Longitudinal Study of Amnesic Patients at High Risk for Alzheimer's Disease: Clinical, Neuropsychological and Magnetic Resonance Spectroscopy Features

Lorena Rami^a Beatriz Gómez-Anson^{b, c} Raquel Sanchez-Valle^a Beatriz Bosch^a
Gemma C. Monte^{b, c} Albert Lladó^a José L. Molinuevo^{a, c}

^aDepartment of Neurology, Alzheimer's Disease and Other Cognitive Disorders Unit, Institute of Neurosciences, and ^bDepartment of Radiology, Diagnostic Imaging Centre (CDI), Hospital Clinic i Universitari de Barcelona, and ^cInstitut d'Investigació Biomèdica August Pi i Sunyer, Barcelona, Spain

Key Words

Alzheimer's disease • Mild cognitive impairment • Spectroscopy • Neuropsychology • Prodromal AD

Abstract

Background/Aims: To prospectively follow up a group of amnesic patients at risk for Alzheimer's disease (AD), to characterize a group of patients whose features were intermediate between amnesic mild cognitive impairment (aMCI) and probable AD, prodromal AD (Prd-AD), and to investigate if these patients were at higher risk for AD conversion. **Methods:** A total of 109 subjects were assessed by neuropsychological evaluation and by ¹H magnetic resonance spectroscopy (¹H-MRS): 27 controls, and 16 aMCI, 34 probable AD and 32 Prd-AD patients. **Results:** Episodic memory and frontal test scores resulted lower in Prd-AD compared to aMCI patients. Prd-AD patients obtained significantly higher scores than AD ones in language, perception, praxis and frontal functions. Although Prd-AD and AD patients had distinct ¹H-MRS features from aMCI ones, there were no ¹H-MRS differences between Prd-AD and AD patients. The AD annual conversion rate after 1 year of follow-up for Prd-AD

(57.1%) was higher than in aMCI patients (20%; $p < 0.01$). A logistic regression, in which all amnesic patients were treated as a single group, showed that the Visual Memory Test was a significant neuropsychological predictor for AD conversion. **Conclusions:** Prd-AD patients are a clinically distinguishable group, with distinct neuropsychological and ¹H-MRS features and a higher conversion rate to probable AD than aMCI patients.

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Introduction

As memory impairment is usually the earliest feature of Alzheimer's disease (AD), amnesic subjects have become a great focus of interest. Amnesic mild cognitive impairment (aMCI) embodies a group of non-demented patients with memory complaints and objective memory impairment but preserved general cognition and normal activities of daily living (ADL) [1]. aMCI is associated with an increased risk for developing AD. About 10–15% of aMCI patients convert to AD per year [2, 3] and almost 50% of these patients progress to AD after 3 years [4].

However, aMCI is heterogeneous and is far from being considered a prodromal stage for AD, since most aMCI patients do not convert to AD in the short term, and up to 44% of patients return to normal [5]. It seems then desirable to find a more homogeneous group of amnesic patients with a higher AD conversion rate to be considered as a prodromal stage for AD.

There is increasing evidence that complex functional activity restrictions significantly increase the risk for progression to AD in patients with isolated memory impairment [6, 7]. Also, additional involvement of ≥ 1 cognitive domains other than memory seems to enhance the risk for progression to AD in amnesic patients [8].

Proton magnetic resonance spectroscopy (^1H -MRS) allows non-invasive in vivo assessment of brain metabolism [9, 10]. Biochemical abnormalities in the posterior cingulate gyrus have been found in patients with aMCI who converted to AD [11]. However, spread of biochemical abnormalities to the neocortical regions has only been described in patients fulfilling criteria for 'probable AD' [11, 12].

The aims of this study were to prospectively follow up a group of amnesic patients at risk for AD, to characterize a group of patients whose clinical and neuropsychological features were intermediate between aMCI and probable AD, therefore named prodromal AD (Prd-AD), and to investigate if these patients were at higher risk for AD conversion.

Methods

Subjects

A total of 109 participants (27 healthy volunteers and 82 patients) were included in the study, which was approved by the hospital ethics committee. Patients were consecutively recruited from the Alzheimer's Disease and Other Cognitive Disorders Unit of the Hospital Clinic in Barcelona. Sixteen patients met criteria for aMCI, 34 for probable AD and 32 for Prd-AD. ^1H -MRS was performed only in 27 controls, and in 14 aMCI, 28 Prd-AD and 31 AD patients, due to MR contraindications/claustrophobia. After complete description of the study, written informed consent was obtained.

