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Ann Rheum Dis 2009;68:812-816; originally published online 1 Jul 2008;
doi:10.1136/ard.2008.091538

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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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Accepted 22 May 2008
Published Online First
10 June 2008

ABSTRACT

Objective: The purpose of this study was to assess and characterise verbal memory impairment in patients with systemic lupus erythematosus (SLE) by the Rey Auditory Verbal Learning Test (Rey AVLT).

Methods: 40 consecutive, unselected patients with SLE 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 with those of 40 healthy controls matched for age, sex and education.

Results: The study group included 40 patients with SLE (37 females, 3 males), median age 33 years (range 20–59), median disease duration 8 years (range 0.3–32). The median disease activity measured by the SLE Disease Activity Index (SLEDAI) was 4 (range 0–16). Median damage measured by the SLICC/ACR (Systemic Lupus International Collaborating Clinics/American College of Rheumatology) 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 patients with SLE was significantly less steep compared with that of 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 with controls ($p = 0.004$). The significance of these findings was maintained after omitting patients with stroke or depression.

Conclusion: Learning ability was impaired in patients with SLE 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 localising brain studies.

Central nervous system (CNS) involvement in systemic lupus erythematosus (SLE) is a common manifestation affecting 14–75% of patients with SLE.^{1,2} The nomenclature of the diverse neuropsychiatric syndromes described in SLE (NPSLE) has been revised repeatedly and has recently been standardised to include 19 defined neuropsychiatric syndromes.³ Despite this standardisation, 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, causing confusion regarding the choice of correct treatment. Nervous system involvement in SLE includes

a wide variety of neurological and psychiatric manifestations. Clinical syndromes of NPSLE range from overt neurological 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%.^{5–7} The aetiology 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.^{8–10}

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 American College of Rheumatology (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 patients with SLE when using these tests.^{13–16} Several studies have attempted to characterise the pattern or profile of cognitive impairment in SLE, aiming to understand better the pathogenesis of these deficits.^{17–21}

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

METHODS

Patients

Forty consecutive, unselected patients with SLE who fulfilled the revised ACR 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 AVLT²³ and evaluation for the presence of depression. Data were collected at the time of entry regarding disease activity as assessed by the SLE Disease

Activity Index (SLEDAI),²⁴ disease damage as assessed by the Systemic Lupus International Collaborating Clinics/ACR (SLICC/ACR) damage index score,²⁵ presence of aPLs (anti-cardiolipin (aCL), anti- β 2 glycoprotein 1 (GPI) and lupus anticoagulant (LAC)), history of thrombosis/pregnancy loss, history of NPSLE and current medication.

Control subjects

Forty healthy control subjects were selected from the Israeli standardisation sample²³ to match the patient group for gender, age by years and education by years.

Rey AVLT

The memory domain was assessed using the recommended Rey AVLT as part of the battery of tests suggested by the ACR ad hoc Committee on NPSLE nomenclature.⁵

The 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 test's 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 AVLT was administered by two certified psychologists in standard fashion.²³ The test consists of 15 common nouns that are read to the participants on five consecutive trials (trials 1–5); 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).

Depression assessment

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

Table 1 The Rey Auditory Verbal Learning Test consists of nine trials which assess the ability to learn and remember lists of nouns with interfering measures

Trial	Definition of task
Trials 1–5	Learning curve: List A: 15 common nouns are read to the patient 5 times –free recall of nouns requested after each trial –number of recalled words recorded at each trial –the exact recalled words are listed
Trial 6	Interference: List B: interference list of 15 other nouns are read once –free recall of nouns requested –number of recalled words recorded
Trial 7	Requested to recall list A without additional reading
Trial 8	Delayed recall: requested to recall list A after 20 min
Trial 9	Recognition: –list of 50 words are read (15 from list A, 15 from list B, 20 new nouns) –requested to identify 15 words of list A

Retrieval = Delayed recall–Recognition.

Statistical analysis

A mixed-design analysis of variance (ANOVA) (SPSS, version 15 for Windows) was conducted to analyse 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 product-moment correlation (two-tailed) was used to analyse the relationships 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 patients with SLE are presented in table 2. The patients' age ranged from 20 to 59 years (median 33 years), and their years of education ranged from 9 to 18 (median 14 years).

