EXTENDED REPORT

Hippocampal atrophy in systemic lupus erythematosus

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Objectives: To determine the frequency and progression of hippocampal atrophy in systemic lupus erythematosus (SLE) and the clinical, laboratory and treatment features associated with its occurrence.
Methods: 150 patients with SLE and 40 healthy volunteers were enrolled in our study. A complete clinical, laboratory and neurological evaluation was performed. Magnetic resonance imaging was carried out using a 2T scanner (Elscint Prestige) and coronal T1-weighted images were used for manual volumetric measurements. Atrophy was defined as values <2 standard deviations from the means of controls.
Results: At entry into the study, the mean right and left hippocampal volumes of patients were significantly smaller than the hippocampal volumes of controls ($p<0.001$). After the follow-up magnetic resonance imaging, a significant progression of reduction in right and left hippocampal volumes in patients was observed ($p<0.001$). At entry, atrophy was identified in 43.9% and at follow-up in 66.7% of patients with SLE. Hippocampal atrophy was related to disease duration ($p<0.001$) total corticosteroid dose ($p=0.01$) and history of central nervous system (CNS) manifestations ($p=0.01$). Progression of atrophy was associated with cumulative corticosteroid dose ($p=0.01$) and number of CNS events ($p=0.01$). Patients with cognitive impairment had more severe hippocampal atrophy than those without.
Conclusion: Disease duration, total corticosteroid dose and greater number of CNS manifestations were associated with hippocampal atrophy in patients with SLE. A significant progression of hippocampal atrophy related to total corticosteroid dose and number of CNS events was observed. Further studies are necessary to confirm these findings.

Systemic lupus erythematosus (SLE) is a multiorgan autoimmune disease with abnormalities in immune regulation.[1–3] Disease activity is characterised by intense inflammatory activity and treatment includes corticosteroids and other immunosuppressive agents.[4]

The hippocampus, located in the temporal lobe, is a structure intimately associated with certain aspects of learning and memory consolidation.[5] Patients exposed to high levels of exogenous[6–8] or endogenous[9–11] corticosteroids are more prone to short-term memory deficits. Previous studies have analysed the reversible and irreversible changes in the hippocampus after exposure to corticosteroids.[12 13] The hippocampus provides negative feedback to the hypothalamic–pituitary–adrenal axis and has a critical role in declarative memory.[14–16] In two studies, reduction in hippocampal volume correlated with mean cortisol level and atrophy was reversible after normalisation of cortisol levels.[10 11]

We aimed to determine the prevalence of hippocampal atrophy in SLE through validated manual magnetic resonance imaging (MRI) segmentation and the clinical, laboratory and treatment features associated with its occurrence. We also wanted to determine whether this atrophy is progressive after the follow-up period and the factors that were associated with the continuous reduction in hippocampal volume.

SUBJECTS AND METHODS

Subjects

A total of 150 consecutive patients with SLE with four or more criteria for SLE[17] seen regularly at our rheumatology unit, University of Campinas, São Paulo, Brazil, were screened prospectively for participation in the study. All patients with SLE were followed using a standardised protocol by the same investigators in the rheumatology unit (LTLC, SA). We excluded patients who were unable to undergo MRI, for instance, patients with claustrophobia ($n=8$) or a pacemaker ($n=2$), as well as patients with previous clinical conditions that could influence cerebral and hippocampal atrophy, such as a history of stroke ($n=10$), arterial hypertension ($n=5$), diabetes mellitus ($n=5$), alcohol and drug misuse ($n=1$), epilepsy[8] and malignancy ($n=1$). None of the patients had renal insufficiency or other pathologies that could influence cerebral atrophy. Patients who fulfilled the American College of Rheumatology (ACR) criteria for rheumatoid arthritis, systemic sclerosis, Sjogren's syndrome (primary or secondary; $n=3$) or other connective tissue diseases and with drug-induced SLE were also excluded. The remaining 107 patients (100 women) were included. We used the classification proposed by the ACR to analyse neuropsychiatric involvement.[18] Records were reviewed to determine past central nervous system (CNS) events. Patients with CNS manifestations secondary to clinical conditions such as infections, arterial hypertension, uraemia, diabetes and drugs were excluded from our study.

