Article

Arq Neuropsiquiatr 2010;68(2):185-188

Limitations in differentiating vascular dementia from Alzheimer's disease with brief cognitive tests

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ABSTRACT

Objective: To investigate the diagnostic value of brief cognitive tests in differentiating vascular dementia (VaD) from Alzheimer's disease (AD). **Method:** Fifteen patients with mild VaD, 15 patients with mild probable AD and 30 healthy controls, matched for age, education and dementia severity, were submitted to the following cognitive tests: clock drawing (free drawing and copy), category and letter fluency, delayed recall test of figures and the EXIT 25 battery. **Results:** VaD patients performed worse than AD patients in category fluency (p=0.014), letter fluency (p=0.043) and CLOX 2 (p=0.023), while AD cases performed worse than VaD patients in delayed recall (p=0.013). However, ROC curves for these tests displayed low sensitivity and specificity for the differential diagnosis between VaD and AD. **Conclusion:** Although the performance of VaD and AD patients was significantly different in some cognitive tests, the value of such instruments in differentiating VaD from AD proved to be very limited.

Key words: Alzheimer's disease, vascular dementia, clock drawing test, delayed recall, diagnosis, EXIT25, neuropsychological tests, verbal fluency.

Limitações em diferenciar demência vascular de doença de Alzheimer através de testes cognitivos breves

RESUMO

Objetivo: Investigar o valor diagnóstico de testes cognitivos breves na diferenciação de demência vascular (DV) e doença de Alzheimer (DA). **Método:** Quinze pacientes com DV, 15 com DA provável e 30 controles saudáveis, pareados em relação à idade, escolaridade e gravidade da demência, foram submetidos aos seguintes testes: desenho do relógio espontâneo e cópia, fluência verbal semântica e fonêmica, teste de evocação de memória de figuras e a bateria EXIT25. **Resultados:** Pacientes com DV apresentaram pior desempenho na fluência verbal semântica (p=0,014), fonêmica (p=0,043), e no CLOX 2 (p=0,023). O grupo com DA obteve pior desempenho no teste de evocação tardia (p=0,013). As curvas ROC aplicadas a esses testes mostraram baixa sensibilidade e especificidade para o diagnóstico diferencial entre DV e DA. **Conclusão:** Embora o desempenho dos pacientes tenha sido diferente em alguns testes, o valor desses instrumentos para o diagnóstico diferencial entre DV e DA parece ser muito limitado.

Palavras-chave: doença de Alzheimer, demência vascular, teste do desenho do relógio, memória de evocação, diagnóstico, EXIT25, testes neuropsicológicos, fluência verbal.

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Received 17 August 2009
Received in final form 27 October 2009
Accepted 11 November 2009

Alzheimer's disease (AD) and vascular dementia (VaD) are the most common causes of dementia in the elderly[1]. The most common subtype of VaD is subcortical ischemic vascular dementia (SVaD), which has slow onset and gradual clinical course, with or without acute motor or sensory deficits[2]. SVaD affects especially the prefrontal subcortical circuit[2], which explains the occurrence of a frontal lobe-

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related cognitive profile, characterized by executive dysfunction and mild memory impairment[3].

In the early stages, AD preferentially affects the medial temporal lobe, temporal limbic structures and reciprocal corticolimbic connections. These areas are critical for declarative memory and their deterioration determine impairment in consolidation of information into long-term memory resulting in accelerated forgetting and poor delayed recall[4]. Deficits in immediate and episodic memory and also in language (eg, naming) are common in AD[4].

SVaD and AD are both related with insidious onset and progressive course and when there is minimal history of prior clinical strokes the differential clinical diagnosis between them may be somewhat difficult[3]. Neuropsychological tests can be useful in differentiating AD from SVaD, especially those assessing memory, executive function and verbal fluency.

In the present study we compared the performance of VaD (especially SVaD) and AD patients in brief cognitive tests, aiming to identify instruments that could prove useful for the differential diagnosis in the clinical setting.

METHOD

Sixty individuals, aged 50 years or older, took part in the study. They were patients and healthy volunteers from two teaching hospitals, the Geriatric Outpatient Clinic of Guilherme Álvaro Hospital in Santos and the Cognitive Neurology Outpatient Clinic from the Hospital das Clínicas of the University of São Paulo School of Medicine in São Paulo, Brazil.

The sample was divided into three groups: patients with VaD according to DSM-IV diagnostic criteria[5]; probable AD patients according to NINCDS-ADRDA criteria[6]; controls without cognitive impairment and free from neurological and psychiatric diseases.

All VaD and AD patients were submitted to appropriate laboratory tests[7] and to magnetic resonance imaging.

Controls were submitted to the Geriatric Depression Scale (GDS)[8] in order to rule out depression. The Cornell scale for depression in dementia[9] and the Jeste and Finkel criteria for psychosis of AD and related dementias[10] were applied to AD and VaD groups to exclude depression or psychosis.