The control group's age ranged from 21 to 58 years (median 31 years) and their years of education ranged from 8 to 17 (median 14 years).

In the patient group, disease duration ranged from 0.3 to 32 years (median 8 years). The disease activity was mild to moderate in most patients (median SLEDAI: 4, range 0–16) and median damage according to the 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 (5–10 mg/day, median 5 mg/day, range 0–60 mg/day).

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 obstetric APS (1 of whom had a stroke as well). Ten patients had aPLs without APS, and 18 patients were aPL negative. Depression as detected by the BDI was seen in 16/40 patients, 4 of whom were treated with antidepressants (selective serotonin reuptake inhibitors (SSRIs)) at the time of study entry. Twenty-one patients fulfilled criteria for NPSLE: 16 patients had 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.

Table 2 Demographic and disease characteristics of the patients with SLE

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

F, females; M, males; SLE, systemic lupus erythematosus; SLEDAI, SLE Disease Activity Index; SLICC/ACR Systemic Lupus International Collaborating Clinics/American College of Rheumatology.

Extended report

Several aspects of the memory domain, as measured by the Rey AVLT were impaired in the SLE group as compared with controls.

Learning rate: trials 1–5 (fig 1)

A mixed-design ANOVA was conducted to analyse the effect of group (SLE vs control) and learning trial (1–5). 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 compared with 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" (fig 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 that had been recalled in the previous trial ($N-1$). In comparing patients with SLE with healthy controls, the rate of additions did not differ; however, the patients with SLE 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 versus trial 8

The groups differed significantly in the number of words recalled in trials 5 and 8, $F(1,78) = 18.33$, $p < 0.001$. Overall, fewer words were recalled in the delayed trial (trial 8) as compared with 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) versus recognition (trial 9) (fig 3)

The control group remembered more words overall in these two trials (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 recognised (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 compared with 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.

Relationships 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.

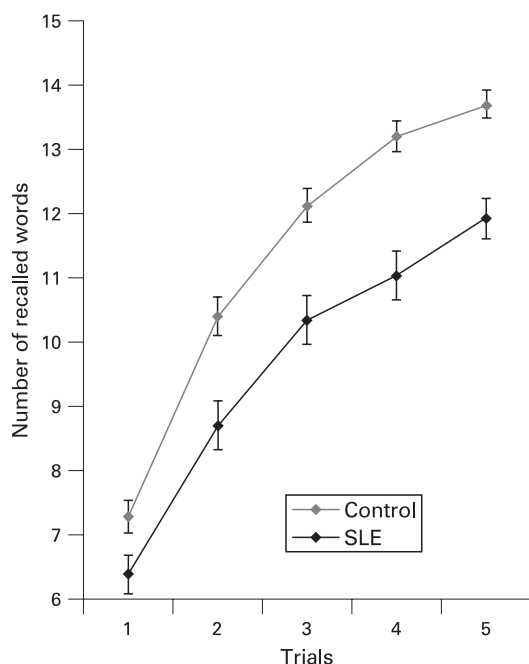


Figure 1 Learning rate: trials 1–5. The learning curve of patients with systemic lupus erythematosus (SLE) over the five learning trials was significantly less steep compared with healthy controls ($p = 0.036$). The control group recalled more words than the patients with SLE in the first 5 trials, $p < 0.001$ (values represent the mean (SEM) of words recalled in each trial).