Criteria for aMCI

aMCI criteria included modified Petersen et al. [1] criteria and 2 additional criteria, similar to Lopez et al. [13]: (1) memory decline according to clinical judgement and preferably corroborated by an informant, (2) impaired memory function for age and education, (3) preserved general cognitive function, (4) intact ADL and (5) non-demented, (6) the memory impairment had to be of the episodic memory type defined by 1.5 SD below the control group mean, taking into account age and educational level, and

(7) absence of psychiatric or medical causes accounting for these memory problems.

A previously validated normative Spanish test, the Delayed Text Memory Test [14], was used as an episodic memory test for determining a 1.5-SD cut-off below the mean, taking into account age and educational level. The Delayed Text Memory Test follows the story recall test paradigm which has been widely used previously [15].

Fifteen of the initial 16 aMCI patients were followed up after 1 year, while 1 patient was lost due to severe medical illness.

Criteria for Prd-AD

Criteria included: (1) memory decline according to clinical judgement and preferably corroborated by an informant, (2) significant episodic memory impairment (1.5 SD below the control mean score, taking into account age and educational level), (3) absence of a psychiatric or medical cause accounting for the memory problem, (4) absence of dementia, (5) either (a) ADL impairment reported by an informant and measured through an ADL questionnaire (Prd-AD1) or (b) an additional cognitive domain significantly affected (1.5 SD below mean of control individuals of comparable age and education) with preserved ADL reported by an informant and measured through an ADL questionnaire (Prd-AD2). Significant impairment in 1 test was sufficient to consider a cognitive dysfunction in any cognitive domain.

Thirteen patients met criteria for Prd-AD1 (5a criteria) and 19 patients for Prd-AD2 (5b criteria). Of the initial 32 Prd-AD patients, 28 were followed up, while 1 refused to be followed up, 2 suffered a severe non-neurological medical illness, and 1 changed residence.

Criteria for AD

Probable AD diagnosis was established by an interdisciplinary clinical committee formed by 2 neurologists and 1 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 non-significant episodic memory impairment were excluded from the study.

Comparison Control Group

Twenty-seven cognitive healthy individuals >60 years of age were included as a comparison group for controlling neuropsychological and ^1H -MRS variables. Participants were collected from primary-care centres in Barcelona. Subjects with any active neurological disease, acute psychiatric symptoms, a Mini-Mental State Examination [16] score <25 or a Delayed Text Memory Test [14] performance 1.5 SD below the mean, taking into account age and educational level, were excluded.

Neuropsychological Assessment

Participants received 1 h battery test by a trained neuropsychologist. A comprehensive neuropsychological battery that included memory, language, praxis, visual perception and frontal function assessment was used. Episodic verbal memory was evaluated with the Encoding Text Memory Test, Delayed Text Memory Test for the Barcelona Test Battery [14] and with the Total Word List Learning and Word List Delayed Recall from the Con-

Table 1. Demographic, genetic and clinical characteristics of controls, and aMCI, Prd-AD and AD patients

	Controls (n = 27)	aMCI (n = 16)	Prd-AD (n = 32)	AD (n = 34)	ANOVA
Age, years	74.3 ± 5.3	72.9 ± 4.8	73.5 ± 3.8	76.4 ± 6.8	n.s.
Education, years	9.4 ± 5.2	7.4 ± 4.2	8.0 ± 4.5	8.4 ± 4.8	n.s.
Sex, % F	63	68.8	65.6	70.6	n.s.
Months since					
1st visit		10.5 ± 8.0	11.0 ± 13.4	14.6 ± 16.2	n.s.
MMSE	27.4 ± 1.0	26.0 ± 2.0	24.8 ± 2.2	22.3 ± 2.9	**
FAQ	0 ± 0	0.8 ± 0.3	2.4 ± 2.8	9.8 ± 5.4	**
apoE, % ε4	16.7	46.7	58.6	48.5	*

Values are means ± SD. n.s. = Non-significant. * $p < 0.05$; ** $p < 0.005$.

