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Neuropsychiatric Predictors of Progression from Amnestic-Mild Cognitive Impairment to Alzheimer's Disease: The Role of Depression and Apathy

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Abstract. The aim of the study is to evaluate whether depression or apathy in patients with amnestic-mild cognitive impairment (MCI) increases the risk of progressing to Alzheimer's disease (AD). We investigated 131 consecutive memory-clinic outpatients with newly-diagnosed amnestic-MCI (mean age 70.8, SD = 6.5). Psychiatric disorders were diagnosed at baseline according to the criteria for depression and apathy in AD. Neuropsychiatric symptoms were assessed with the Neuropsychiatric Inventory (NPI). Follow-up examinations were conducted after six months and annually for four years. Neurologists diagnosed AD at follow-up using NINCDS-ADRDA criteria. Cox proportional hazard models with 95% confidence intervals were used to test the hypothesis that apathy or depression increases the risk of developing AD. At baseline, 36.6% amnestic-MCI patients had a diagnosis of depression and 10.7% had apathy. Patients with both amnestic-MCI and an apathy diagnosis had an almost sevenfold risk of AD progression compared to amnestic-MCI patients without apathy (HR = 6.9; 2.3–20.6), after adjustment for age, gender, education, baseline global cognitive and functional status, and depression. Furthermore, the risk of developing AD increased 30% per point on the NPI apathy item (HR = 1.3; 1.1–1.4). There was no increased risk of developing AD in amnestic-MCI patients with either a diagnosis or symptoms of depression. In conclusion, apathy, but not depression, predicts which patients with amnestic-MCI will progress to AD. Thus, apathy has an important impact on amnestic-MCI and should be considered a mixed cognitive/psychiatric disturbance related to ongoing AD neurodegeneration.

Keywords: Cognitive deficits, dementia, early detection, MCI, neuropsychiatric symptoms

INTRODUCTION

Mild cognitive impairment (MCI) is characterized by cognitive deficits not severe enough to fulfill dementia criteria. MCI can be classified as amnestic (memory deficits) or non-amnestic (deficits in other domains, e.g., verbal or executive functioning), and can feature dysfunction in single or multiple domains [1]. Amnestic-MCI has a good predictive value for identifying people at high risk of developing dementia [2–5], although the condition is heterogeneous because a substantial number of people remain stable or improve [2, 4,5]. Thus, there is a need to identity factors that might increase the possibility of identifying which MCI pa-

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tients will develop dementia, particularly Alzheimer's disease (AD).

There is a high prevalence of neuropsychiatric disturbances in patients with MCI [6–8], including aggression, agitation, depression, anxiety, and apathy. Symptoms of anxiety [9] can predict which MCI patients will develop dementia, and some studies [10] report an increased AD risk in MCI patients with depression, whereas others [9,11] report no increased risk. Recent evidence suggests that apathy increases the risk of conversion from cognitive impairment to dementia [12–14], but the interpretation of these findings is hampered by short follow-ups (one/two years) [12,14], the outcome of all dementia types, and the MCI criteria applied; one study used the Mini-Mental State Examination (MMSE) based definition [12,13] and another included all MCI subtypes [14]. Thus, there is a need for studies investigating the role of apathy and depression on the development specifically of AD, with longer follow-up periods, and an extensive clinical diagnosis of the amnestic form of MCI.

Apathy and depression are prevalent in AD [15], and depression has been shown to increase neuropathological changes in the hippocampus at the time of AD diagnosis [16]. It has been hypothesized that depression may play a differential role in MCI, as depression itself can primarily cause cognitive deficits. There is a need to establish whether depression and apathy have distinct roles in MCI, and whether early AD diagnosis prediction can be increased by considering both the diagnosis and milder symptoms of depression or apathy.

In the current study we examined whether depression or apathy predict progression from amnestic-MCI to AD in a large sample of patients who were followed for up to four years. Amnestic-MCI patients attending outpatient care in specialized memory clinics were followed, and both symptoms as well as diagnoses of apathy and depression were assessed.

METHOD

The study population comprised 131 consecutive patients with newly-diagnosed amnestic-MCI, examined at three participating memory clinics in Rome, Italy. At baseline and every follow-up, subjects underwent a thorough neurological and psychiatric examination, and extensive cognitive assessment by neuropsychologists. Caregivers and next-of-kin were also interviewed.

Sociodemographic information was collected at baseline. Maximum educational level was dichotomized into low ($<$ 8 years) and high ($\geqslant$ 8 years). Basic Activities of Daily Living (ADL) and Instrumental-ADL (higher score indicates higher loss of instrumental functions) were used as continuous variables.

