A Longitudinal Follow-Up of 550 Mild Cognitive Impairment Patients: Evidence for Large Conversion to Dementia Rates and Detection of Major Risk Factors Involved

Ana Espinosa a, Montserrat Alegret b, Sergi Valero a, b, Georgina Vinyes-Junquera a, Isabel Hernández a, Ana Mauleón a, Maite Rosende-Roca a, Agustín Ruiz a, Oscar López c, d, e, Lluís Tarraga a and Mercè Boada f

a Memory Clinic of Fundació ACE, Institut Català de Neurociències Aplicades, Barcelona, Spain
b Psychiatry Department, Hospital Universitari Vall d'Hebron, CIBERSAM, Universitat Autònoma de Barcelona, Spain
c Department of Neurology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA
d Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA
e Department of Psychology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA
f Hospital Universitari Vall d’Hebron - Institut de Recerca, Universitat Autònoma de Barcelona (VHIR-UAB), Spain

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Abstract. The most recent studies about mild cognitive impairment (MCI) are focused on the search for factors that make patients more vulnerable to conversion to dementia, mainly Alzheimer’s disease (AD). The aim of this study was to determine which neuropsychological test performances, including episodic memory profiles, and genetic risk factors (APOE ε4) better predict early conversion to dementia among the four MCI subtypes. Data from 550 MCI patients were analyzed for the purpose of this study and were classified according to Petersen’s criteria (2004), and also taking into account the absence (probable MCI) or presence (possible MCI) of comorbidities that could explain cognitive deficits. MCI cases were divided into Probable amnestic (Pr-aMCI) (n = 115), probable non-amnestic (Pr-naMCI) (n = 37), possible amnestic (Pss-aMCI) (n = 234), and possible non-amnestic (Pss-naMCI) (n = 164), single or multiple domain. In the whole MCI sample, regression analysis showed that low performances on Orientation, Verbal Delayed Recall of the Word List Learning test from WMS-III, and Luria’s Clock test were associated with conversion to dementia, independently of APOE ε4 allele. Cox proportional-hazards showed that the Probable MCI subtype, presence of storage memory impairment, multiple domain condition, and presence of at least one ε4 allele increased the risk of conversion to dementia. Multivariate survival and Kaplann-Meier analyses showed that the Pr-aMCI with storage memory impairment had the most and closest risk of conversion to dementia. In conclusion, the Pr-aMCI subset of patients had 8.5 times more risk of converting to dementia than the Pss-naMCI group, who displayed the slowest conversion rate to dementia.

Keywords: Amnestic, cognition, dementia conversion, genetics, mild cognitive impairment, risk factors

Supplementary data available online: http://www.j-alz.com/issues/34/vol34-3.html#supplementarydata03
INTRODUCTION

Mild cognitive impairment (MCI) is a clinically heterogeneous syndrome. Its first classification was based on memory impairment, but it was later expanded to other cognitive domains. According to Petersen et al. [1] classification, MCI would comprise four broad subgroups depending on memory performance and the number of impaired cognitive functions: amnestic single (aMCI-sd) and multiple domains (aMCI-md), and non-amnestic single (naMCI-sd) and multiple domains (naMCI-md). Other classification schemes have taken into account the presence (possible MCI) or absence (probable MCI) of comorbidities (i.e., cerebrovascular disease, history of head trauma encephalopathy, infectious diseases, or developmental disabilities) that could explain observed cognitive deficits [2, 3].

Over the last decades, most research on MCI [4] has been focused on searching for factors which make patients more vulnerable to conversion to dementia, in particular Alzheimer’s disease (AD). Recently, the International Working Group for New Research Criteria for the Diagnosis of AD introduced the definition of prodromal AD to describe a symptomatic disease phase or the predementia stage of AD [5].

The annual conversion rate of amnestic MCI to AD reported in different studies rises from 10–19% [6–8], 30% [9, 10], to 40% [11]. Some recent studies suggested that the risk of AD increases when additional domains besides memory are impaired, probably because they are in a more advanced stage of the neurodegenerative disease [12–16].

In contrast, other studies have found lower conversion rates to AD in aMCI-md and naMCI, than in those with aMCI-sd, suggesting that neuropsychological variables other than memory are not useful to predict progression to AD [9, 17].

Although it is well known that memory is one of the main risk factors to dementia conversion in MCI [5–7, 18–21], one of the most frequent limitations of several studies consists of the lack of an exhaustive assessment of memory functioning and the scarce sample size analyzed. In some cases, a recognition memory test in the memory assessment was missing [22, 23], impeding a comprehensive detection of which parameters of episodic memory (failures in encoding, storage, retrieval, or recognition) are the most vulnerable to prodromal AD and other dementias.