sortium to Establish a Registry for Alzheimer's Disease (CERAD) battery [17]. Episodic visual memory (Visual Memory Test) was assessed with the drawing memory recall of the constructive praxis from the CERAD battery [17]. Semantic memory was studied with the semantic fluency (animals) [18]. The Boston Naming Test was used for assessing language (confrontation naming) [18]. Praxis was determined by constructive praxis from the CERAD battery and by ideomotor praxis using 5 gesture imitations [19]. Visual perception was assessed by the Overlapping Figures Test [19] and by the Perceptual Digital Test [20]. Frontal functions were evaluated by phonetic fluency Controlled Oral Word Association Test (FAS) [21], Trail Making Test part A [22] and by Similarities measuring verbal abstract reasoning [23].

Neuropsychological normative data had previously been collected from a sample of healthy elders from Barcelona [20, 24].

ADL Assessment

The Pfeffer Functional Activities Questionnaire (FAQ) [25] was used for assessing patients' functional activities. The FAQ comprises 10 items, which evaluate a variety of ADL and complex cognitive/social functions.

The FAQ has been used previously for MCI informant-reported functional assessment. According to Tabert et al. [26], the FAQ (informant-reported) has the best sensitivity and specificity properties in predicting AD after a 2-year follow-up in MCI patients. Taking this into account, together with the FAQ contents, we considered that ADL were impaired if the FAQ score was ≥ 3 .

All the aMCI and Prd-AD2 patients performed < 3 in the FAQ and all the Prd-AD1 patients ≥ 3 .

Neurobiology

Genotype. Apolipoprotein (apoE) genotyping was performed through polymerase chain reaction amplification and *HhaI* restriction enzyme digestion as previously described [27]. The presence of at least 1 ε4 allele made the subject to be considered as an apoE ε4 carrier.

¹H-MRS. MR studies were obtained using a 1.5T GE magnet and the head coil. 3D-IR SPGR axial (min. TE, TI = 450, flip angle = 15, bandwidth = 15.63, Fov = 25 × 20, thickness = 1.5, 128 locations, matrix = 256 × 192, 1 NEX) and conventional PD/T₂-weighted fast spin echo; oblique images were obtained on all subjects to evaluate brain anatomy, to exclude brain pathology

and for MRS localization purposes. Single-voxel spectroscopy (PRESS, TR = 1,500; TE = 35; 8 NEX) was then obtained from 3 voxels 2 × 2 × 2 cm, localized according to the previously reported patterns of regional metabolic changes described in aMCI and AD: posterior cingulate (P-Cing), left temporal pole (L-TPole) and left temporal/parietal cortex (L-TParietal). Care was taken not to include cerebrospinal fluid from the ventricles or scalp fat in the volumes of interest.

Automatic and manual pre-scanning was performed in all cases. This resulted in all spectra having good quality (≤ 6 Hz of full width at half height of the unsuppressed water peak and percentages of water suppression $> 96\%$). Raw data of all spectra were transferred to a dedicated SUN workstation and post-processed using the LC model [28]. This is an external reference, previously validated, and automated method that provides apparent absolute metabolite concentration determinations of different metabolites contained in a known basis set used as reference and the goodness of these calculations as expressed by their standard deviations (SD). A dedicated N-acetylaspartate (NAA) phantom was built to calculate the calibration factor. There were stable (SD $< 5\%$) phantom determinations during the study. As recommended, no T₁ or T₂ corrections were performed, and metabolite concentrations having an SD as provided by the LC model $< 20\%$, except for glutamate (Glu) (figures $< 40\%$ SD), were accepted for this study. Metabolite concentrations (millimol) of NAA, creatine/phosphocreatine (Cr), choline-containing compounds (Cho), myo-inositol (mI) and Glu, and ratios to Cr were determined. A similar methodology has been previously applied [29, 30].

Statistical Methods

All statistical analyses were performed with the SPSS package for Windows (V.11.0). Analyses of variance (ANOVA) and Bonferroni post-hoc comparisons were used to determine demographic, clinical, neuropsychological and ¹H-MRS differences among groups. Categorical patient characteristics were compared using χ^2 test for association. Related t Student analyses were used to compare baseline and follow-up neuropsychological performance in the aMCI and Prd-AD groups. In the small samples (e.g. converters and non-converters in the aMCI group), non-parametric Wilcoxon rank test was used for case-control comparison of cognitive measures.

