LEXICAL SEMANTIC MEMORY IN AMNESTIC MILD COGNITIVE IMPAIRMENT AND MILD ALZHEIMER´S DISEASE

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ABSTRACT - *Objective*: To study lexical semantic memory in patients with amnestic mild cognitive impairment (aMCI), mild Alzheimer's disease (AD) and normal controls. *Method*: Fifteen mild AD, 15 aMCI, and 15 normal control subjects were included. Diagnosis of AD was based on DSM-IV and NINCDS-ADRDA criteria, and that of aMCI, on the criteria of the International Working Group on Mild Cognitive Impairment, using CDR 0.5 for aMCI and CDR 1 for mild AD. All subjects underwent semantic memory tests (Boston Naming-BNT, CAMCOG Similarities item), Rey Auditory Verbal Learning Test (RAVLT), Mini-Mental Status Examination (MMSE), neuropsychological tests (counterproofs), and Cornell Scale for Depression in Dementia. Data analysis used Mann-Whitney test for intergroup comparisons and Pearson's coefficient for correlations between memory tests and counterproofs (statistical significance level was p<0.05). *Results*: aMCI patients were similar to controls on BNT and Similarities, but worse on MMSE and RAVLT. Mild AD patients scored significantly worse than aMCI and controls on all tests. *Conclusion:* aMCI impairs episodic memory but tends to spare lexical semantic system, which can be affected in the early phase of AD.

KEY WORDS: semantic memory, mild cognitive impairment, Alzheimer's disease, neuropsychological tests.

Memória léxico-semântica no comprometimento cognitivo leve amnéstico e doença de Alzheimer leve

RESUMO - *Objetivo:* Estudar a memória léxico-semântica no comprometimento cognitivo leve amnéstico (aCCL), doença de Alzheimer (DA) leve e controles normais. *Método*: Incluímos 15 pacientes com DA leve, 15 com aCCL e 15 controles normais, usando os critérios DSM-IV, NINCDS-ADRDA e CDR 1 para DA, e os do International Working Group on Mild Cognitive Impairment, e CDR 0,5 para aCCL. Todos os sujeitos passaram por testes de memória semântica (Teste de nomeação de Boston - TNB, item de Similaridades do CAMCOG), teste de aprendizado auditivo-verbal de Rey (TAAVR), Mini-Exame do Estado Mental (MEEM), testes neuropsicológicos (contraprovas) e Escala Cornell para Depressão em Demência. A análise dos dados usou o teste de Mann-Whitney para comparações entre os grupos e o coeficiente de Pearson para correlação entre testes e contraprovas (nível de significância p<0,05). *Resultados*: Os pacientes com aCCL foram semelhantes aos controles no TNB e Similaridades, mas inferiores no MEEM e TAAVR. Pacientes com DA leve tiveram performance inferior à de sujeitos com aCCL e controles em todos os testes. *Conclusão*: O aCCL prejudica a memória episódica, mas tende a poupar o sistema léxico-semântico, que pode estar afetado na fase inicial da DA.

PALAVRAS-CHAVE: memória semântica, comprometimento cognitivo leve, doença de Alzheimer, testes neuropsicológicos.

Mild cognitive impairment (MCI) is one of the most used concepts for cognitive impairment which do not fulfill criteria for dementia. It can be conceived as a clinical entity for patients in the border zone between normal aging and very early dementia, most commonly probable Alzheimer's disease (AD)[1]. It's assumed that there is a continuum in cognitive decline and, in MCI, subjects have cognitive complaints, more often forgetfulness, with intact activities of daily living[1,2]. MCI can be classified according to the clinical presentation of symptoms as amnestic MCI (aMCI), multiple domain or single non-memory domain MCI[1,2]. Like AD, its diagnosis is essentially clinic and neuropsychological assessment is a crucial part of the diagnostic process. Memory is the most studied cognitive domain, since it appears to be the

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most affected and the first to decline, but it is not a unitary system. Tulving has divided it in five principal components: episodic, semantic, working, perceptual representation system and procedural memory[3]. Episodic memory (the capacity for encoding personal experiences and conscious recollection of events) is, by far, the most studied memory system in AD and MCI, and its deficit is a *sine qua non* condition for the diagnosis of dementia.

Semantic memory can briefly be defined as the capacity to acquire and retain general knowledge about the world, its basic meanings and facts, as well as words and their meanings. Thus, its deficit signifies the loss of concepts that have been part of one's store of knowledge[3,4]. Semantic memory in MCI is not enough investigated and some studies are controversial concerning its impairment[5-7]. Several approaches can be made to study semantic memory, like tests of priming, general knowledge, category fluency and object or picture naming[8].

Our aim is to evaluate this specific kind of memory performance in patients diagnosed as aMCI and mild AD and our approach privileges the lexical aspect of the semantic memory, because language is essential to codify, signify and retain our experience[9].

METHOD

We studied 45 subjects, comprising 15 with aMCI and 15 with mild AD attended at the Unit for Neuropsychology and Neurolinguistics (UNICAMP Clinic Hospital), and 15 controls. Routine laboratory examinations for dementia assessment (including B12 and folate dosage, sorology for syphilis, thyroid hormones) and brain computed tomography was carried out in all patients. The local ethics committee approved this research.

