th>Gender</th>
<th>F/M: 37/3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>median -33 yrs (range 20-59)</td>
</tr>
<tr>
<td>Disease duration</td>
<td>median -8 yrs (range 0.3-32)</td>
</tr>
<tr>
<td>Disease activity (SLEDAI)</td>
<td>median - 4 (range 0-16)</td>
</tr>
<tr>
<td>Accrued damage (SLICC/ACR damage index score)</td>
<td>median - 0 (range 0-4)</td>
</tr>
<tr>
<td>History of stroke</td>
<td>5/40 (12.5%)</td>
</tr>
<tr>
<td>Depression (at time of study entry)</td>
<td>16/40 (40%)</td>
</tr>
<tr>
<td>Corticosteroid use (all doses)</td>
<td>23/40 (57.5%)</td>
</tr>
<tr>
<td>5-10 mg/d</td>
<td>15/40 (37.5%)</td>
</tr>
<tr>
<td>12.5-20mg/d</td>
<td>6/40 (15%)</td>
</tr>
<tr>
<td>&gt;20mg/d (50mg, n=1; 60mg, n=1)</td>
<td>2/40 (5%)</td>
</tr>
<tr>
<td>Median - 5mg/d (range 0-60mg/d)</td>
<td></td>
</tr>
</tbody>
</table>

Twelve patients had the antiphospholipid syndrome (APS), 5 of whom had a history of stroke, 3 had a history of arterial thrombosis, 3 had a history of venous thrombosis and 2 had obstetrical APS (1 of whom had a stroke as well). Ten patients had antiphospholipid antibodies (aPL) without APS and 18 patients were aPL negative. Depression as detected by the Beck depression inventory was seen in 16/40 patients, 4 of whom were treated with anti-depressants (SSRI) at the time of study entry. Twenty one patients fulfilled criteria for NPSLE including: 16 patients with depression, 5 had a history of stroke (1 of whom also had depression), 2 had peripheral neuropathy (both had depression as well) and 1 had seizures. The NPSLE criteria refer to features that had ever been present and not recent features except depression which was assessed at the time of study entry. Several aspects of the memory domain, as measured by the Rey-AVLT were impaired in the SLE group as compared to controls.
Learning rate-Trial 1 to 5 (figure 1): A mixed design ANOVA was conducted to analyze the effect of group (SLE vs. control) and learning trial (1 to 5). The former is a between subjects factor and the latter a within subjects factor. Overall the control group recalled more words than the patient group in the first 5 trials of the test, $F(1,78)=22.33, p<0.001$. There was also a significant increase in the number of words recalled from trial to trial, $F(4,312)=272.09, p<0.001$. The Group by Learning interaction reached significance as well, $F(4,312)=2.61, p=0.036$, indicating that the patient group learning rate was significantly lower as compared to the control group. The mean ± SEM number of recalled words increased from trial 1 to trial 5 in the control group from: 7.28±0.24 to 13.70±0.21 and in the SLE group from 6.38±0.30 to 11.93±0.3(p<0.036).

"Additions" and "Omissions" (figure 2): The number of additions is the sum of new words recalled in each trial ($N$) that were not recalled in the previous trial ($N-1$). The number of omissions is the sum of words not recalled in a particular trial ($N$), but had been recalled in the previous trial ($N-1$). In comparing SLE patients to healthy controls the rate of additions did not differ, however the SLE patients omitted significantly more words than the control group from trial to trial [ for group: $F(1,78)=19.01, p<0.001$; for trials: $F(3,234)=7.82, p<0.001$] and for group by trial interaction: $F(3,234)=2.9, p=0.034$ indicating that the SLE group increased the number of words omitted from trial to trial whereas the control group omitted a constant number of words across trials.

Retention- Trial 5 vs. Trial 8: The groups differed significantly in the number of words recalled in trial 5 and 8, $F(1,78)=18.33, p<0.001$. Overall, fewer words were recalled in the delayed trial (Trial 8) as compared to Trial 5, $F(1,78)=43.19, p<0.001$, however the forgetting rate of the two groups did not differ significantly $F(1,78)=1.0, p>0.05$.

Retrieval efficiency-Delayed recall (Trial 8) vs. Recognition (Trial 9) (figure 3): The control group remembered more words overall in these 2 trials (8 and 9) than the patient group ( trial 8: 12.48±0.38 vs.10.25±0.49; trial 9: 14.5±0.11 vs.13.8±0.24), $F(1,78)=12.99, p<0.001$. More words were correctly recognized (trial 9) than recalled (trial 8), $F(1,78)=115.18, p<0.001$. The difference between recall and recognition was significantly greater in the SLE group as compared to controls, $F(1,78)=8.82, p=0.004$ This finding indicates impaired retrieval in the SLE group.

The significance of the findings for all the above memory measures was maintained after omitting patients with stroke or depression.

Relations between the different memory measures and disease measures: No correlation was found between: disease duration, disease activity (SLEDAI), damage (SLICC), steroid treatment or other medications and memory impairment. No correlation was seen between memory measures and the presence of depression.
Discussion

Memory impairment, poor concentration and difficulty in performing mental tasks are frequent complaints in SLE patients [30]. Patients and physicians alike tend to attribute these complaints to the impact of a chronic debilitating disease as well as to depression [31, 32].