Logistic regression was used to compare outcomes in the groups at 1 year, adjusted for other prognostic factors. Significance was defined at the $p < 0.05$ level, and at $p < 0.005$ for multiple comparison and correlation analysis.

Results

Demographics and apoE Genotype

Demographic characteristics are summarized in table 1. There were no statistical differences among the 4 groups of the study (control, aMCI, Prd-AD and mild AD) in age, years of education or gender. Bivariate analyses were also performed for age, gender and education, and we did not find any statistical difference among the groups.

apoE genotype was performed in 24 control, 15 aMCI, 30 Prd-AD and 33 AD subjects. There was a significant difference in the percentage of $\epsilon 4$ allele carriers between controls and the 3 patients groups ($p < 0.01$). There were no differences in the percentage of $\epsilon 4$ allele carriers among the patients groups (table 1).

Neuropsychological Features at Baseline Visit

Controls versus aMCI and Prd-AD Patients. The means and SD of the neuropsychological test scores are summarized in table 2. As expected, subjects with aMCI and Prd-AD presented greater memory impairment than control subjects ($p < 0.005$). They also showed significantly poorer outcome in the frontal functions tests (Trail Making Test-A) than controls ($p < 0.005$). Visual perception and naming capacities (Perceptual Digital Test and Boston Naming Test, respectively) resulted significantly impaired in the Prd-AD group with respect to controls.

Prd-AD versus aMCI and AD Patients. Delayed Text Memory Test and Visual Memory Test scores were significantly lower in the Prd-AD compared to aMCI patients ($p < 0.05$). The Trail Making Test-A score was also lower in the Prd-AD than in the aMCI group ($p < 0.05$). There were no further differences in cognitive functions.

There were no differences between Prd-AD and AD patients in any of the episodic memory and frontal measures. However, Prd-AD patients obtained significantly higher scores than AD ones in the Perceptual Digital Test, the Boston Naming Test, the Constructive Praxis Test, the Idemotor Praxis Test, the Trail Making Test-A, the Overlapping Figures Test and the Semantic Fluency Test.

Secondary Area Affected in the Prd-AD2 Patients. Of the Prd-AD2 patients, 43.8% presented significant impairment (< 1.5 SD) in frontal tests; 25% of them presented visual perception impairment, 12.5% concomitant frontal and language function impairment and 18.8% concomitant frontal and visual perception impairment.

¹H-MRS Changes

Table 3 summarizes metabolic values (mean and SD) showing significant differences between groups (ANOVA and Bonferroni post-hoc analysis).

ANOVA analyses showed significant differences between groups in mI/Cr, NAA, Cr and Glu in the P-Cing, and in NAA and Cho in the L-Tpole ($p < 0.005$).

Prd-AD and AD patients had lower NAA, Cr and Glu values in the P-Cing region, and lower NAA in the L-Tpole ($p < 0.01$), than aMCI ones. Prd-AD and AD patients also had higher mI/Cr in the P-Cing than controls ($p < 0.001$).

There were no metabolic differences between Prd-AD and AD patients.

One-Year Follow-Up: Conversion Rate, Clinical and Neuropsychological Differences between Converters and Non-Converters

At 1 year of follow-up, 3 of the 15 aMCI patients (20%) and 16 of the 28 Prd-AD ones (57.1%) had progressed to AD ($\chi^2 = 5.46$; $p < 0.05$). In simple bivariate logistic regression models, individuals fulfilling criteria for Prd-AD patients were 5.3 times as likely as aMCI patients to progress to AD (OR 5.33, 95% CI 1.22–23.19). After 1 year of follow-up, 63.6% of Prd-AD1 patients and 52.9% of Prd-AD2 patients converted to AD. There were no significant differences in the rate of conversion between both Prd-AD groups.

Furthermore, 5 of the 15 aMCI patients progressed to Prd-AD (33.4%), 6 aMCI (40%) remained stable, while 1 aMCI (6.1%) returned to normal values in memory performance after the 1-year follow-up.