This study was approved by the ethics committee of our institution and informed written consent was obtained from each subject.

Clinical, serological and treatment features of patients with SLE

Data on sex, age at onset of disease and disease duration were collected for each patient. Disease duration was defined as the time from initial manifestation clearly attributable to SLE until the day of MRI acquisition. All clinical manifestations and laboratory test findings were recorded. The following

Abbreviations: ACR, American College of Rheumatology; CNS, central nervous system; MRI, magnetic resonance imaging; SLE, systemic lupus erythematosus; SLEDAI, Systemic Lupus Erythematous Disease Activity Index; SLICC/ACR DI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index clinical manifestations were analysed: malar rash, discoid lesions, subacute cutaneous lesions, photosensitivity, oral ulcers, arthritis, serositis, nephritis, neurological and psychiatric involvement, thrombocytopenia, haemolytic anaemia, Raynaud's phenomenon, thrombosis, myositis, lung involvement and lymphadenopathy.

Nephritis was diagnosed on the basis of proteinuria >0.5 g/l with abnormal urinary sediment or histological findings. Nephrotic syndrome was defined as proteinuria >3.5 g/day. Haematological changes were ascribed to lupus only in the absence of bone marrow suppression (leucopenia <4000 cells/mm^3; thrombocytopenia <100 000/mm^3; haemolytic anaemia with positive Coombs' test). Antinuclear antibodies were determined by indirect immunofluorescence using HEp 2 cells as the substrate and were considered to be positive if higher than 1:40. Anti-double-stranded DNA antibodies were determined by indirect immunofluorescence using crithidia as substrate and were considered to be positive if higher than 1:10. Precipitating antibodies to extractable nuclear antigens, including Ro (Sjogren's syndrome A), La (Sjogren's syndrome B) and Sm, were detected by immunodiffusion or microhaemagglutination. Anti-cardiolipin antibodies of the immunoglobulin G and immunoglobulin M isotypes were measured by enzyme-linked immunosorbent assay as described.[19] Lupus anticoagulant activity was detected by coagulation assays in platelet-free plasma obtained by double centrifugation, following the recommendation of the subcommittee on lupus anticoagulant of the Scientific and Standardization Committee of the International Society of Thrombosis and Homeostasis.[20]

CNS manifestations were recorded following ACR case definitions[18] and were divided into present (active or past CNS involvement) or absent (never presented CNS involvement). A complete neurological examination, and cognitive and psychiatric charts, was prospectively applied to all patients to identify CNS involvement. The Mini-Mental State Examination[21] was applied to all participants.

All participants were submitted to a battery of standardised neuropsychological tests to screen for possible impairment in one or more of the following cognitive domains: simple attention, complex attention, memory, visuospatial processing, language, reasoning or problem solving, psychomotor speed and executive functions.[21–24] The individual test results were converted into standard scores, which were compared with the available normative data.[21–24] Regarding any of the eight cognitive domains, subjects with a total score >2 standard deviations (SD) below the normative value were considered to be impaired. Cognitive dysfunction was classified as mild if there were deficits in less than three dimensions, as moderate if there were deficits in three or four dimensions and as severe if there were deficits in at least five dimensions.[25 26]

Assessment of depression was based on clinical interview and the Beck Depression Inventory.[27 28] Scores from 10 to 17 on the Beck Depression Inventory were considered to indicate mild depression, from 18 to 24 moderate depression and >24 severe depression. Anxiety was evaluated using the Hospital Anxiety and Depression Scale.[29] The presence of psychosis was determined by the Brief Psychiatry Rating Scale.[30]

For history of CNS involvement, we reviewed the medical charts of patients. Disease activity was measured by the Systemic Lupus Erythematous Disease Activity Index (SLEDAI) and was considered to be active if scores were >8 points.[31] Cumulative SLE-related damage was determined by the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SLICC/ACR DI)[32] in all patients with SLE at the time of MRI.

Total doses of corticosteroids and other immunosuppressant drugs used since the onset of disease were calculated by careful review of the medical charts. Doses of oral and parenteral corticosteroids were analysed and converted to the equivalent doses of prednisone. The cumulative dose of corticosteroids used was calculated by the sum of daily dosages versus time (days) of treatment.

