

Magnetic resonance imaging study cannot individually distinguish individuals with mild cognitive impairment, mild Alzheimer's disease, and normal aging

Estudo por ressonância magnética não pode diferenciar individualmente os indivíduos com declínio cognitivo leve, doença de Alzheimer leve e envelhecimento normal

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ABSTRACT

Objective: To evaluate the volumetric and spectroscopy aspects of hippocampus in patients with mild Alzheimer's disease (AD) and mild cognitive impairment (MCI). **Methods:** A series of patients older than 65 years and with memory deficit were studied. **Results:** The evocation of words test presented a significant reduction in the number of words recalled by the patients with MCI and mild AD as compared with the control group. Bilateral reduction of the hippocampus volume in the AD group was observed when compared to the control group. There were no statistical differences in the values of NAA/Cr, ml/Cr, Cho/Cr and ml/NAA between the groups. **Conclusions:** Magnetic resonance imaging study failed to individually distinguish patients with MCI, mild AD and normal aging. However, patients with mild AD presented loss of asymmetry between the right and left hippocampus, and a reduction in hippocampus volume.

Key words: Alzheimer disease, dementia, mild cognitive impairment, hippocampus, magnetic resonance imaging, spectroscopy.

RESUMO

Objetivo: Avaliar volume e espectroscopia do hipocampo em pacientes com doença de Alzheimer leve e declínio cognitivo leve. **Métodos:** Foi estudada uma série de pacientes com 65 anos de idade ou mais, com déficit de memória. **Resultados:** O teste de evocação de palavras mostrou redução significativa no número de palavras lembradas pelos pacientes com declínio cognitivo leve e doença de Alzheimer leve, em comparação com o grupo controle. Foi observada redução bilateral do volume do hipocampo no grupo com doença de Alzheimer quando comparado com o grupo controle. Não houve diferença estatística nos valores de NAA/Cr, ml/Cr, Cho/Cr e ml/NAA entre os grupos. **Conclusão:** Estudo pela ressonância magnética não diferencia individualmente os pacientes com declínio cognitivo leve, doença de Alzheimer leve e envelhecimento normal. No entanto, pacientes com quadro leve de doença de Alzheimer apresentam perda de assimetria entre os hipocampus direito e esquerdo e redução no volume do hipocampo.

Palavras-Chave: doença de Alzheimer, demência, comprometimento cognitivo leve, hipocampo, ressonância magnética, espectroscopia.

Elderly individuals with mild cognitive impairment (MCI) are part of a continuum between normal aging with its cognitive difficulties and fully-fledged dementia. However, there is a growing body of evidence suggesting that MCI might precede the onset of Alzheimer's disease (AD). Longitudinal studies have demonstrated that subjects with MCI present a progression rate of 10–15% per year to AD, contrasting with 1–2%, in a similar analysis, in the general population using a similar age range¹.

Declarative memory is related to the involvement of mesial structures of the temporal lobe, especially the

hippocampus^{2,3}. Studies using magnetic resonance imaging (MRI) may provide *in vivo* analysis of specific regions of the temporal lobe showing a strong correlation between abnormal neuroimaging findings and the scores obtained on cognitive tests^{4,5}. A number of authors have reported that volumetric-structural study and spectroscopy analysis might be useful in the investigation of patients with MCI in order to diagnose patients with a higher risk of developing AD⁶⁻⁸.

In advanced phases of AD, major hippocampus atrophy with a decrease in N-acetyl aspartate (NAA) and an increase

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Conflict of interest: There is no conflict of interest to declare.

Received 11 March 2012; Received in final form 22 October 2012; Accepted 30 October 2012.

in mio-inositol (mI) is a common finding^{7,9}. Furthermore, the reduction in the concentration of NAA is inversely proportional to the number of senile plaques¹⁰.