In this study we attempted to assess the prevalence, characteristics and pattern of memory impairment in a cohort of 40 consecutive, non-selected SLE patients. Twenty patients fulfilled the criteria for NPSLE, 13 based on the presence of depression alone and 7 due to stroke, seizures or peripheral neuropathy.

Several aspects of the memory domain, as measured by the Rey-AVLT were found to be impaired in the SLE group as compared to controls. The learning curve of SLE patients was significantly less steep as compared to healthy controls and the rate of words omitted from trial to trial was higher in the SLE group. In addition, retrieval, as measured by the difference between delayed recall and recognition was less efficient in SLE patients compared to controls. These findings suggest inefficient and impaired learning strategies in the SLE patients. The significance of these finding was maintained after omitting patients with stoke or depression. Thus, despite its prevalence, memory impairment could not be explained by the presence of depression or other manifestations of NPSLE including a history of stroke. Moreover this memory impairment could not be explained by steroid use, disease duration, disease activity as measured by SLEDAI or disease severity and residual damage as reflected by the SLICC/ACR damage index score. Our findings are consistent with other studies where cognitive impairment did not correlate with disease activity, involvement of other organ systems or the effects of chronic illness or its treatment [33, 34]. Carlomagno et al. have shown that cognitive impairment is a stable symptom of CNS involvement in SLE over time and is not related to changes in disease activity [34].

Cognitive impairment has been associated with various auto-antibodies including anti-neuronal and lymphocytotoxic antibodies [33, 34], anti-ribosomal P antibodies [37, 38, 39], persisted presence of anti-phospholipid antibodies [40-43] and possibly anti- NR2 antibodies [44, 45] as well as increased levels of serum matrix metalloproteinase 9 (MMP-9), suggesting an association with small vessel cerebral ischemic events [46]. Indeed in our cohort 22 patients were found to have antiphospholipid antibodies on repeated tests, 12 of whom had the antiphospholipid syndrome, suggesting that the high prevalence of these antibodies may account, at least in part for the high prevalence of memory impairment. The pattern of memory deficit seen in the present study resembles that seen in patients with frontal lobe damage [47, 48]. Prefrontal regions are crucial, during encoding and retrieval, for the utilization of mnemonic strategies [49]. Patients with prefrontal damage often demonstrate extensive free-recall deficits along with relatively preserved recognition leading to inadequate usage of organizational strategies, similar to our findings in SLE patients [50]. Localization of these cognitive deficits possibly suggests that this impairment may be due to direct neurotoxicity (possibly autoantibody mediated) or possible localized ischemic injury. Glanz et al studied 50 right handed SLE patients, as compared to 30 right
handed healthy controls and found SLE patients to be impaired on measures of psychomotor speed/fluency, verbal speed/fluency and verbal memory and suggest that this pattern of performance is consistent with left hemisphere dysfunction. They conclude that the observed deficits were not clearly attributable to vascular lesions and suggest immune mediated effects on specific brain regions [20]. Processing speed and working memory impairments are the hallmark of cognitive dysfunction in multiple sclerosis [18]. Shucard et al compared SLE patients to controls and demonstrated that, similar to MS, SLE patients use a chunking strategy to obtain correct responses and reduce cognitive demands of the task [18]. The pattern of memory deficit seen in the present study, with an inefficient learning strategy as reflected by an impaired learning curve, repeated omissions and impaired retrieval warrants further localizing brain studies to better characterize and understand potential mechanisms for memory impairment in these patients.

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**Figure legends:**

**Figure 1. Learning rate: trials 1 to 5**

The learning curve of SLE patients, over the five learning trials was significantly less steep as compared to healthy controls ($p=0.036$).

**Figure 2. Omission of words (trials 2-5)**

The rate of words omitted from trial to trial was higher in the SLE group as compared to healthy controls ($p=0.034$).

**Figure 3. Retrieval efficiency (Recall vs. Recognition, trial 8 vs. trial 9)**

The difference between delayed recall and recognition was greater for SLE patients compared to healthy controls ($p=0.004$) indicating less efficient retrieval in SLE patients.
References:


Figure 1.
Learning rate: trials 1 to 5
The learning curve of SLE patients, over the five learning trials was significantly less steep as compared to healthy controls ($p = 0.036$).

The control group recalled more words than the SLE patients in the first 5 trials, $p<0.001$
(values represent the mean ±SEM of words recalled at each trial)
Figure 2.
Omission of words (trials 2-5)
The rate of words omitted from trial to trial was higher in the SLE group as compared to healthy controls \( (p=0.034) \).

The SLE group omitted overall more words than the controls, \( p<0.001 \) (values represent the mean ±SEM of words omitted at each trial).
Figure 3.
Retrieval efficiency (Recall vs. Recognition, trial 8 vs. trial 9)
The difference between delayed recall and recognition was greater for SLE patients compared to healthy controls \((p<0.004)\) indicating less efficient retrieval in SLE patients.

- The control group remembered overall more words than the SLE group in the 2 trials (8 and 9), \(p<0.001\) and \(p<0.05\) respectively.
- More words were correctly recognized (trial 9) than recalled (trial 8), \(p<0.001\) (values represent the mean ±SEM of words recalled or recognized).