A logistic regression, in which all amnesic patients (aMCI and Prd-AD) were treated as a single group, was performed. Age resulted a significant demographic predictor of AD conversion ($p < 0.05$). The Visual Memory Test also turned out to be a significant neuropsychological predictor of AD conversion ($p < 0.05$). Visual Memory Test scores were lower in converters versus non-converters at baseline [3.95 (SD = 2.69); 1.86 (SD = 2.66); $t = 2.36$; $p < 0.05$].

Table 2. Neuropsychological results of controls, aMCI, Prd-AD and AD-4

	Controls (n = 27)	aMCI (n = 16)	Pr-AD (n = 32)	AD-4 (n = 34)	ANOVA post-hoc
<i>Memory</i>					
E Text Memory	10.6 ± 2.7	6.1 ± 1.5	5.6 ± 2.5	4.8 ± 2.3	CTR vs. aMCI** CTR vs. Prd-AD** CTR vs. AD**
Del Text Memory	10.2 ± 2.2	4.0 ± 2.6	2.3 ± 2.3	1.7 ± 2.0	CTR vs. aMCI** CTR vs. Prd-AD** CTR vs. AD**
Vis Mem	8.7 ± 2.4	4.9 ± 2.6	2.5 ± 2.7	1.3 ± 2.3	aMCI vs. AD* CTR vs. aMCI* CTR vs. Prd-AD** CTR vs. AD**
List Learning	17.2 ± 3.6	10.9 ± 3.3	10.4 ± 3.8	9.2 ± 3.9	aMCI vs. Prd-AD* aMCI vs. AD** CTR vs. aMCI** CTR vs. Prd-AD**
List Recall	4.3 ± 2.1	1.1 ± 1.6	1.0 ± 1.4	0.8 ± 1.9	CTR vs. AD** CTR vs. aMCI** CTR vs. Prd-AD**
Sem Flu	18.2 ± 5.2	13.0 ± 4.1	12.7 ± 3.8	10.4 ± 3.7	CTR vs. AD** CTR vs. aMCI* CTR vs. Prd-AD** CTR vs. AD**
<i>Language</i>					
BNT	51.0 ± 3.8	47.4 ± 3.1	47.0 ± 3.9	38.7 ± 8.6	CTR vs. AD** aMCI vs. AD** Prd-AD vs. AD**
<i>Praxis</i>					
Cons Px	10.5 ± 1.1	9.5 ± 1.7	9.6 ± 1.7	7.9 ± 2.5	CTR vs. AD** Prd-AD vs. AD*
Ideom Px	5.0 ± 0	5.0 ± 0	5.0 ± 0	4.3 ± 1.9	CTR vs. AD** aMCI vs. AD** Prd-AD vs. AD**
<i>Perception</i>					
Ov Fig	10.0 ± 0	9.9 ± 0.2	10.0 ± 0.2	9.3 ± 1.2	CTR vs. AD** aMCI vs. AD** Prd-AD vs. AD**
PDT	13.9 ± 1.5	12.8 ± 2.2	12.1 ± 1.7	10.3 ± 2.9	CTR vs. AD** aMCI vs. AD** Prd-AD vs. AD*
<i>Frontal</i>					
FAS	23.7 ± 11.1	20.6 ± 6.7	19.4 ± 10.1	18.9 ± 10.4	CTR vs. Prd-AD** CTR vs. AD** aMCI vs. AD*
TMT-A	69.8 ± 28.1	83.0 ± 16.8	103.9 ± 43.8	113.0 ± 51.8	
Similarities	15 ± 4.8	12.0 ± 3.4	12.0 ± 3.2	9.0 ± 4.5	

Values are means ± SD. CTR = Control; E Text Memory = Encoding Text Memory Test; Del Text Memory = Delayed Text Memory Test; Vis Mem = Visual Memory Test (free recall of the CERAD drawings); List Learning = Total Wordlist Learning from CERAD battery; List Recall = Word List Delayed Recall from CERAD battery; Sem Flu = Semantic Fluency Test (animals); BNT = The Boston Naming Test; Cons Px = Constructive Praxis Test from the CERAD battery; Ideom Px = Ideomotor Praxis Test by 5 gesture imitation; Ov Fig = Overlapping Figures Test; PDT = Perceptual Digital Test; FAS = phonetic fluency Controlled Oral Word Association Test; TMT-A = Trail Making Test-A. * p < 0.05: significant Bonferroni post-hoc comparison; ** p < 0.005: significant Bonferroni post-hoc comparison.