Studies during mild or initial stages of AD show that the MRI alterations are discrete, and some have reported controversial results regarding the expected reduction in hippocampus volume¹¹⁻¹⁶ and the changes in proton spectroscopy parameters^{7,17-21}. This controversy has stimulated new studies aimed at a more precise differential diagnosis between: (a) patients with MCI, (b) patients with MCI as a preclinical form of AD, and (c) patients at the initial stage of AD.

This study was performed with the aim of investigating patients with MCI and mild AD using volumetric-structural MRI and spectroscopy analysis, to evaluate volumetric analysis of the hippocampus and possible alterations in NAA, mI and choline (Cho) in the hippocampus.

METHODS

We studied a series of 22 right-handed patients over 65 years of age, with memory deficit complaints, evaluated for the first time during the years of 2002 and 2003 at the Cognitive Neurology Unit, Federal University of Pernambuco Hospital, comprising 11 patients with MCI and 11 with mild AD, based on NINCDS-ADRDA²². Patients with mild AD scored 1 in the Clinical Dementia Rating (CDR)²³. To evaluate the staging severity of the cognitive deficit, CDR score of 0.5 was used for MCI patients whose cognitive deficit was not severe enough to interfere with the day-to-day life and usual activities. The AD patients presented memory impairment associated with one or more cognitive disorders such as dysphasia, apraxia, agnosia or disturbance in executive functioning; progressive social or occupational impairment and a clear decline from previous level of functioning and reported continuing cognitive decline. No specific treatment for the cognitive impairment was used until after the MRI evaluation.

Patients with moderate/severe AD stages and those with previous chronic/degenerative or psychiatric disorders and those on neuropsychiatry medication were excluded. The control group consisted of 15 healthy subjects, also over 65 years of age.

All the participants (or their legal representative) gave their formal written consent. The research protocol was approved by the Ethics Committee of the Federal University of Pernambuco.

Acquisition and analysis of MRI

MRI was performed using a *Magnetom Sonata* 1.5 Tesla (Siemens). The clinical profile of the patient was unknown to the examiner during the analysis of the MRI data.

We used a volumetric sequence with images in T1, MP-RAGE (time repetition, TR=9.7 ms; echo time, ET=4 ms; inclination angulations 12°), matrix of 256x128 mm, vision range of 200 mm, with coronal sections 3 mm thick obtained perpendicularly to the

longer axis of the hippocampus. A sequence with approximately 12 to 15 slices across the entire extension of the hippocampus was obtained²⁴.

Hippocampal atrophy was considered when the volume was smaller than the mean minus two standard deviations (mean - 2SD), calculated using the data of the control group¹¹.

The experimental parameters of MRI used were a STEAM sequence (ET=20 ms; TR=1.500 ms; number of acquisitions=128).

The major photonic resonance was identified and read from right to left: (a) NAA (2.03 ppm); (b) creatine (Cr, 3.03 ppm); (c) Cho (3.23 ppm); (d) mio-inositol (mI) (3.56 ppm). The ratios of NAA/Cr, mI/Cr, Cho/Cr, mI/Cr and mI/NAA were analyzed.

RESULTS

The individual data are shown in Table 1. Table 2 shows demographic variables, the total Mini-Mental State Examination (MMSE) scores, and the results of the evocation of words test in the three evaluated groups. The statistical analysis did not show any significant differences between genders and educational background. Regarding age, there was a significant difference ($p<0.05$) between the control group and the group with mild AD, but there were no statistical differences between the control group and the group with MCI. There were also statistical differences between ages, when the MCI and the AD groups were compared ($p=0.0451$, Mann-Whitney test).

The total MMSE scores obtained for MCI and AD significantly decreased compared with the control group ($p<0.05$). The word evocation test presented a significant reduction in the number of words recalled by the patients with MCI (3.3 ± 1.2 ; $p<0.01$) and with mild AD (0.9 ± 0.9 ; $p<0.001$) as compared to the control group (7.6 ± 1.4). There was also a statistical difference between the groups with MCI and mild AD ($p=0.0013$, Mann-Whitney test).

