Archives of Gerontology and Geriatrics 52 (2011) 190–196

Contents lists available at ScienceDirect

Archives of Gerontology and Geriatrics

journal homepage: www.elsevier.com/locate/archger

Neuropsychological profile of prodromal Alzheimer's disease (Prd-AD) and their radiological correlates

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ARTICLE INFO

Article history:
Received 30 November 2009
Received in revised form 17 March 2010
Accepted 19 March 2010
Available online 8 April 2010

Keywords:
Cognitive disorders
Neuropsychological tests
Dementia
Alzheimer's disease
Mild cognitive impairment
Magnetic resonance imaging

ABSTRACT

This study describes the cognitive profile of Prd-AD, the neuropsychological tests that may predict progression to dementia, and to study their brain structural correlates. We enrolled 24 stable amnesics who did not develop dementia after two years follow-up; 27 patients were considered as Prd-AD, in the initial visit, since they fulfilled NINCDS-ADRDA criteria after two years; 31 Alzheimer's disease (AD) patients and 27 controls (CTR). Structural magnetic resonance imaging (MRI), as well as a neuropsychological battery was performed at the initial visit. The key findings were: Prd-AD patients were characterized by prominent episodic memory dysfunction and minimal semantic memory and executive dysfunction. Semantic fluency test (Sem-Flu), delayed text memory test (Del-text-mem) and memory alteration test (M@T) (including both episodic and semantic memory), together with trail making test A (TMT-A), resulted significant predictors for dementia development in this group of amnesic patients. This optimal predictive model obtained an estimated accuracy of 53% after two years follow-up. M@T and semantic Sem-Flu test performance presented high correlation with decreased gray matter density in the left lateral temporal lobe. We conclude that Prd-AD is characterized by prominent episodic memory dysfunction and minimal semantic memory and executive dysfunction which are related with left medial, inferior and lateral temporal density loss, predominantly in the left side.

1. Introduction

The diagnosis of AD has traditionally required the presence of dementia. However, there is a need to identify subjects with AD in the predementia stage in order to develop and apply therapeutic interventions that could modify the course and prognosis of the disease. Recently, new research diagnostic criteria have been proposed that consider the possibility of performing the diagnosis before dementia appears. This means making the diagnosis in the prodromal or very early stage of the disease, which is characterized by certain degree of neuropsychological impairment without reaching the threshold of dementia (Dubois et al., 2007). It is therefore relevant to identify the specific cognitive dysfunction pattern of those patients who are in the early, Prd-AD and who will develop AD related dementia in a very short-term.

Although structural imaging and other biological variables contribute to improve prediction of AD in amnesic patients, cognitive testing has also demonstrated in several studies better predictive accuracy than other biological variables for assessing progression to dementia (Devanand et al., 2007; Fleisher et al., 2008). In addition, cognitive examination is an accessible tool for any clinician despite the degree of technological development of their working place. Although episodic memory deficit is a common neuropsychological symptom of incipient AD, which is related with the early pathological involvement of medial temporal lobe structures, it is not specific and some patients with episodic memory impairment do not finally develop AD. This fact could partially explain the observed heterogeneous evolution of amnesic mild cognitive impairment (aMCI) patients. There are some discrepancies on the role of other cognitive domain dysfunction in order to improve the sensitivity and specificity for detecting Prd-AD patients. Although some studies only describe episodic memory as the neuropsychological profile of Prd-AD (Tounsi et al., 1999; Sarazin et al., 2007), other longitudinal studies

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doi:10.1016/j.archger.2010.03.016

show that amnesic patients with additional involvement of other cognitive domains have an increased risk for progression to AD (Bozoki et al., 2001; Lopez et al., 2003). It is therefore necessary to describe the neuropsychological profile of Prd-AD in order to improve early AD recognition by clinicians.

Neuroimaging techniques are able to mark distinct structural and metabolic changes in AD patients in their prodromal stage (Ackl et al., 2005; Jack et al., 2005). Voxel base morphometry (VBM) is a technique that allows the detection of regional brain matter loss by voxel-wise comparison of grey matter (GM) volumes and density between groups of subjects. VBM has been shown to be sensitive in detecting changes in GM volumes in prodromal or early AD (Chételat et al., 2005). Several studies have described GM loss in the medial and inferior temporal lobe, together with the frontal lobes of amnesic patients who progressed to AD within a short-term period (Jack et al., 2005). These suggests that this anatomical areas could be marking early Prd-AD, which could also be related with the incipient memory and disexecutive dysfunction observed in these patients. However, only a few studies have studied the association between cognitive test performances and the specific brain density loss of Prd-AD patients.

The aims of this study are to describe the cognitive profile of Prd-AD, to describe the neuropsychological tests that may predict a quick evolution to dementia in Prd-AD, and to study their brain structural correlates.