Table 3. In vivo metabolites in the aMCI, Prd-AD and AD groups

	Controls	aMCI	Prd-AD	AD	F	p	ANOVA post-hoc
Ino/Cr P-Cing	0.77 ± 0.90	0.85 ± 0.80	0.88 ± 0.12	0.88 ± 0.13	5.64	<0.005	CTR vs. AD** CTR vs. Prd-AD**
NAA P-Cing	8.38 ± 0.90	8.67 ± 1.21	7.75 ± 1.06	7.29 ± 1.01	8.59	<0.001	CTR vs. AD** aMCI vs. Prd-AD* aMCI vs. AD**
Cr P-Cing	5.48 ± 0.69	5.65 ± 0.65	5.01 ± 0.55	4.88 ± 0.62	7.77	<0.001	CTR vs. AD** CTR vs. Prd-AD* aMCI vs. Prd-AD* aMCI vs. AD**
Glu P-Cing	7.21 ± 1.10	8.00 ± 0.97	6.68 ± 1.26	6.56 ± 1.55	4.92	<0.005	aMCI vs. Prd-AD* aMCI vs. AD**
NAA L-TPole	6.54 ± 1.03	6.81 ± 1.20	5.52 ± 0.84	5.78 ± 1.53	4.91	<0.005	aMCI vs. Prd-AD* aMCI vs. AD**
Cho L-TPole	1.52 ± 0.28	1.60 ± 0.26	1.39 ± 0.32	1.24 ± 0.26	6.01	<0.005	CTR vs. Prd-AD* CTR vs. AD* aMCI vs. AD*

Values are means ± SD. CTR = Control. * p < 0.05: significant Bonferroni post-hoc comparison; ** p < 0.005: significant Bonferroni post-hoc comparison.

Table 4. Percentage of aMCI and Prd-AD patients declining (>0.5 SD per domain) in the second neuropsychological exam, after 1 year of follow-up

Cognitive area	aMCI %	Prd-AD1 %	Prd-AD2 %	p
Verbal memory	31.3	44.4	31.3	n.s.
Visual memory	12.5	22.2	18.8	n.s.
Semantic memory	18.8	44.4	50	**
Language	37.5	55.6	37.5	n.s.
Praxis	25	44.4	26.7	n.s.
Visual perception	31.3	11.1	25	n.s.
Frontal function	50	66.7	68.8	n.s.

n.s. = Non-significant. ** p < 0.05.

Within the Prd-AD group, logistic regression analysis failed to find any predictors of conversion. There were no neuropsychological differences between Prd-AD converters and non-converters at baseline. In aMCI, the Delayed Text Memory Test and Semantic Fluency Test scores were lower in converters versus non-converters at baseline (p < 0.05). Logistic regression analysis failed to find any neuropsychological or demographic predictors of conversion in the aMCI group.

The percentage of patients who declined in their neuropsychological performance was variable for each cognitive domain (table 4). The percentage of Prd-AD1 and

Prd-AD2 patients declining >0.5 SD after 1 year of follow-up was greater than the percentage of aMCI patients, although only the semantic memory test score reached statistical difference.

In relation to ¹H-MRS, Prd-AD converters showed, in the L-TParietal at baseline, a significantly lower absolute NAA mean [6.86 (1.04) vs. 7.97 (1.14); t = 2.5, p < 0.05], a lower absolute Cho mean [1.03 (0.18) vs. 1.21 (0.24); t = 2.17, p < 0.05] and a lower absolute Cr mean [4.32 (0.66) vs. 5.04 (0.77); t = 2.5, p < 0.05] than non-converters. aMCI converters showed, in the P-Cing at baseline, a significantly higher Cho/Cr mean [0.21 (0.01)

vs. 0.18 (0.01); $t = -3.1$, $p < 0.01$] than non-converters. Logistic regression analysis also failed to find any ^1H -MRS predictors of conversion in the Prd-AD and aMCI groups.

There were no differences in the frequency of apoE $\epsilon 4$ carriers between Prd-AD converters and non-converters. Logistic regression analysis did not find apoE to be a predictor of conversion.