Volumetric study of hippocampus

Both groups presented a smaller volume of the left hippocampus, when compared with the contralateral right hippocampus ($p=0.0049$, Wilcoxon paired test). Patients with mild AD presented no significant differences between the right and left hippocampi. Regarding the control group values, hippocampal atrophy was considered to be present when the right hippocampus was smaller than 1.67 cm³ and the left hippocampus smaller than 1.58 cm³. Using this criterion, it was observed that only one of the patients with mild AD presented bilateral hippocampal atrophy (patient #10 in Table 1, right 1.20 cm³ and left 1.18 cm³).

Figure shows a bilateral reduction of the hippocampus volume in the AD group as compared to the control group (right side: 2.08 ± 0.42 cm³ versus 2.61 ± 0.47 cm³, respectively; left side: 1.96 ± 0.39 cm³ versus 2.46 ± 0.44 cm³, respectively; $p<0.05$).

Table 1. Individual data obtained in the control, mild cognitive impairment and mild Alzheimer's disease groups.

Patient #	Age (years)	Gender	Schooling (years)	MMSE (0–30)	Word evocation (0–10)	Hippocampal volume (cm ³)		NAA/Cr		mI/Cr	
						Right	Left	Right	Left	Right	Left
CONTROL GROUP											
1	68	F	8	26	6	3.21	2.52	1.34	1.28	0.86	0.59
2	69	F	8	29	7	2.07	2.24	1.38	1.31	0.75	0.83
3	74	F	8	29	8	2.30	2.20	1.27	1.42	0.52	0.92
4	70	F	9	28	7	2.46	2.34	1.80	1.35	0.65	1.40
5	73	F	9	29	6	2.53	2.42	1.25	1.31	0.66	0.69
6	78	F	9	29	9	2.85	2.85	1.60	1.17	0.84	0.81
7	67	F	12	29	6	2.21	2.10	–	–	1.08	0.52
8	67	F	12	30	6	2.28	2.07	2.26	1.67	1.16	0.78
9	69	F	16	30	10	2.45	2.11	1.20	1.11	0.63	0.74
10	72	M	16	30	9	2.64	2.12	1.21	1.13	1.17	1.07
11	73	M	16	30	6	3.35	3.07	1.07	1.50	1.07	1.19
12	66	F	12	29	9	3.56	3.59	1.34	1.23	0.84	0.66
13	83	F	9	30	9	2.82	2.70	1.38	1.36	0.83	0.89
14	67	F	16	29	8	1.96	1.99	1.24	1.35	0.59	0.68
15	74	M	16	28	8	2.38	2.59	0.95	1.43	0.79	1.00
MILD COGNITIVE IMPAIRMENT											
1	68	F	9	27	0	2.67	2.45	1.40	1.17	0.85	0.69
2	68	F	10	24	3	2.21	1.92	1.29	1.29	0.97	0.93
3	71	M	16	27	3	2.67	2.07	1.95	1.69	0.65	0.85
4	71	M	16	28	3	2.16	2.08	0.85	1.16	0.38	0.77
5	75	F	9	27	3	3.00	2.72	1.24	1.42	0.60	0.65
6	72	F	10	28	4	2.46	2.04	1.15	1.03	0.59	0.77
7	73	F	11	28	4	1.93	1.95	0.86	1.08	1.06	1.04
8	77	M	16	28	4	3.15	3.00	1.11	1.32	0.57	0.96
9	78	F	16	28	4	1.85	1.91	1.06	1.13	0.56	0.74
10	83	F	8	24	4	2.51	2.42	1.20	1.21	0.80	0.88
11	75	M	16	28	4	2.80	2.46	1.38	1.36	0.83	0.89
MILD ALZHEIMER'S DISEASE											
1	78	F	12	25	0	2.43	2.67	1.29	1.56	0.86	0.63
2	81	F	8	20	1	1.70	1.94	1.15	0.98	0.92	0.98
3	87	F	9	18	0	1.92	1.83	1.11	1.20	0.55	0.92
4	83	F	12	27	3	1.82	2.00	1.80	0.52	0.60	1.03
5	87	F	12	26	2	1.97	1.76	1.24	1.17	1.00	0.71
6	66	F	12	19	1	2.41	2.28	1.00	1.31	1.05	1.00
7	83	M	16	27	1	2.57	2.25	0.86	1.16	0.38	0.77
8	69	F	16	22	0	2.04	1.81	1.29	1.44	0.55	0.81
9	74	F	12	27	1	2.29	2.18	1.26	0.90	0.63	0.74
10	85	F	12	22	0	1.20	1.18	1.95	1.21	0.86	1.06
11	79	F	8	23	1	2.52	1.65	1.23	1.38	0.57	0.72