We based the diagnosis of aMCI, on the following criteria of the International Working Group on Mild Cognitive Impairment[1]: (i) the person is neither normal nor demented; (ii) there is evidence of cognitive deterioration shown by either objectively measured decline over time and/or subjective report of decline by self and/or informant in conjunction with objective cognitive deficits; and (iii) activities of daily living are preserved and complex instrumental functions are either intact or minimally impaired. We included only patients older than 50 years and CDR (Clinical Dementia Rating)[10] of 0.5.

The diagnostic process consisted of a detailed interview with the patient and informant. All patients were submitted to the Mini Mental Status Examination (MMSE; Brazilian adapted version)[11] and to the Cambridge Mental Disorders of the Elderly Examination (CAMDEX)[12], which comprises structured interviews with the patient and, separately, with an informant, evaluating the patient's current medical and psychiatric status and family history. They were also submitted to the CAMDEX cognitive test battery (CAMCOG), which includes eight subscales: memory, orientation, language, attention, abstract thinking or similarities, calculation and perception. At this phase, we didn't apply the similarities subscale.

We considered a diagnosis of aMCI if the clinical history and cognitive performance pointed to an exclusive memory deficit (poor performance on CAMCOG's memory items). For probable AD diagnosis, we used the criteria of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and Alzheimer's Disease and Related Disorders Association (ADRDA)[13], including only patients classified as CDR 1. Exclusion criteria were history of other neurological or psychiatric diseases, head injury with loss of consciousness, use of sedative drugs until 24 hours before the neuropsychological assessment, drug or alcohol addiction and prior exposition to neurotoxic substances. The control group consisted of subjects with CDR 0 without previous history of neurological or psychiatric disease, or memory complaints.

Neuropsychological evaluation comprised following tests:

1) Episodic memory was evaluated with Rey auditory verbal learning test (RAVLT)[14], which consists of fifteen words read aloud for five consecutive trials (List A), followed by a free-recall test. After the fifth trial, a new interference list of fifteen words is presented (List B) followed by a free-recall test of that list. Soon afterwards, a free-recall of the first list is tested without new presentation. After a twenty-minute delay period, subjects are again required to recall words from List A. Finally, the patient must identify List A words from a list of fifty words which includes Lists A and B and twenty other words phonemically or semantically related to lists A and B.

2) Semantic memory: (a) patients were given the sixty items of the Boston Naming Test[15] (BNT- Brazilian version). BNT score was the sum of spontaneous correct responses plus correct responses following a semantic cue. (b) CAMCOG's subscale of similarities between pairs of nouns. The patients were asked " In what way are they alike?" for the pairs apple/banana, chair/table, shirt/dress and animal/vegetal. The score was calculated as the number of correct responses (zero to two for each pair; maximum score 8).

3) Control tests comprised: (a) Visual perception subtests of Luria's Neuropsychological Investigation (LNI; maximum score 20)[16]. (b) Verbal fluency (VF) for animals' category (the score was the total number of different animals´ names given by patient during one minute). (c) Attention: The forward and backward digit span subtest of WAIS-R[17]. (d) Cornell Scale for Depression in Dementia (CSDD)[18].

Data analysis by means of Statistica software 6.0 used Mann-Whitney test for intergroup comparisons of demographic and cognitive scores, as well as Pearson coefficient for correlation between memory tests and counterproofs. Statistical significance considered was p<0.05.

RESULTS

The results of neuropsychological evaluation are shown on Table. aMCI subjects were similar to controls concerning age (p=0.343), education (p=0.578),

Table. Demographics and neuropsychological test results of amnestic mild cognitive impairment (AMCI), Alzheimer´s disease(AD), and control subjects

	MCI (n=15) Mean ± SD	AD (n=15) Mean ± SD	Controls (n=15) Mean ± SD	p value for group effect
Age	66.26±10.27[b]	75.66±7.65[a,c]	69.40±7.28[b]	< 0.05
Education (years)	5.93±4.18	4.86±4.76	6.73±3.59	NS
MMSE	26.86±2.50[a,b]	22.53±3.06[a,c]	29.06±0.70[b,c]	< 0.01
Similarities	7.00±1.19[b]	4.86±1.80[a,c]	7.33±1.04[b]	< 0.001
BNT	51.06±7.78[b]	38.73±8.64[a,c]	53.66±4.11[b]	< 0.001
Mean RAVLT	7.06±1.48[a,b]	4.60±1.12[a,c]	9.60±1.63[b,c]	< 0.001
A7- RAVLT	4.26±2.54[a,b]	1.00±1.25[a,c]	9.40±3.20[b,c]	< 0.001
VF	13.86±3.85[a,b]	10.20±3.44[a,c]	19.46±3.31[b,c]	< 0.01
fDS	4.60±0.82	4.73±1.03	4.93±0.79	NS
bDS	3.13±0.99[a]	3.13±0.51[a]	3.93±1.09[b,c]	< 0.05
Visuo-spatial LNI	18.80±1.01[b]	17.33±1.39[a,c]	18.66±1.11[b]	< 0.01