MRI acquisition

All subjects underwent MRI examination using the Escint Prestige 2T scanner (Haifa, Israel). Coronal T1-IR (3 mm thick, flip angle 120°, repetition time 6800 ms, echo time 129 ms, matrix 252×328, field of view 21×23 cm) images were analysed using anatomical guidelines obtained from a standardised protocol[33] for manual segmentations of hippocampal and total brain volumes (fig 1). Quantification and analysis were carried out by one investigator (ADC) blind to the patients' clinical data. The evaluation was cross-checked by other investigators with experience in MRI analysis (SA, FC). This method has been previously compared with other segmentation programmes,[34] and intraobserver (r = 0.90) and interobserver (r = 0.85) variations were determined.

The control group for the MRI protocol consisted of 40 healthy volunteers (36 women) with a mean age of 31.8 (SD 10.2; range 20–55) years. Patients and controls were statistically comparable in age and sex.

Image processing

Manual delineation of hippocampi boundaries was carried out using the Scion Image program (NIH, Bethesda, Maryland, USA). Anatomical guidelines for outlining the hippocampus followed a specific protocol previously described.[35] Once the outline had been defined, the slice area was calculated automatically by the computer program. We then calculated the total volumes (mm^3) as the sum of each area multiplied by the slice thickness. To determine hippocampal atrophy even in the presence of diffuse atrophy, and also to correct for individual variation of the size of the head, we corrected all hippocampal absolute volumes for each respective individual cerebral volume. This correction consisted of dividing the mean total brain volume of the control group by the patient's brain volume. In each patient, the calculated hippocampal volume was then multiplied by this ratio.[36] This correction for brain volume assumes a linear relationship between hippocampi and brain volumes.[36]

In addition, asymmetry index was determined by the ratio of the smaller to the larger structure for each subject.

Atrophy was determined when corrected volumes or asymmetry index were <2 SD from the mean of the control group.

Statistical analysis

We compared hippocampal volumes of patients with SLE with controls, using the two-sample t test. We further subdivided patients with SLE into two groups: patients with and without CNS involvement. We carried out analysis of variance to test for differences among hippocampal volumes in these groups, with Tukey's pairwise post hoc comparisons when necessary. This procedure includes corrections for multiple comparisons. Demographic data between groups were compared using the χ^2 test. Follow-up volumes were compared by paired t test with Bonferroni's correction for multiple comparisons. Linear regression was used to analyse the association of cerebral and hippocampal volumes with disease duration and total corticosteroid use.

Volumetric measurements were expressed in cm^3 and are shown as mean (SD). Significance was considered at $\alpha = 5\%$.

RESULTS

Demographic data

A total of 107 patients with SLE (100 women) with a mean age of 32.2 years (SD = 11.2; range 18–54) met the inclusion