MMSE: Mini-Mental State Examination; NAA: N-acetyl aspartate; Cr: creatine; mI: mio-inositol.

The left and right hippocampi of the group with mild AD presented reductions of 20.3 and 20.3%, respectively, compared with the control group. There was no statistically significant difference between groups.

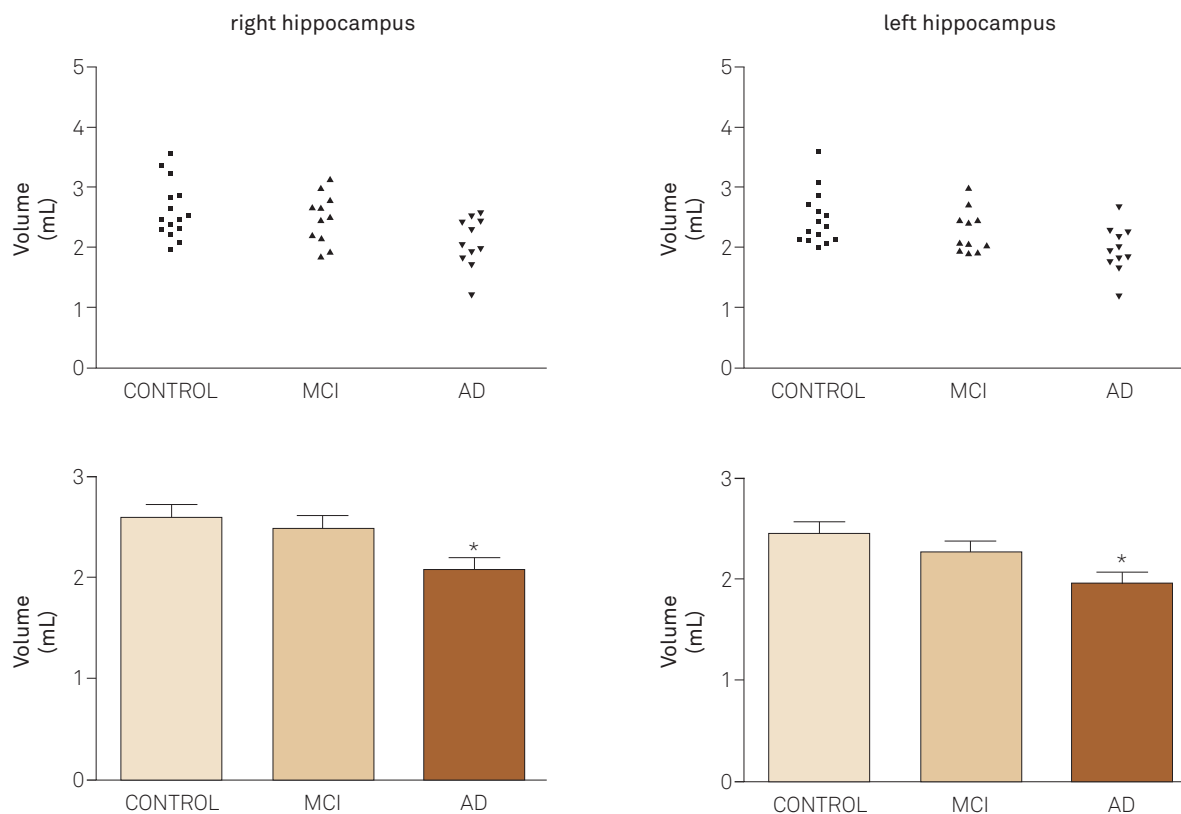
Proton spectroscopy of hippocampus

There were no statistical differences in the values of NAA/Cr, mI/Cr, Cho/Cr and mI/NAA between the right and left hippocampi in each group or between the groups themselves (Tables 3 and 4).