2. Subjects and methods

A total of 109 participants (82 patients and 27 healthy volunteers) were included in this nested cohort study, which was approved by the local ethics committee. Patients were consecutively recruited from the AD and other cognitive disorders Unit at the Hospital Clinic in Barcelona. MRI was performed at baseline. All participants were clinically and neuropsychological evaluated at baseline and annually during a two-year prospective follow-up period. After complete description of the study, written informed consent was obtained from all the participants. A retrospective analysis of the baseline visit was performed, with the patients classified as a function of their clinical evolution (nested cohort design).

2.1. Inclusion criteria for amnesic patients

(1) Memory decline according to clinical judgment and preferably corroborated by an informant at baseline; (2) significant episodic memory impairment (1.5 × SD) below the control mean score, taking into account age and educational level, according to previously validated normative Spanish test: the Del-text-mem at baseline; (3) do not meet probable AD according to DSM-IV and NINCDS-ADRDA criteria, taking into account clinical and objective functional and neuropsychological results at baseline; (4) CDR = 0.5 at baseline; (5) absence of a psychiatric or medical cause accounting for the memory problems at baseline.

This group of patients was retrospectively divided in two groups, taking into account their evolution after two years (nested cohort design): Prd-AD ($n = 27$): amnesic patients who fulfilled international AD criteria after two years follow-up; stable amnesic patients (S-Amn) ($n = 24$): patients who did not fulfill international AD criteria after two years follow-up.

Criteria for AD ($n = 31$): probable AD diagnosis was established by an interdisciplinary clinical committee formed by two neurologists and one neuropsychologist. DSM-IV and NINCDS-ADRDA criteria were applied, taking into account clinical and objective functional and neuropsychological results. All AD patients included were mild AD (global deterioration scale: 4 stage). Atypical AD variants with nonsignificant episodic memory impairment were excluded from the study.

Comparison CTR group: 27 cognitively healthy individuals over 60 years of age were included as a comparison CTRl group. Participants were collected from primary care centers in Barcelona. Subjects with any active neurological disease, acute psychiatric symptoms, a Mini Mental state Examination (MMSE) score below 25 or a Del-Text-Mem performance 1.5 × SD below the mean, taking into account age and educational level, were excluded.

2.2. Neuropsychological and functional assessment

Participants received 1-h battery test by a trained neuropsychologist. A comprehensive neuropsychological battery that included memory, language, praxis, visual perception and frontal functions assessment was used. Neuropsychological normative data was collected previously from a sample of healthy elders from Barcelona (Rami et al., 2007a). The Boston naming test (BNT) was used for assessing language (confrontation naming). Praxes were assessed by constructive praxis (Cons-Px) from the Consortium to Establish a Registry for Alzheimer's disease (CERAD) battery and by ideomotor praxis (Ideom-Px) using five gesture imitations. Visual perception was assessed by overlapping figures (Ov-figure) and by the perceptual digital test (PDT) (Rami et al., 2007a). TMT-A was used in order to asses processing speed. Frontal functions were assessed by phonetic fluency COWAT (FAS), and by similarities measuring verbal abstract reasoning. Five memory tests were included in the study: logical verbal memory was assessed with the encoding text memory test (E-Text-Mem), Del-Text-Mem for the Barcelona test battery. Episodic visual memory (Vis-Mem) was assessed with the drawing memory recall of the Cons-Px from the CERAD battery. Semantic memory was assessed with the semantic fluency (animals, fruits and vegetables) (Sem-Flu) and M@T (Rami et al., 2007b), which includes a comprehensive episodic and semantic memory assessment.

The Pfeffer functional activities questionnaire (FAQ) (Pfeffer et al., 1982) was used for assessing patient's functional activities. The FAQ (informant-reported) impairment presents good sensitivity and specificity for predicting AD after two-year follow-up in amnesic patients (Tabert et al., 2002).

2.3. MRI acquisition

MRI studies were obtained on a 1.5T GE magnet. 3D-IR SPGR coronal (IRP SPGR, TE Min, TR = 12, Prep Time 450, FOV 25, 1.5 mm thickness, 128 locations, 1 NEX) and conventional PD/T2-weighted Fast Spin Echo, oblique images of the entire brain were obtained, for quantization of brain volumes, to evaluate brain anatomy, and exclude pathology. Regular MRI quality assurance was performed.

2.3.1. Structural MRI analysis

MRI were transferred to a SUN Ultra 60 workstation and converted into Analyze format using the MRIcro software (Chris Rorden, University of South Carolina, USA). Images were then analyzed using VBM analysis (SPM2, Wellcome Department of Cognitive Neurology, UK), on a MATLAB 6.5 (Mathworks, USA) platform. Customized template and prior images were obtained and the optimized VBM procedure was applied (http://dbm.neuro.uni-jena.de/vbm/vbm2-for-spm2/cross-sectional-data-segmentation/) (Chételat et al., 2005; Hirata et al., 2005). Briefly, VBM analysis performs a comparison of matter concentration among different groups of subjects. First, VBM achieves the spatial normalization of all MR images to the same stereotactic space. After normalization, the procedure involves segmenting tissue from the normalized images, smoothing and performing a statistical analysis by the general linear model (GLM). At the