In this study we report a longitudinal follow-up of 550 MCI individuals, representing one of the largest single-site clinical MCI series reported worldwide. Routine clinical and neuropsychological follow-up of people with MCI allowed us to comprehensively estimate conversion rates in different MCI subtypes and to determine neuropsychological test performances, including the episodic memory profiles that predict early conversion to dementia in different MCI subtypes.

METHODS

Subjects

For the purpose of this study, data was analyzed from a sample of 550 individuals who visited the Diagnostic Unit of Fundació ACE (Barcelona, Spain) between January 2006 and November 2011 and were diagnosed as MCI. These patients had the following characteristics: a Clinical Dementia Rating Scale (CDR) [24] of 0.5, older than 60 years of age, functionally literate, no severe auditory or visual abnormalities including glaucoma and cataracts, and available DNA sample. Their medical records were reviewed to classify them according to Petersen’s criteria [1, 6] (amnestic and non-amnestic, single and multiple domains) and Lopez et al. [2] classification. Possible MCI was assigned only when vascular or psychiatric etiology was suspected.

Diagnostic adjudication

All subjects were recruited and assessed at the Fundació ACE and all diagnoses were assigned at a consensus conference among neurologists, neuropsychologists, and social workers. All subjects had at least one follow-up (mean follow-up time: 26.6 months; range: 6–68 months) and were older than 60, and all follow-up diagnoses were made with full knowledge of prior classification and prior neurobehavioral data. At time of enrollment, all patients fulfilled MCI Petersen’s diagnostic criteria [1, 6], including subjective memory complaints, normal general cognition, preserved performance in activities of daily living, absence of dementia, and a measurable impairment in one or more cognitive functions. All MCI subjects had a CDR rating of 0.5 and none were taking any dementia medication (i.e., acetylcholinesterase inhibitors or memantine).

Domain Pattern Impairment (DPI): Amnestic and non-amnestic single and multiple domain MCI criteria

MCI was subclassified as aMCI-sd, aMCI-md, naMCI-sd, and naMCI-md fulfilling Petersen’s criteria [1, 6], including subjective memory complaints,
normal general cognition, preserved performance in activities of daily living, absence of dementia, and a measurable impairment in memory function, with or without deficit in other cognitive domains (amnestic MCI single domain or amnestic MCI multiple domain).

Memory Pattern Impairment (MPI): Storage and retrieval amnestic MCI criteria

The amnestic MCI patients (aMCI-sd and aMCI-md) with impaired delayed verbal recall for whom recognition testing did not improve performance were classified as having an “Encoding/Storage” pattern of memory loss. In contrast, patients with impaired verbal delayed recall, but for whom testing using a recognition format resulted in greatly improved performance were classified as having a “Retrieval” deficit.

Possible and probable MCI criteria

Similar to Lopez et al. [2] classification, but extending it to the non-amnestic MCI groups (naMCI-sd and naMCI-md), all MCI subjects were reclassified as possible MCI when there were comorbidities that could explain or contribute to cognitive deficits; and they were classified as probable MCI when there were none. Therefore, subjects were classified as having Pss-aMCI when there were psychiatric, neurological (i.e., cerebrovascular disease, history of head trauma encephalopathy, infectious diseases, or developmental disabilities), or systemic illnesses that could cause cognitive deficits or when there was insufficient information. In the present study, for the Pss-aMCI and Pss-naMCI groups, only those subjects with cerebrovascular disease and psychiatric disorders (anxiety or depression) were included. In contrast, subjects were classified as having Pr-aMCI or Pr-naMCI if there were no neurological, psychiatric, or systemic illnesses that could explain their cognitive deficits.

Converters and non-converters MCI criteria

Subjects who converted to dementia, that is AD [25, 26], vascular dementia [27], mixed dementia (AD with cerebrovascular disease), frontotemporal dementia [28, 29], or dementia with Lewy bodies [30] over the study period, were classified as MCI converters. All of these subjects had a CDR [24] of 1. In contrast, those subjects who remained stable during follow-ups were classified as Stable or non-MCI converters. Finally, patients who normalized performance, with or without subjective memory complaints (n = 10), were excluded from this study.