DISCUSSION

Patients with MCI and mild AD displayed an involvement of declarative memory, which suggests a progressive degenerative process.

Similar studies showed great discrepancy in sensitivity and specificity regarding the determination of hippocampus volumetry^{11,14,25}. The inclusion of patients in moderate and advanced phases might have contributed to the clear presence of hippocampus atrophy previously reported²⁵.



* $p < 0.05$ versus control group.

Figure. Right and left hippocampal volumes observed in the control, mild cognitive impairment (MCI), and mild Alzheimer's disease (AD) groups. The upper panels show individual values and in the lower panels data are shown as means \pm standard error of the mean (SEM) in the respective groups.

Table 2. Demographic characteristics and the scores on the Mini-Mental State Examination (MMSE) and number of words recalled in the control, mild cognitive impairment (MCI) and mild Alzheimer's disease (AD) groups.

	Control (n=15)	MCI (n=11)	AD (n=11)
Age (years)	71 \pm 5	74 \pm 5	79 \pm 7 ^{a,b}
Gender (man)	3/15 (20%)	4/11 (36%)	1/11 (9%)
Schooling (years)	12 \pm 3	13 \pm 4	12 \pm 3
MMSE (0–30)	29 \pm 1	27 \pm 2 ^a	24 \pm 4 ^{a,b}
Word evocation	7.6 \pm 1.4	3.3 \pm 1.2 ^a	0.9 \pm 0.9 ^{a,b}

^a $p < 0.05$ versus control (Dunn's test); ^b $p < 0.05$ versus MCI (Mann-Whitney's test)

Our study showed that the right hippocampus was larger than the left one in the control group, thus confirming previous reports²⁶. The group with MCI maintained asymmetry of volume between the right and left hippocampi, as did the control group.

The comparison of hippocampal volume between the three groups in this study demonstrated that the patients with mild AD presented a bilateral decrease in volume, although the majority (91%) still did not present significant hippocampus atrophy, when studied individually, considering the methods employed in the present study. Curiously, Sullivan et al.²⁷ reported that the reduction in the gray matter of the temporal lobe related to aging relatively spared the hippocampus in a study comprising 72 healthy subjects aged between 21 and 70 years.

As far as the patients with MCI are concerned, the results of our study are in agreement with that of Soinen et al.¹², who studied 16 patients with age-associated memory impairment and did not find any differences in hippocampal volume as compared to a control group. It is important to stress that the concept of age-associated memory impairment differs from MCI, because it is established by comparing the results of memory tests in young adults. Thus, maybe this group of patients is at the lowest level of performance for normal aging. However, other studies have demonstrated that the presence of hippocampus atrophy does not necessarily indicate dementia progression¹³ and that patients with MCI that did not progress to dementia did not present any reduction in hippocampus volume in comparison with controls¹⁶.

A common limitation is that some neuropsychological tests still lack standard analysis in such disorders. Another important issue is the need of a standard nomenclature for the structural and anatomical limits of the hippocampus in order to better interpret results obtained by various groups of investigators^{6,11,14}. Serial longitudinal time measurements of the hippocampus have also been regarded as particularly relevant in this kind of study⁸. However, the use of such long-term measurements is impracticable when the specialist needs to make an accurate diagnosis at the first clinical and neuroradiologic evaluation of the individual with cognitive deficit complaints as was the case in the present series.

Table 3. Values of NAA/Cr, ml/Cr, Cho/Cr and ml/NAA obtained on proton spectroscopy of hippocampus in control, mild cognitive impairment (MCI), and mild Alzheimer's disease (AD) groups.