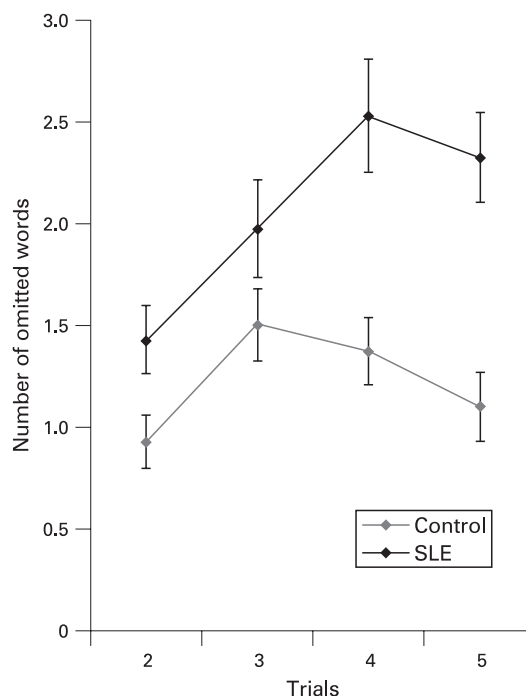


Figure 2 Omission of words (trials 2–5). The rate of words omitted from trial to trial was higher in the systemic lupus erythematosus (SLE) group compared with healthy controls ($p = 0.034$). The SLE group omitted overall more words than the controls, $p < 0.001$ (values represent the mean (SEM) of words omitted at each trial).

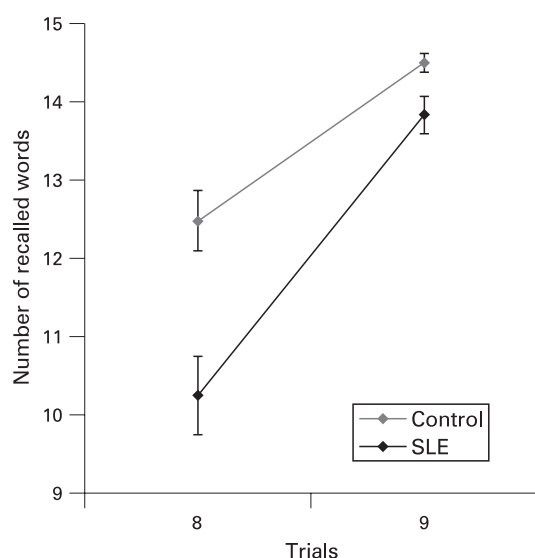


Figure 3 Retrieval efficiency (recall vs recognition, trial 8 vs trial 9). The difference between delayed recall and recognition was greater for patients with systemic lupus erythematosus (SLE) than for healthy controls ($p = 0.004$), indicating less efficient retrieval in patients with SLE. The control group remembered overall more words than the SLE group in the two trials (8 and 9), $p < 0.001$ and $p < 0.05$, respectively. More words were correctly recognised (trial 9) than recalled (trial 8), $p < 0.001$ (values represent the mean (SEM) of words recalled or recognised).

DISCUSSION

Memory impairment, poor concentration and difficulty in performing mental tasks are frequent complaints in patients with SLE.³⁰ Patients and doctors 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 patients with SLE. 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 with controls. The learning curve of patients with SLE was significantly less steep as compared with that of 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 patients with SLE compared with controls. These findings suggest inefficient and impaired learning strategies in the patients with SLE. The significance of these findings was maintained after omitting patients with stroke 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 the 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 autoantibodies including antineuronal and lymphocytotoxic antibodies,^{35 36} antiribosomal P antibodies,^{37–39} the persistent presence of aPLs^{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 ischaemic events.⁴⁶

Indeed, in our cohort, 22 patients were found to have aPLs on repeated tests, 12 of whom had the APS, 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 utilisation of mnemonic strategies.⁴⁹ Patients with prefrontal damage often demonstrate extensive free-recall deficits along with relatively preserved recognition, leading to inadequate usage of organisational strategies, similar to our findings in patients with SLE.⁵⁰ Localisation of these cognitive deficits possibly suggests that this impairment may be due to direct neurotoxicity (possibly autoantibody mediated) or possible localised ischaemic injury. Glanz *et al* studied 50 right-handed patients with SLE and compared them with 30 right-handed healthy controls. They found patients with SLE to be impaired on measures of psychomotor speed/fluency, verbal speed/fluency and verbal memory, and they 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 patients with SLE with controls and demonstrated that, similar to patients with multiple sclerosis, patients with SLE use a chunking strategy to obtain correct responses and reduce the 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 localising brain studies to characterise and understand better the potential mechanisms for memory impairment in these patients.

Competing interests: None.

Ethics approval: The study was approved by the institutional ethical committee.

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