MMSE, mini-mental status examination; fDS, forward digit span; bDS, backward digit span; VF, verbal fluency; BNT, Boston naming test; A7- RAVLT, delayed recall of Rey auditory verbal learning test; a, significantly different from controls; b, significantly different from AD; c, significantly different from MCI; NS, non-significant.
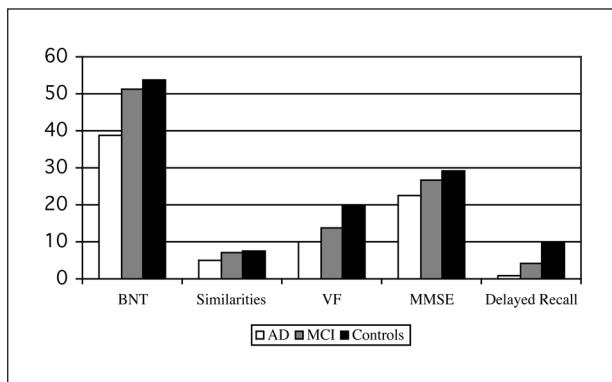

Figure. Distribution of mean scores of AD, aMCI and control subjects on main neuropsychological tests (abbreviations as in Table 1).

CAMCOG's item of similarities (p=0.42) and Boston Naming Test (p=0.56), but they performed worse on the MMSE (p=0.01), backward digit span (p<0.05), verbal fluency (p=0.0006), immediate (p=0.0004) and delayed recall (p=0.0001) of RAVLT.

AD patients were older than aMCI (p=0.01) and control subjects (p=0.03). Their educational level was inferior to that of controls (though not statistically significant). They scored lower than controls and aMCI subjects on all tests, except on forward digit span. The cognitive performance of mild AD was worse than aMCI, which was inferior to controls (Figure and Table).

The analysis of relationships between tests and counterproofs in the groups showed statistically significant correlations only between VF and RAVLT delayed recall in AD group (r=0.545; p<0.05) and between VF and BNT in aMCI group (r=0.540; p<0.05). Scores on Cornell Scale for Depression did not correlate to any of cognitive tests.

DISCUSSION

On all cognitive tests, the three groups showed a continuum of decreasing cognitive ability, with mild AD patients performing worse than aMCI subjects, who were inferior to controls. AD patients´ older age and lower educational level may have contributed to their poor test performance, at least partly. As expected, aMCI and mild AD patients were impaired on episodic memory test (RAVLT), particularly in the delayed recall task. Their low RAVLT scores could not be explained by depression (since there was no correlations with Cornell Depression Scale), but verbal fluency may have influenced this task, at least in the dementia group.

aMCI patients were similar to controls on tests of semantic memory (BNT and Similarities) but worse on verbal fluency task, which involves semantic knowledge, as well as language, executive function and short-term memory. Short-term memory may have influenced verbal fluency, since aMCI subjects had low scores on backward digit span test.

Thus, aMCI patients showed dissociation in their performance on semantic and episodic memory tasks. This finding was expected, since it is well established that these memories constitute two different subsystems of declarative memory[3,19-21], a fact confirmed by functional MRI study[22] showing that semantic and episodic tasks activate different brain

regions in patients with AD. Usually, impairment of semantic memory (semantic amnesia) is associated to dysfunction or lesion in the inferior, anterior and lateral temporal lobe, restricted to neocortex. Generally, the lesion does not include medial temporal structures, like hippocampus or any other limbic areas, which are very important for acquisition of new memories[4]. In aMCI, the initial pathologic damage is in medial temporal structures, mainly entorhinal cortex, which causes episodic memory deficits. Petersen et al.[23] showed that patients with aMCI had pathologic findings involving medial temporal lobe structures, suggesting a transitional state of evolving AD. Pennanen et al.[24], in a voxel based morphometry study, also found a unilateral medial temporal atrophy in individuals with MCI. Most of these aMCI cases (approximately 80%) will have converted to full-blown dementia syndrome after 6 years follow-up[2], thus constituting cases of very early AD. As the disease progresses, other areas are involved, including temporal neocortex, what can explain the difficulties with semantic knowledge in mild AD.

Semantic amnesia presents as difficulties in naming objects, finding words during conversation and understanding the meaning of known words and facts[4]. This is probably because most of our semantic memories are verbally coded. When we name an object, we create a code and categorize it in a complex system of relationships[9]. So, there is a superposition of language and memory concepts, especially when we are dealing with naming tests like BNT. Semantic memory deficits are commonly seen in AD, even in the early phase, but not necessarily in patients in pre-dementia state, like aMCI[25]. For example, Delazer et al.[5] showed that retrieval of people names was normal in a group of MCI patients in comparison with healthy controls. In contrast, Dudas et al.[6] and Adlam et al.[7], by using a more comprehensive test battery, found semantic memory deficits particularly in the item recognition, cross-modal associative memory and semantic knowledge for people in MCI patients. We have found that aMCI impairs episodic memory while sparing lexical semantic system, which can be affected in the early phase of AD.

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