APOE genotyping

The APOE ε4 allele was identified with commercial kits for APOE rs429358 (SNP112) and rs7412 (SNP158) from Roche Diagnostics (Germany). The APOE alleles were amplified using LightCycler ApoE Mutation Detection Kit (Roche diagnostics, Germany) and were detected using real-time PCR technology (LightcyclerR 480 System, Roche Diagnostics, Germany) following the manufacturer’s instructions. To check the quality of the results, different compound heterozygotes for APOE SNPs were verified in an independent research laboratory. Only one blood sample was not genotyped due to it being accidentally damaged.

Clinical assessment

All participants received standardized neurobehavioral exams, including neurological examination, neuropsychological testing, and social work evaluations.

Information about vascular risk factors (including hypertension, hypercholesterolemia, diabetes mellitus, history of stroke, heart disease, and family history of dementia) was provided by the patients or their caregivers. All subjects were examined with the Mini-Mental State Examination [31], Hachinski Ischemia Scale [32], and CDR [24]. The MRI scans, or more usually CT scans, were available for review. A comprehensive neuropsychological protocol was administered to all subjects. MCI with vascular disease were identified according to an algorithm previously described in detail [33]. Briefly, several expressions of significant vascular disease (e.g., hypertension, angina pectoris) and findings on MRI (or CT), associated with vascular disease were required for a classification of possible MCI of vascular etiology.

Neuropsychological assessment

The neuropsychological battery of Fundació ACE (NBACE) [34] was administered to all MCI patients. This diagnostic procedure included tests sensitive to processing speed, orientation, attention, verbal learning and memory, language, visuoperception, gnosia, praxis, and executive functions, including the following tests: Temporal, Spatial and Personal Orientation; Digit spans (forwards and backwards), Block Design...
Data from the 550 MCI individuals of this study were classified in the following MCI subtypes: Probable amnestic MCI subjects (Pr-aMCI) \( (n = 115; \text{20.9}\%) \), possible amnestic MCI subjects (Pss-aMCI) \( (n = 234; \text{42.5}\%) \), probable non-amnestic MCI individuals (Pr-naMCI) \( (n = 37; \text{6.7}\%) \), and possible non-amnestic MCI individuals (Pss-naMCI) \( (n = 164; \text{29.8}\%) \). In the whole sample, most of MCI patients displayed a multiple domain impairment \( (n = 451; \text{88}\%) \) whereas a single domain affection appeared only in 99 subjects \( (n = 99; \text{12}\%) \). Regarding amnestic MCI individuals, a storage pattern of memory impairment was observed in 299 subjects \( (65\%) \) and a retrieval impairment was found in 120 subjects \( (35\%) \).

Demographic, clinical, and genetic data of patients are detailed in Table 1. The prevalence of subjects in MCI subtypes was as follows: 20.9% Pr-aMCI, 42.5% Pss-aMCI, 6.7% Pr-naMCI, and 29.8% Pss-naMCI. Average follow-up time for all the subjects was 26.6 months (SD: 15.5, range: 6–68). Although no statistically significant differences among MCI groups were found in age and gender, they did significantly differ in educational level (see Table 1). All the analyses were adjusted by age, gender, and education.

According to the DPI classification criteria [4], most of MCI patients displayed a multiple domain cognitive impairment, and multiple domain was more common in amnestic compared to non-amnestic MCI. Average follow-up time for all the subjects was 26.6 months (SD: 15.5, range: 6–68). Although no statistically significant differences among MCI groups were found in age and gender, they did significantly differ in educational level (see Table 1). All the analyses were adjusted by age, gender, and education.

Regarding APOE genotype, the comparison of APOE ε4 genotyping (presence or absence of at least one APOE ε4 allele) among MCI groups showed a higher frequency of ε4 allele among Pr-aMCI than in Pss-aMCI patients \( (\chi^2 = 553.90; p < 0.001) \). Regarding APOE genotype, the comparison of APOE ε4 genotyping (presence or absence of at least one ε4 allele) among MCI groups showed a higher frequency of ε4 allele in Pr-aMCI than in Pss-aMCI, Pr-naMCI, and Pss-naMCI groups. There was no subject with the ε2 alleles (see Table 1). The Pr-aMCI had a higher frequency of ε4 allele than the rest of subjects (that is, Pss-aMCI, Pr-naMCI, and Pss-naMCI groups together) \( (\chi^2 = 32.53; p < 0.0001) \).