	Control (n=15)		MCI (n=11)		AD (n=11)	
	Right	Left	Right	Left	Right	Left
NAA/Cr	1.38±0.33	1.33±0.15	1.23±0.30	1.26±0.19	1.29±0.32	1.17±0.29
ml/Cr	0.81±0.20	0.85±0.24	0.72±0.20	0.83±0.12	0.75±0.23	0.85±0.14
Cho/Cr	0.87±0.18	0.87±0.14	0.83±0.16	0.78±0.15	0.84±0.13	0.90±0.14
ml/NAA	0.61±0.20	0.64±0.17	0.61±0.24	0.68±0.14	0.61±0.22	0.70±0.18

NAA: N-acetyl aspartate; Cr: creatine; ml: mio-inositol; Cho: choline.

Table 4. Frequency of patients with mild cognitive impairment (MCI) or mild Alzheimer's disease (AD) using different values of the mean±1.0, 1.5, and 2.0 standard deviations (SD) of each of the hippocampal metabolites analyzed.

Metabolite	SD	MCI		AD	
		Right	Left	Right	Left
NAA/Cr	-1.0	2 / 11 (18%)	5 / 11 (45%)	2 / 11 (18%)	3 / 11 (27%)
	-1.5	2 / 11 (18%)	2 / 11 (18%)	1 / 11 (9%)	3 / 11 (27%)
	-2.0	0 / 11 (0%)	1 / 11 (9%)	0 / 11 (0%)	3 / 11 (27%)
ml/Cr	+1.0	1 / 11 (9%)	0 / 11 (0%)	0 / 11 (0%)	0 / 11 (0%)
	+1.5	0 / 11 (0%)	0 / 11 (0%)	0 / 11 (0%)	0 / 11 (0%)
	+2.0	0 / 11 (0%)	0 / 11 (0%)	0 / 11 (0%)	0 / 11 (0%)
Cho/Cr	+1.0	1 / 11 (9%)	1 / 11 (9%)	1 / 11 (9%)	1 / 11 (9%)
	+1.5	1 / 11 (9%)	1 / 11 (9%)	0 / 11 (0%)	0 / 11 (0%)
	+2.0	0 / 11 (0%)	1 / 11 (9%)	0 / 11 (0%)	0 / 11 (0%)
ml/NAA	+1.0	1 / 11 (9%)	1 / 11 (9%)	2 / 11 (18%)	4 / 11 (36%)
	+1.5	1 / 11 (9%)	1 / 11 (9%)	1 / 11 (9%)	2 / 11 (18%)
	+2.0	1 / 11 (9%)	0 / 11 (0%)	1 / 11 (9%)	1 / 11 (9%)

NAA: N-acetyl aspartate; Cr: creatine; ml: mio-inositol; Cho: choline.

The ratio value of metabolites NAA/Cr, ml/Cr, Cho/Cr and ml/NAA did not show any significant differences between controls vs. MCI or mild AD patients. Additionally, there was no asymmetry in the metabolic relations between the two hippocampi. Various studies have mentioned the finding of a fall in NAA/Cr^{7,19,20,28}, with an increase in ml/Cr^{7,19}, favoring the diagnosis of AD. Some authors report that in the MCI patients there is an initial reduction in the NAA/Cr ratio^{20,21}. However, others have reported an initial increase in the ml/Cr ratio^{7,18}.

We conclude that the MRI study failed to individually distinguish patients with MCI, mild AD and normal aging.

However, if we consider the three groups of patients, the mild AD ones presented: 1) advanced age; 2) lower scores on the MMSE; 3) lower scores on the word evocation test; 4) loss of asymmetry between the right and left hippocampi; and 5) reduction in the volume of the hippocampi.

ACKNOWLEDGMENT

The authors wish to acknowledge H. Cartaxo, MD and P.B. Santos Filho, PhD, for their help during the volumetric and spectroscopic MRI evaluation.

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