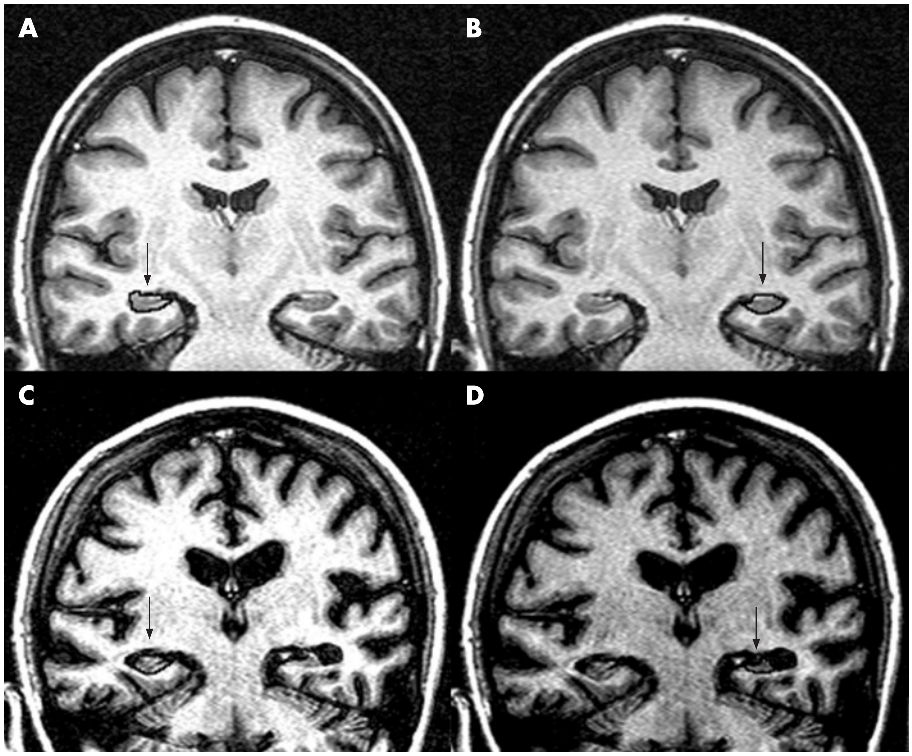

Figure 1 Example of segmentation of hippocampal volume. (A, B) Hippocampal segmentation (arrows) of a control; (C, D) hippocampal segmentation (arrows) of a patient.

and exclusion criteria. The mean duration of disease at entry into the study was 64.5 months (SD 48.50; range 1–372 months). All patients were on corticosteroids, with doses varying from 5 to 100 mg of prednisone. Antiphospholipid antibodies were positive in 32 patients. Active SLE disease was observed in 54 patients, with a mean SLEDAI score of 14.0 (SD 5.9; range 9–20). In all, 122 episodes of CNS manifestations were observed in 64 patients (table 1).

Active CNS disease at the time of MRI was observed in 30 of 64 patients with a history of CNS involvement. The mean SLICC/ACR DI score at entry into the study was 2.3 (SD 1.8; range 0–5). Table 1 shows the cumulative clinical and CNS events at entry into the study.

MRI was repeated in 60 patients after a mean follow-up period of 19 months (SD 2.2; range 12–25). Forty of these patients presented CNS events during the follow-up period, with a mean SLEDAI score of 12.4 (SD 3.8; range 3–20). The mean SLICC/ACR DI score at follow-up was 3.1 (SD 1.7; range 0–6).

Hippocampal volumes

At entry into the study, the mean right hippocampal volume of patients was 32.6 cm^3 (SD 3.3) and the mean left hippocampus volume was 30.8 cm^3 (SD 3.3). In controls, we observed a mean right hippocampal volume of 35.7 cm^3 (SD 3.1) and a mean left hippocampal volume of 34.8 cm^3 (SD 3.3). A significant difference was observed between the right ($p = 0.002$) and the left ($p = 0.001$) hippocampal volumes of patients and controls (fig 2).

Individual analysis

Hippocampal atrophy was identified in 47 of 107 (43.9%) patients and distributed as follows: 20 of 47 (42.6%) patients with left hippocampal atrophy, 10 (21.3%) patients with right hippocampal atrophy and 17 (36.2%) patients with bilateral hippocampal atrophy.

Group analysis

The degree of hippocampal volume loss correlated independently with disease duration ($r = 0.89$; $p<0.001$), the presence

Table 1 Neuropsychiatric manifestations in 64 patients at entry into the study and 40 patients at follow-up

Neuropsychiatric manifestations	Number of CNS events (%) at entry into the study	Number of CNS events (%) during follow-up
Headache	39 (32)	7 (10.3)
Cognitive impairment	35 (27)	40 (58.8)
Mood disorder	13 (11)	5 (7.3)
Acute confusional state	10 (8.1)	3 (4.4)
Anxiety	7 (5.7)	3 (4.4)
Psychosis	6 (4.9)	3 (4.4)
Mononeuropathy	4 (3.3)	0
Cranial neuropathy	3 (2.5)	1 (1.4)
Myelopathy	3 (2.5)	4 (5.9)
Aseptic meningitis	1 (0.8)	2 (2.9)
Movement disorder	1 (0.8)	0
Total number of events	122	68

CNS, central nervous system.