With regard to the clinical variables, such as hypercholesterolemia, hypertension, diabetes, heart disease, smoking habit, alcohol abuse, stroke, and family history of dementia, none of them showed statistically significant differences among
Table 1

<table>
<thead>
<tr>
<th>Comparison of demographic, clinical, and genetic data between groups</th>
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</thead>
<tbody>
<tr>
<td>Pr-aMCI</td>
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<td>-------</td>
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<tr>
<td>n (%)</td>
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<tr>
<td>Gender, n (%)</td>
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<td>Education in years, n (%)</td>
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<td>&gt;6</td>
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<tr>
<td>Age in years (mean/SD)</td>
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<td>MMSE (mean/SD)</td>
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<td>HIS (mean/SD)</td>
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<tr>
<td>APOE 4 (ε4 or ε4/ε4), n (%)</td>
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<tr>
<td>ε2/ε3 n (%)</td>
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<td>ε2/ε4 n (%)</td>
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<td>ε3/ε3 n (%)</td>
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<td>ε3/ε4 n (%)</td>
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<tr>
<td>Hypercholesterolemia</td>
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<td>Hypertension</td>
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<td>Diabetes</td>
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<td>Heart disease</td>
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<td>Smoking habit</td>
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<td>Alcohol</td>
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<td>Family history of dementia</td>
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</table>

Pr-aMCI, probable amnestic mild cognitive impairment; Pss-aMCI, possible amnestic mild cognitive impairment; Pr-naMCI, probable non-amnestic mild cognitive impairment; Pss-naMCI, possible non-amnestic mild cognitive impairment; MMSE, Mini-Mental State Examination; HIS, Hachinski Ischemia Scale; SD, standard deviation; $^1\chi^2$; $^2F$.

The four MCI groups. However, Pr-aMCI and Pr-naMCI subjects obtained lower scores on Hachinski Ischemia Scale than Pss-aMCI and Pss-naMCI groups (Table 1).

The ANCOVA showed statistically significant differences among groups in several neuropsychological variables (Table 2). Ideomotor praxis, repetition, and verbal comprehension variables were not introduced in the analysis because they were practically a constant in all groups. However, Bonferroni post-hoc multiple comparisons analyses revealed that only performance on Verbal Delayed Recall and Recognition memory subtests of the WMS-III showed statistically significant differences among the four MCI groups. Moreover, in order to report effect of presence or absence of at least one APOE ε4 allele at baseline, mean comparisons were executed and only Conconstructional Praxis ($p=0.02$) and Delayed recall ($p=0.004$) showed differences among four groups.

Follow-up analysis of MCI patients (mean follow-up time: 26.6 months; range: 6–68 months) indicated that Pr-aMCI converted to dementia in a higher proportion (30.4% Stable versus 69.6% Converters) than Pss-aMCI (47.4% Stable versus 52.6% Converters), followed by Pr-naMCI (54.1% Stable versus 45.9% Converters), and Pss-naMCI (77.4% Stable versus 22.6% Converters), respectively ($\chi^2 = 65.78; p=0.001$).

Survival time of conversion to dementia differed substantially among MCI subtypes. Patients with Pr-aMCI were the nearest to dementia conversion. Median time for the Pr-aMCI was 21 months (15.91–26.09 [95% CI]), while for the Pss-aMCI it was 34 months (28.78–39.22 [95% CI]) (Wald = 11.91; $p=0.001$; OR = 2.658), followed by Pr-naMCI with a mean time of 42 months (33.77–50.23 [95% CI]) (Wald = 61.87; $p=0.001$; OR = 4.717), and finally for the Pss-naMCI, it was 62 months (52.30–71.72 [95% CI]) (Wald = 32.59; $p=0.001$; OR = 2.870) (Fig. 1). A total of 257 (45.5%) subjects developed dementia during follow-up. Of these, 117 (45.5%) developed AD, 51 (19.8%) vascular dementia, 50 (19.5%) mixed dementia, 25 (9.7%) frontotemporal dementia, 12 (4.7%) dementia with Lewy bodies, and 2 (8%) Parkinson dementia. In the analyses below, we first report factors associated with a risk to develop any dementia syndrome during follow-up, concerning the whole sample, followed by the analysis for each of the four MCI subtypes.