The three groups were matched by age, gender and education. The Mini-Mental State Examination (MMSE) with education-adjusted scores[11] and the NEUROPSI battery[12] were administered to all participants as part of the diagnostic workup. The NEUROPSI is a brief neuropsychological test baterry developed to assess a wide spectrum of cognitive functions, namely orientation, attention, memory language, visuoperceptual abilities and executive functions. VaD and AD patients had mild dementia, according to MMSE scores. The Hachinski Ischemic Scale (HIS)[13] was only administered to demented groups.

The study was approved by the Ethics Committee of the Guilherme Álvaro Hospital in Santos and Hospital das Clínicas of the University of São Paulo School of Medicine in São Paulo, Brazil. All subjects signed a written informed consent.

Neuropsychological assessment

A brief cognitive battery was administered to all groups and comprised tests pertaining to memory and executive functions: delayed recall test of 10 simple figures (visual memory test)[14], Executive Interview (EXIT25)[15]; category verbal fluency (animals/min.); phonemic verbal fluency (F-A-S); Executive clock drawing task (CLOX 1= on free drawing and CLOX 2=on copy)[16].

Statistical analysis

Data were analyzed with SPSS (Statistical Package for Social Sciences version 14.0) software. The three groups were compared on socio-demographic variables and neuropsychological scores by Kruskal-Wallis test. Mann-Whitney test was employed to compare the scores from VaD and AD and ROC curves were used to determine accuracy in the differential diagnosis between them. Spearman's correlation coefficients were calculated to determine whether one variable of interest was associated with another. All statistical tests were interpreted at the 5% significance level ($p<0.05$).

RESULTS

Fifteen VaD patients (5 female and 10 male; mean age=69.4 years; mean schooling=7.7 years), 15 AD patients (10 female and 5 male; mean age=76.0 years; mean schooling=5.8 years) and 30 controls (19 female and 11 male; mean age=72.3 years; mean schooling=7.0 years) were evaluated. VaD group was composed by 13 patients with SVaD and two with cortical-subcortical VaD. Four out of the 15 AD patients had slight subcortical white-matter changes in the periventricular regions on MRI.

The three groups were adequately matched by age, gender and years of education. Moreover, AD and VaD patients did not show any statistical difference in MMSE and NEUROPSI scores, suggesting a similar severity of dementia.

Performance of the three groups was significantly different in all cognitive tests, which were able to discriminate AD and VaD patients from controls with good accuracy (Table 1).

Demographic, clinical and neuropsychological data from AD and VaD groups are depicted in Table 2.

VaD patients displayed worse performance on CLOX 2, semantic and phonemic verbal fluency than AD, while

Table 1. Neuropsychological data from control group, AD and VaD patients.

Variable	Controls	AD	VaD	P value
MMSE	28.5 (1.6)	21.0 (3.3)	20.8 (3.2)	p<0.001
NEUROPSI	102.3 (13.2)	63.6 (12.1)	64.8 (10.5)	p<0.001
EXIT25	5.4 (2.9)	13.9 (4.8)	14.7 (4.8)	p<0.001
Category fluency	16.1 (4.4)	10.2 (4.2)	6.6 (2.2)	p<0.001
FAS	30.7 (11.3)	19.5 (10.2)	12.3 (8.9)	p<0.001
CLOX 1	13.8 (2.4)	8.3 (4.3)	7.3 (4.2)	p<0.001
CLOX 2	14.7(1.3)	12.5 (3.7)	10.3 (4.5)	p<0.001
Delayed recall	9.9 (0.3)	2.1 (1.9)	4.4 (2.6)	p<0.001

AD: Alzheimer's disease; VaD: vascular dementia; MMSE: Mini-Mental State Examination; FAS: phonemic verbal fluency. Values are mean and standard deviation (in parenthesis).

Table 2. Demographic, clinical and neuropsychological data from AD and VaD groups.

Variable	AD	VaD	p value
Age	76.0 (7.1)	69.4 (11.3)	0.135
Educational level (years)	5.8 (3.4)	7.7 (5.5)	0.320
HIS	1.9 (1.1)	8.2 (2.6)	**<0.001**
MMSE	21.0 (3.3)	20.7 (3.2)	0.917
NEUROPSI	63.6 (12.1)	64.8 (10.5)	0.604
EXIT25	13.9 (4.8)	14.7 (4.8)	0.866
Category fluency	10.2 (4.2)	6.6 (2.2)	**0.014**
FAS	19.5 (10.2)	12.3 (8.9)	**0.043**
CLOX 1	8.3 (4.3)	7.3 (4.2)	0.724
CLOX 2	12.5 (3.7)	10.3 (4.5)	**0.023**
Delayed recall	2.1 (1.9)	4.4 (2.6)	**0.013**

AD: Alzheimer's disease; VaD: vascular dementia; HIS: Hachinski Ischemic Scale; MMSE: Mini-Mental State Examination; FAS: phonemic verbal fluency. Values are mean and standard deviation (in parenthesis). Statistically significant p values are displayed in bold.

the AD group presented worse performance on delayed recall. ROC curves were calculated for these tests, displaying low sensitivity or specificity values (Table 3).