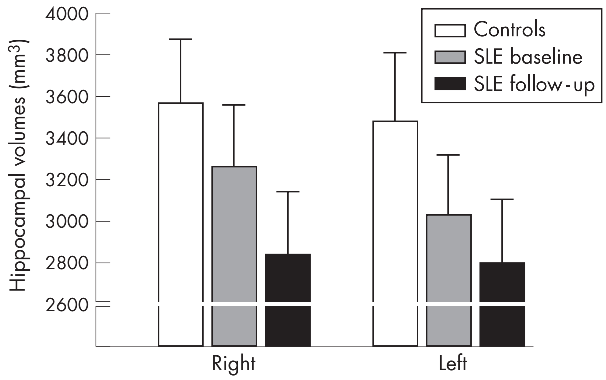

Figure 2 Mean right and left hippocampal volumes in controls and patients with systemic lupus erythematosus at baseline and at follow-up. Line with horizontal crossbar above each bar represents 1 standard deviation.

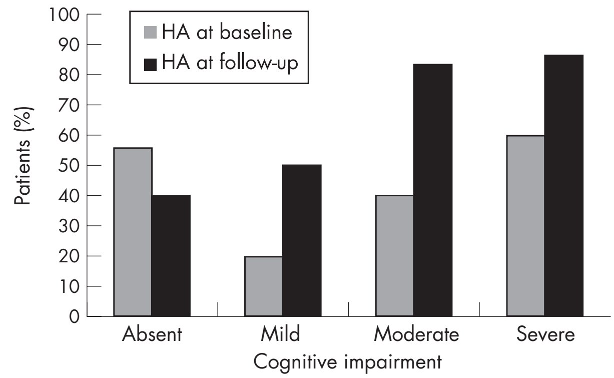

Figure 3 Percentages of patients with hippocampal atrophy (HA) at baseline and follow-up magnetic resonance imaging according to the presence and degree of cognitive impairment in 60 patients.

of CNS manifestations ($r = 0.65$; $p = 0.01$) and cumulative corticosteroid dose ($r = 0.74$; $p = 0.01$). When we further subdivided patients with active and past CNS involvement, we observed that hippocampal reduction was associated with past ($r = 0.9$; $p<0.001$) but not with active CNS involvement.

SLICC/ACR DI scores correlated strongly with the degree of hippocampal atrophy ($r = 0.87$; $p = 0.001$), but when cognitive dysfunction was excluded from the SLICC scores, the correlation was not significant ($r = 0.3$; $p = 0.4$). An association between hippocampal atrophy and the presence of antiphospholipid antibodies ($r = 0.5$; $p = 0.06$) was observed. No association between hippocampal atrophy and SLEDAI scores ($r = 0.43$; $p = 0.08$) was observed. On visual analysis, hyperintense areas and areas of cerebral micro-infarcts were observed in 50 patients. A significant association between these findings and hippocampal atrophy ($p = 0.01$) was observed.

Cognitive evaluation

We observed cognitive impairment in 35 patients: 20 had severe, 10 had moderate and 5 had mild cognitive impairment. We observed that patients with cognitive impairment had a more significantly reduced hippocampal volume when compared with patients with SLE without cognitive impairment ($r = 0.9$; $p = 0.001$). Patients with severe cognitive impairment had a more pronounced reduction in hippocampal volumes than patients with moderate or mild cognitive impairment ($p = 0.002$). In relation to different domains of cognitive dysfunction, hippocampal atrophy was associated with lower scores on general memory ($p = 0.015$), verbal memory ($p = 0.01$) and delayed recall ($p = 0.01$).

Follow-up analysis

After the follow-up MRI, group analysis showed a significant progression of reduction in right (mean 28.2 cm^3 (SD 3.1)) and left (mean 27.9 cm^3 (SD 1.2)) hippocampal volumes in patients ($p<0.001$; fig 3).

Individual analysis showed that the follow-up MRI yielded a considerable increase in the number in patients with hippocampal atrophy. We observed atrophy in 40 of 60 (66.7%) patients: 32 (53.3%) bilaterally, 4 (6.7%) with right hippocampal atrophy and 4 (6.7%) with left hippocampal atrophy. Progression of hippocampal atrophy correlated with cumulative corticosteroid dose ($r = 0.69$; $p = 0.01$) and number of CNS events during the follow-up period ($r = 0.72$; $p = 0.01$).