In terms of the single or multiple MCI classification (DPI), in the whole sample, median survival time was 36 months (19.98–52.02 [95% CI]) for the single domain MCI, and 27 months...
Table 2

The ANCOVA comparing neuropsychological scores between MCI groups

<table>
<thead>
<tr>
<th></th>
<th>Pr-aMCI M (SD)</th>
<th>Pr-aMCI M (SD)</th>
<th>Pr-naMCI M (SD)</th>
<th>Pss-aMCI M (SD)</th>
<th>Pss-naMCI M (SD)</th>
<th>F (3, 537)</th>
<th>Eta²</th>
<th>Pss-aMCI Pr-naMCI Pss-naMCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global orientation</td>
<td>13.51 (1.67)</td>
<td>13.90 (1.41)</td>
<td>14.15 (1.22)</td>
<td>14.47 (1.03)</td>
<td>12.05***</td>
<td>0.06</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>Verbal learning and memory WMS-III</td>
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<tr>
<td>Learning (Trials 1+2+3+4)</td>
<td>15.79 (5.11)</td>
<td>17.19 (4.80)</td>
<td>22.61 (5.90)</td>
<td>22.61 (4.80)</td>
<td>72.54***</td>
<td>0.29</td>
<td>NS</td>
<td>0.001*** 0.001***</td>
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<tr>
<td>Delayed recall</td>
<td>0.78 (1.03)</td>
<td>1.40 (1.34)</td>
<td>4.61 (1.92)</td>
<td>5.22 (1.78)</td>
<td>38.87***</td>
<td>0.05</td>
<td>0.001***</td>
<td>0.001*** 0.001***</td>
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<tr>
<td>Recognition memory</td>
<td>17.76 (2.77)</td>
<td>18.82 (2.72)</td>
<td>21.49 (1.63)</td>
<td>21.86 (1.86)</td>
<td>75.79***</td>
<td>0.30</td>
<td>0.001***</td>
<td>0.001*** 0.001***</td>
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<td>Attention and working memory</td>
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<tr>
<td>Forward digits</td>
<td>6.61 (1.66)</td>
<td>6.48 (1.74)</td>
<td>6.84 (1.83)</td>
<td>6.60 (1.45)</td>
<td>0.68</td>
<td>0.00</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>Backward digits</td>
<td>3.49 (3.90)</td>
<td>3.13 (1.46)</td>
<td>3.62 (2.04)</td>
<td>3.53 (1.45)</td>
<td>4.92**</td>
<td>0.03</td>
<td>NS</td>
<td>NS</td>
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<td>Praxis</td>
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<tr>
<td>Block design</td>
<td>3.04 (1.06)</td>
<td>3.02 (1.07)</td>
<td>3.32 (0.87)</td>
<td>3.06 (1.10)</td>
<td>0.92</td>
<td>0.01</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>Imitation</td>
<td>3.05 (1.02)</td>
<td>3.01 (1.05)</td>
<td>3.35 (0.97)</td>
<td>3.37 (0.87)</td>
<td>4.73**</td>
<td>0.03</td>
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<tr>
<td>Language</td>
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<tr>
<td>Visual learning (15-BNT)</td>
<td>12.68 (2.41)</td>
<td>12.64 (2.39)</td>
<td>13.25 (1.90)</td>
<td>13.32 (1.87)</td>
<td>4.00*</td>
<td>0.02</td>
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<tr>
<td>Visual perception</td>
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<tr>
<td>Poppelreuter test (responses)</td>
<td>8.96 (1.43)</td>
<td>9.80 (1.36)</td>
<td>9.32 (0.80)</td>
<td>9.22 (1.15)</td>
<td>3.47*</td>
<td>0.02</td>
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<tr>
<td>Luria's Clocks test</td>
<td>2.67 (1.36)</td>
<td>2.63 (1.31)</td>
<td>3.04 (1.13)</td>
<td>2.73 (1.13)</td>
<td>1.48</td>
<td>0.01</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>The 15-Objects test</td>
<td>11.45 (2.10)</td>
<td>11.19 (1.95)</td>
<td>12.76 (3.54)</td>
<td>12.44 (1.81)</td>
<td>1.52</td>
<td>0.09</td>
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<td>NS</td>
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<td>Executive functions</td>
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<tr>
<td>SKT (time in seconds)</td>
<td>41.82 (16.82)</td>
<td>45.75 (20.54)</td>
<td>40.13 (12.85)</td>
<td>41.13 (13.89)</td>
<td>2.32</td>
<td>0.08</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>SKT (error)</td>
<td>4.29 (5.19)</td>
<td>4.63 (5.28)</td>
<td>3.67 (3.33)</td>
<td>3.24 (4.59)</td>
<td>2.75*</td>
<td>0.02</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>PVF</td>
<td>9.13 (4.09)</td>
<td>7.81 (4.07)</td>
<td>9.90 (4.28)</td>
<td>9.19 (3.94)</td>
<td>6.69***</td>
<td>0.04</td>
<td>0.011*</td>
<td>NS</td>
</tr>
<tr>
<td>SVF</td>
<td>11.22 (4.09)</td>
<td>11.02 (3.35)</td>
<td>13.17 (5.41)</td>
<td>12.91 (3.57)</td>
<td>11.85***</td>
<td>0.06</td>
<td>NS</td>
<td>0.034* 0.001***</td>
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<tr>
<td>Similarities WAIS-III</td>
<td>7.66 (3.13)</td>
<td>7.80 (3.09)</td>
<td>8.84 (2.53)</td>
<td>8.46 (2.60)</td>
<td>3.87*</td>
<td>0.02</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Global Cognitive Clock Test</td>
<td>4.82 (2.22)</td>
<td>4.91 (2.07)</td>
<td>5.95 (1.60)</td>
<td>5.64 (1.72)</td>
<td>8.17***</td>
<td>0.05</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Global orientation summary of Temporal + Spatial + Personal orientations; WMS-III, Wechsler Memory Scale, Third Edition; Abbreviated BNT, Boston Naming Test with 15 visual items; Recognition memory, correct answers; Block Design, WAIS-III; SKT, Automatic Inhibition Syndrome Kurztest; PVF, phonemic verbal fluency; SVF, semantic verbal fluency; WAIS-III, Weschler Adult Intelligence Scale, Third edition; M, mean; SD, standard deviation; NS, p ≥ 0.05; *p ≤ 0.05; **p ≤ 0.01; ***p ≤ 0.001.
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Fig. 1. Survival time of conversion to dementia. Non-converters MCI (n = 293) were censored (53.3%).