DISCUSSION

AD and VaD (mostly SVaD) patients evaluated in this study performed significantly different in four cognitive tests: AD patients performed worse on the delayed recall test, while VaD patients performed worse on semantic and phonemic verbal fluency and in the subtest "CLOX 2" (on copy) of the Executive Clock Drawing Task. However, ROC curve analysis revealed that these tests had low accuracy for the differential diagnosis between the two conditions.

Greater impairment in delayed recall tests in AD in comparison to VaD is well recognized[17]. Delayed recall impairment is caused by deficits in storage of new information due to neurofibrilllary pathology of medial temporal areas, such as hippocampus, entorhinal cortex and amygdala[17].

In our study, VaD patients performed significantly worse in a category fluency task (animals) than the AD group. However, there is no consensus in the literature about the performance in category fluency as being better or worse in VaD than in AD, with some authors reporting no differences[18] or even a reverse pattern, i.e., worse performance on this task in AD when compared to VaD[19].

Phonemic verbal fluency is a good test to assess executive functions and the integrity of prefrontal cortex. In the present study performance in this task was found to be significantly more impaired in VaD than in AD. This finding is consistent with an early report by Canning et al. in which VaD subjects produced significantly less words with letter F than their AD counterparts[20].

Many authors have described executive dysfunction as an important cognitive feature of VaD, especially SVaD[2,17]. The impaired performance in this task can be explained by damage to the dorsolateral prefrontal system, which is interconnected with the basal ganglia and thalamus in a

Table 3. Results of ROC curve analysis of cognitive tests in differentiating VaD from AD.

Cognitive test	AUC- ROC	Cut-off	Sensitivity	Specificity
Category fluency	0.762	< 9*	86.7%	66.7%
FAS	0.716	<13*	60.0%	60.0%
CLOX 2	0.742	< 14*	93.3%	60.0%
Delayed recall	0.764	< 4#	86.7%	66.7%

FAS: phonemic verbal fluency; AUC-ROC: area under the ROC curve; *to diagnose VaD; #to diagnose AD.

frontal subcortical loop, including the dorsolateral caudate nucleus, lateral dorsomedial globus pallidus internus, and anterior and dorsomedial nucleus of the thalamus. Phonemic fluency impairment can indicate that this circuit is disrupted at one or more of these subcortical loci or in the white matter tracts that interconnect them with the dorsolateral prefrontal lobe[21].

Royall et al.[16] described that CLOX 1 places high demands on executive control functioning, since patients are required to perform in a novel context, whereas CLOX 2 represents a purer measure of visoconstructional ability. However, their study included only patients with AD, together with a control group, but not patients with subcortical dementia. By contrast, we found that CLOX 1 did not discriminate AD from VaD, although VaD patients performed worse in the CLOX 2 task. This finding can be explained by greater executive dysfunction and visuo-constructive impairment in VaD compared to AD, as already observed by other investigators[22,23]. Libon et al.[23] showed that only AD patients' performance in CLOX 1 improved in relation to CLOX 2 when compared to VaD associated with SVaD. These authors concluded that the copy condition may be sensitive to executive dysfunction and the impaired performance of AD patients in CLOX 1 might be explained by deficient semantic knowledge. Cosentino et al.[24] administered the clock drawing (command and copy) to AD, VaD and Parkinson dementia groups. They considered that clock drawing to command demands activation of large-scale neuronal networks, including semantic knowledge and executive control. They observed that CLOX 1 was unable to distinguish dementia subtypes. These findings support CLOX 2 as a measure of executive deficits and highlight the important role of adding a copy task when administrating the clock drawing test.

The EXIT25 is an executive functions' test described by Royall et al.[15]. It was selected for our study in order to identify possible differences in executive functioning between AD and VaD. In contrast to our first expectation, we found no statistical difference between the performance of the two groups, either for the total score and its subtests, although it differentiated demented patients from controls. A possible explanation for this finding is that AD and VaD groups were composed exclusively by mildly demented subjects.

ROC curve analysis showed that the statistical differences described above were not sufficient to attain good diagnostic accuracy for the discrimination between VaD and AD. Although considering that the evaluation of a larger sample of patients could result in a better discriminatory value of the current approach, we may conclude that brief cognitive tests, such as those used in this study, do not differentiate VaD (especially SVaD) from AD and that additional neuropsychological testing, together with neuroimaging and clinical information, are necessary for the differential diagnosis of these two common dementing conditions.

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