We observed cognitive impairment in 40 of 60 patients after the follow-up period: 22 with severe, 12 with moderate and 6 with mild cognitive impairment. We observed that patients with hippocampal atrophy and normal cognitive function at entry into the study presented with cognitive impairment during the follow-up period (fig 3). The severity of cognitive impairment was directly associated with the degree of hippocampal volume loss ($r = 0.89$; $p = 0.001$). In relation to different domains of cognitive dysfunction, no difference with regard to entry into the study was observed, with hippocampal atrophy being associated with lower scores on general memory ($p = 0.01$), verbal memory ($p = 0.02$) and delayed recall ($p = 0.01$).

DISCUSSION

We observed a frequency of hippocampal atrophy of 44% in our study and a considerable progression of hippocampal volume loss and atrophy during the follow-up period. Both the presence and the progression of hippocampal atrophy correlated with disease duration, total corticosteroid dose and history of CNS manifestations. The number of CNS events was associated with progression of hippocampal atrophy during the follow-up period. The short follow-up period did not allow us to determine whether hippocampal volumes may return to normal ranges or whether the progression of hippocampal atrophy stops after withdrawal of corticosteroids.

At the start of the study, we observed a small proportion of patients with bilateral atrophy. We did not identify any cause for the predominance of unilateral atrophy in our patients, although after a follow-up period most of the patients presented bilateral hippocampal atrophy.

Hippocampal atrophy has been shown previously in several diseases, such as epilepsy,[36] and is related to memory impairment.[5–11] Therefore, we excluded patients with epilepsy in addition to those with clinical conditions associated with cerebral atrophy, such as stroke, arterial hypertension[37] and diabetes mellitus,. The relationship between epilepsy and hippocampal atrophy is well determined in the literature.[38]

Although ageing may have some effect on the brain and hippocampal atrophy,[39] this effect was minimised by a comparison with volunteers of the same age range.

The hippocampus is the prominent target structure for the activity of corticosteroids in the brain.[40] Corticosteroid hormones have been shown to reduce the number of branch points and length of dendrites in the hippocampus of rats, to cause dendritic atrophy of pyramidal neurones[41] and to lead to reduction of CA3 and CA4 hippocampal neurones.[42] In patients with Cushing's syndrome, previous studies have shown that the reduction in hippocampal volume correlated with mean cortisol level and that atrophy was reversible after normalisation of cortisol levels.[10 11]

Whether corticosteroids cause cell death and neuronal loss, or atrophy or degeneration, is not clearly understood. Most studies of animal models report only atrophy of dendritic branches.[40–42] Although this can be the first step and progress to neuronal loss, neuronal cell death was found only in a few studies.[40] Our study suggests that hippocampal atrophy in SLE is one of the consequences of CNS damage induced by the inflammatory process, which is most likely potentiated by prolonged use of corticosteroids.

We observed that hippocampal atrophy was associated with the presence of cognitive dysfunction in SLE, especially memory function. Patients with severe cognitive impairment had more pronounced loss of hippocampal volume when compared with those who had mild or no cognitive impairment . The increased hippocampal atrophy observed in our study may explain the high frequency of cognitive impairment observed in patients with SLE.[1–4] We also observed that patients with white matter lesions had hippocampal atrophy more frequently than patients without these lesions. Similar findings were described in patients with Alzheimer's disease.[43] The presence of antiphospholipid antibodies had a tendency to be associated with hippocampal atrophy, supporting the theory that small vessel disease may contribute to hippocampal atrophy and cognitive impairment.[43] We also observed that hippocampal atrophy was a predictor for cognitive impairment. The patients who had a normal cognitive function test and hippocampal atrophy at entry into the study presented cognitive impairment during the follow-up study.

We showed that structural MRI abnormalities may be associated with cognitive dysfunction in patients with SLE and also that hippocampal atrophy is progressive over time. Furthermore, we showed that hippocampal atrophy may be predictive of cognitive impairment in patients with SLE. Longer follow-up studies are necessary to confirm these findings and to determine whether the hippocampal loss is reversible and the factors that may contribute to it.

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