Table 3
MCI subtype, APOE ε4, and conversion to dementia

<table>
<thead>
<tr>
<th>MCI subtype</th>
<th>AD</th>
<th>VaD</th>
<th>MD</th>
<th>DLB</th>
<th>FTD</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pr-aMCI (n = 89)</td>
<td>ε4 (%)</td>
<td>58 (52.5)</td>
<td>6 (7.5)</td>
<td>8 (10.0)</td>
<td>3 (3.8)</td>
<td>5 (6.3)</td>
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<tr>
<td>Status</td>
<td>Absent</td>
<td>35 (76.1)</td>
<td>3 (6.5)</td>
<td>4 (8.7)</td>
<td>1 (2.2)</td>
<td>3 (6.5)</td>
</tr>
<tr>
<td>Pr-saMCI (n = 125)</td>
<td>ε4 (%)</td>
<td>39 (31.7)</td>
<td>38 (30.9)</td>
<td>30 (24.0)</td>
<td>5 (4.1)</td>
<td>10 (8.1)</td>
</tr>
<tr>
<td>Status</td>
<td>Absent</td>
<td>16 (45.2)</td>
<td>10 (27.0)</td>
<td>6 (16.2)</td>
<td>1 (2.7)</td>
<td>4 (10.8)</td>
</tr>
<tr>
<td>Pr-naMCI (n = 20)</td>
<td>ε4 (%)</td>
<td>8 (47.1)</td>
<td>0 (0.0)</td>
<td>2 (13.3)</td>
<td>2 (11.8)</td>
<td>5 (29.4)</td>
</tr>
<tr>
<td>Status</td>
<td>Absent</td>
<td>6 (40.0)</td>
<td>0 (0.0)</td>
<td>2 (13.3)</td>
<td>2 (11.8)</td>
<td>5 (33.3)</td>
</tr>
<tr>
<td>Pss-saMCI (n = 39)</td>
<td>ε4 (%)</td>
<td>12 (32.4)</td>
<td>7 (18.9)</td>
<td>11 (29.7)</td>
<td>2 (8.3)</td>
<td>5 (15.5)</td>
</tr>
<tr>
<td>Status</td>
<td>Absent</td>
<td>6 (46.2)</td>
<td>3 (22.1)</td>
<td>4 (30.8)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

AD, Alzheimer’s disease; VaD, vascular dementia; MD, mixed dementia; DLB, dementia with Lewy bodies; FTD, frontotemporal dementia; PD, Parkinson’s disease.

(23.18–30.82 [95% CI]) for multiple domain MCI (Wald = 3.23; \( p = 0.072; \) OR = 1.56). For the four MCI subtypes (see Supplementary Table 1; available online: http://www.j-alz.com/issues/34/vol34-3.html#supplementarydata03), there were only significant differences for Pr-aMCI with a median survival time of 38 months (19.98–56.02 [95% CI]) for the single domain MCI, and 20 months (15.13–24.87 [95% CI]) for multiple domain MCI (Wald = 3.62; \( p = 0.057; \) OR = 2.09). In contrast, no statistically significant differences were found among single and multiple domains MCI in any other group, that is, it was not significant for Pss-aMCI, for Pr-naMCI, or for Pss-naMCI.