Discussion

Patients fulfilling proposed Prd-AD criteria showed characteristic clinical, neuropsychological and neurobiological (^1H -MRS) features and a higher conversion rate to probable AD than aMCI. We consider that Prd-AD patients were in the prodromal stage of the disease, since they were close to fulfilling probable AD criteria, their memory impairment and their ^1H -MRS characteristics were similar to mild AD, and more than half of them became probable AD within 1 year of follow-up.

The concept of 'prodromal Alzheimer's disease' was introduced by Dubois [31] a few years ago to refine the concept of aMCI. Although diagnostic criteria were proposed [32], no studies have been carried out for determining the neuropsychological and clinical profile and the conversion rate of this group of patients. Our operational definition of Prd-AD, different from the Dubois criteria, was based on clinical judgement and objective neuropsychological and functional measures. Applying these criteria, we found a 5.3 times higher conversion rate in Prd-AD patients with respect to aMCI ones after 1 year of follow-up. Patients fulfilling Prd-AD criteria showed greater cognitive decline after 1 year of follow-up than aMCI patients in most cognitive domains assessed; however, only the semantic memory domain reached statistical differences between both groups. This fact may suggest that semantic memory is a key domain when patients, in this continuum, get closer to AD conversion. When amnesic patients were treated as a single group, the Visual Memory Test was a psychological predictor for AD conversion with significantly lower scores in the converters at baseline. Visual memory impairment may suggest bilateral medial temporal lobe damage in these patients that could be related to an increased risk for progression to AD.

Prd-AD had lower NAA, Cr and Glu in the P-Cing, and NAA in L-Tpole, compared to aMCI. There were no significant differences in ^1H -MRS between Prd-AD and AD. Previous evidence has shown that ^1H -MRS may

identify early metabolic changes in the P-Cing, a region known to be metabolically involved in aMCI in nuclear medicine studies [33]. ^1H -MRS has shown that aMCI patients may present elevated mI, but no changes in NAA in this region, while patients fulfilling criteria for 'probable AD' already show impairment in the neuronal NAA marker [11, 34]. Our results demonstrate that patients with Prd-AD already have features of neuronal dysfunction/loss (decreased NAA) in the P-Cing, similar to AD, and that these changes extend to cortical regions, such as the temporal pole. Additionally, our study shows how Prd-AD converters presented metabolic changes in the L-TParietal cortex at baseline, compared to non-converters, thus supporting the view that the neuropathologic extension to cortical brain regions is related to the progression towards AD [35].

Although original aMCI criteria implied preserved ADL, some authors have described mild instrumental ADL decline in aMCI patients [36–38]. This fact may noteworthy contribute to the clinical heterogeneity of aMCI, since it may mix patients with different degrees of deterioration. According to previous studies, our longitudinal findings showed that amnesic patients with ADL impairment had a higher risk for developing AD after 1 year of follow-up [6, 7]. These results support the idea that amnesic with and without ADL impairment may be considered 2 different clinical groups.

The Prd-AD group of patients with episodic memory and other cognitive domain impairment with preserved ADL present some similarities to the 'MCI multidomain with memory disorder' described by Lopez et al. [13] and to the MCI+ group defined by Bozoki et al. [8]. According to Bozoki et al. [8], our longitudinal findings showed that amnesic patients with additional involvement of ≥ 1 cognitive domains other than memory had an increased risk for progression to AD. These results support the idea that amnesic patients with additional cognitive domain impairment should be considered a distinct clinical group. Bozoki et al. [8] found that praxis measured by Block Design was the most frequent additional abnormal cognitive domain in the MCI+ group. By contrast, we found frontal dysfunction to be the most frequent additional affected domain in our Prd-AD patients. This fact agrees with previous studies, in which frontal impairment was proposed as a cognitive risk factor for AD progression [39–41].

We recognize that one limitation of our study is that the follow-up was of only 1 year. As few aMCI patients returned to normal and subjects with aMCI showed a substantial decline on tests after 1 year, additional con-

versions to AD could be expected at longer follow-up intervals. In this sense, although our study characterized a group of patients with a higher risk to convert to AD within a year, it would be of interest to perform further studies with longer follow-up of these cohorts to establish the long-term rate of conversion.

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