Heterogeneity analysis for DPI (Supplementary Table 1) in the four MCI subtypes, suggested that DPI (\( p = 0.008 \)) showed heterogeneous effects among the four MCI subtypes.

Regarding the storage or retrieval MPI for the whole aMCI group, median survival time was 27 months.
Fig. 2. Multivariate survival analysis. Non-converters MCI (n = 293) were censored (53.3%).

(22.33–31.67 [95% CI]) for the storage group, and 31 months (24.54–37.46 [95% CI]) for the retrieval MPI group (Wald = 3.55; p = 0.059; OR = 1.34). However, for the amnestic MCI subtypes (Supplementary Table 1), there were not statistically significant differences on survival time among storage and retrieval groups, that is, it was not significant for Pr-aMCI, neither for Pss-aMCI, in heterogeneity analysis (p = 0.393).

With regard to APOE, the presence of at least one ε4 allele did significantly increase conversion to dementia in the whole MCI group, with a survival median time of 31 months (23.76–38.24 [95% CI]) for carriers of ε4 and 44 months (38.43–49.57 [95% CI]) for non-carriers (Wald = 19.89; p = 0.001; OR = 1.80). In the analysis for each of the four MCI subtypes (see Supplementary Table 1), only the Pss-aMCI group showed statistically significant differences for carriers of ε4. No statistically significant differences were found in the Pss-naMCI, Pr-aMCI, or Pr-naMCI groups. However, heterogeneity analysis for APOE ε4 (p = 0.330) (Supplementary Table 1) in the four MCI found no heterogeneous effects among the four MCI subtypes.

Moreover, in the four MCI subtypes, the regression analysis stratified by APOE ε4 allele showed that performance on Orientation, Verbal Delayed Recall, and Luria’s Clocks test. Heterogeneity analysis for NBACE tests (Supplementary Table 1) in the four MCI subtypes, suggested that only Orientation (p = 0.032) and Recognition (p = 0.017) showed heterogeneous effects among the four MCI subtypes.

Finally, a multivariate survival analysis without adjusting for gender, age, and education, was carried out combining the possible-probable, amnestic-non amnestic, and storage-retrieval groups. The results showed that the probable amnestic-storage group had the highest risk of conversion to dementia, having 8.5 times more risk to convert to dementia than the possible...
non-amnestic MCI group, the group that resulted to have the slowest conversion to dementia (see Fig. 2).

**DISCUSSION**

In this study we report a follow-up of 550 classified MCI individuals, representing one of the largest single-site clinical MCI series reported worldwide. Although the classification of MCI into probable or possible subtypes had been previously used, in our knowledge, this is the first study applying it in the non-amnestic group, allowing us to increase the accuracy of the MCI classification.

The main finding of this paper was that the Probable MCI condition had higher risk of early conversion to dementia than the rest of MCI individuals. Moreover, subjects with memory impairment (Pr-aMCI and Pss-aMCI) converted earlier to dementia than the non-amnestic ones. However, except for the Pss-naMCI group, and according to a previous study [3], the progression among the groups is very similar.

In accordance with previous reports, the aMCI were found more frequently than the na-MCI type [35–37]. In our study, probable MCI is more frequent than possible MCI subtype. The prevalence for the aMCI (20.9% for Pr-aMCI and 42.5% for Pss-aMCI, respectively); for the naMCI the prevalence was 6.7% for Pr-naMCI and 29.8% for Pss-naMCI. Pr-aMCI displayed a higher risk to develop dementia than Pss-aMCI. Conversely, Pr-naMCI converted more to dementia than the Pss-naMCI group.

According to previous reports [38–40], most patients, irrespective of MCI subtype, who converted to dementia, mainly developed the AD type (45.5%). In our sample, patients with aMCI had more risk of conversion to dementia than naMCI group, but in both cases, mainly to AD.

In terms of DPI, a major distribution of multiple domain patterns was found among all MCI subtypes in our sample, with a major number of Pr-aMCI subjects with multiple domains impaired. Similar results have been reported by other groups [2, 15], but not all [35]. Our data supports that the traditional amnestic single-domain MCI (aMCI-sd) [6] is rarely diagnosed when a comprehensive neuropsychological battery is applied, because other cognitive impairments are frequently found when neuropsychological evaluation is expanded [43]. More importantly, the naMCI group displaying impairment in several cognitive domains was associated with a faster conversion to AD and dementia compared to naMCI-sd group. This result would suggest that impairment in one cognitive domain alone (other than memory) is a rather benign condition [36]. Furthermore, this result also suggests that memory impairment is not always the first symptom of even the common dementia disorders, and neither is memory impairment specifically associated with an increased rate of progression to dementia [36, 44, 45]. Moreover DPI showed heterogeneous effects, specifically in Pr-aMCI subtype.

In terms of MPI, storage memory deficit was more frequent among Pr-aMCI than in the Pss-aMCI group. It is important to include a recognition memory test in the memory assessment. For obvious reasons, it is impossible to determine a storage memory deficit, without a recognition test. According to other authors [22, 23], a storage deficit is correlated with a higher risk of conversion to dementia for all MCI subtypes compared to a retrieval deficit memory.

Similar to previous genetic studies [46], the distribution of APOE alleles in MCI in our series revealed that ε3 was the most frequent (62.5%) and ε2 the least (8.0%) frequent allele. Interestingly, there were no MCI subjects with the ε2/ε2 haplotype, which has been related to protection against late-onset AD [47]. In the present study, the APOE ε4 allele was more frequent in Pr-aMCI than in the rest of MCI subtypes. Although the APOE ε4 allele was significant after survival analysis only for Pss-aMCI, heterogeneity analysis showed that APOE ε4 allele had homogeneous effects in the four MCI subtypes. The presence or absence of at least one ε4 allele affected the conversion rate, supporting the evidence of the degree of clinical heterogeneity that surrounds the MCI syndrome, and suggesting that the ε4 allele may be associated with accelerated neurodegeneration in the development and progression of several neurodegenerative diseases [48, 49]. This also points out the importance of improving diagnosis and follow-up of all the MCI groups. However, APOE ε4 is the strongest genetic risk factor for sporadic AD. Thus, it is no surprise that the presence of even a copy of the allele shortens the time to dementia. Regarding the genetic risk characteristics for conversion to dementia in terms of the ε4 allele, according to previous literature, possession of an ε4 allele was associated with an increase of the risk of developing AD [50]. In our sample, for aMCI carriers of ε4, they are about 1.7 times more likely to develop AD than non-carriers, and still, for the naMCI carriers of ε4, they are about 1.2 times more likely to develop AD than non-carriers.

Our results suggest that it is very important to include tests sensitive to delayed recall (including a
recognition memory task), orientation, and visuospatial gnosia in the neuropsychological assessment of all MCI subtypes. For the Pss-naMCI group, our results are in accordance with a previous study [42] where a poor performance on Delayed recall in non-amnestic MCI predicts progression to dementia, overall in those patients with a multiple domain impairment especially in global orientation and visuospatial gnosia (Luria’s clock tests). Our study demonstrated that Orientation and verbal recognition memory are of great importance in the assessment of the amnestic and non-amnestic probable MCI subtypes. This is important because memory might be preserved in na-MCI, but a poor performance in the Recognition task in the Pr-naMCI might be preserved in na-MCI, but a poor performance in the Recognition task in the Pr-naMCI constitutes a risk factor for conversion to dementia. Moreover, the performance’s effect on Orientation, Delayed Recall, or Luria’s clock tests are interestingly similar in those MCI subjects with the presence of at least one ε4 allele and those without or one ε4 allele. That is, neuropsychological capability of conversion to dementia is independent of being a carrier or not of one ε4 allele.

A limitation of the present study was that cerebrospinal fluid (CSF) biomarkers were not available. However, taking into account that our study aimed to detect prodromal dementia, not only AD, it was not a crucial issue. Moreover, CSF biomarker analysis was not a mandatory technique in Spain for MCI diagnosis when this project was conducted. Even today, lumbar puncture is not mandatory for MCI diagnosis in the clinical routine in our country.

However, we are currently carrying out a further prospective and longitudinal study using this MCI subtypes classification, with CSF biomarkers available. In summary, follow-up analysis suggested that the probable amnestic-storage group had the highest risk of conversion to dementia, having 8.5 times more risk to convert to dementia than the possible non-amnestic MCI group, the group that resulted in the slowest conversion to dementia. However, our study demonstrates high conversion rates in all MCI categories which strongly support a therapeutic intervention in Proba ble amnestic-storage individuals (that is, with recognition memory impairment), orientation, impairment, and multiple domain impairment, because almost all of them convert to dementia, especially to AD.

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