Cognitive examination

Global cognitive functioning was assessed with MMSE [17]. Specific cognitive domains were assessed with the standardized and validated Mental Deterioration Battery (MDB) [18] and other tests. We assessed verbal memory (MDB Rey's 15-word Immediate Recall and Delayed Recall); short term visual memory (MDB Immediate Visual Memory); logical reasoning (MDB Raven's Progressive Matrices' 47); language (MDB Phonological Verbal Fluency and Sentence Construction); and simple constructional praxis (MDB Copying Drawings and Copying Drawings with Landmarks). Long-term visual memory and complex constructional praxis were measured with Delayed Recall and Copy of Rey-Osterrieth picture. Frontal abilities of attentive shifting and control were evaluated with the Stroop test Interference time. Test impairment was defined using normative data according to age and education [18].

MCI diagnosis

Diagnosis of MCI was made according to established criteria [1] by trained neurologists who interviewed patients and next-of-kin. Patients with amnestic-MCI of either single or multiple domains impaired [1] were included. Criteria for MCI were: subjective complaint of memory deficits; absence of dementia according to the diagnostic examination by the clinical neurologist (CDR $<$ 0.5), and normal everyday functioning on ADL; and abnormal memory functioning for age according to standard cutoffs [18]. For single domain amnestic-MCI, objective cognitive impairment included impairment in any memory test according to the normative data [18], but normal functioning on visuospatial, language, and executive functioning. For multidomain amnestic-MCI, impairment was required in memory and one or more other domains [1]. These criteria were used by the neurologists to make a diagnosis of MCI based on clinical judgment. To identify a homogenous group of MCI patients, and reduce the possibility of including a heterogeneous syndrome with non-AD related etiologies, exclusion criteria were

applied. MCI patients with Major Depressive Disorder were excluded if meaningful clinical improvement in cognition (defined as no longer fulfilling MCI criteria) accompanying improvement in depression was observed within six months of antidepressant treatment initiation. Patients with potential vascular impairment were excluded if they had Hachinski Ischemic scale score > 4 or MRI evidence of white matter lesions identified through consensus by a neuropsychologist expert in neuroimaging and a neuroradiologist. Finally, a thorough clinical examination was used to exclude patients with secondary cognitive deficits due to somatic disorders such as unbalanced diabetes, heart disease, or other major medical illnesses causing secondary cognitive impairment.

Diagnosis of psychiatric diseases

Patients underwent a structured interview that included diagnostic criteria for depression and apathy in AD [19,20]. Diagnosis was made by the examining psychiatrist. Compared to the criteria for Major Depressive Disorder, the criteria by Olin and colleagues [19] for the diagnosis of depression in AD have three distinctions. First, only three symptoms are required to be present, rather than five. Second, there are eleven categories of symptoms rather than nine. Third, these criteria do not require that symptoms are stable within a two-week period, but that the symptoms might fluctuate over the fortnight. Thus, these criteria are more sensitive for identifying depression in patients with cognitive impairment.

Apathy was diagnosed on the basis of the criteria set forth by Starkstein and collaborators [20], which require the presence of lack of motivation in addition to at least one symptom in each of these three domains: 1) diminished goal-directed behavior: a) lack of effort, b) dependency on others to structure activity; 2) diminished goal-directed cognition: a) lack of interest in learning new things or in new experiences, b) lack of concern about one's personal problems; and 3) diminished concomitants of goal-directed behavior: a) unchanging affect, b) lack of emotional responsivity to positive or negative events. The symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning. The symptoms are not due to a diminished level of consciousness or direct physiological effect of a substance (e.g., a drug of abuse or a medication).

Psychiatric symptoms

Behavioral and psychological symptoms were assessed using the Neuropsychiatric Inventory (NPI) [21] through interview with the informant. NPI symptoms of depression or apathy were used as continuous variables, and also dichotomized: no relevant symptoms (score$=0-1$) vs. presence of symptoms (score$=2-12$). A cutoff of $2+$ was used to examine the role of milder symptoms of apathy in patients without a diagnosis of a clinical Apathy disorder.

AD diagnosis

Patients were evaluated six months after baseline and on annual visits for up to four years to detect progression to AD. Diagnosis of probable AD was made by a clinical neurologist according to NINCDS-ADRDA criteria.

Ethics

After complete description of the study to subjects and informants, written informed consent was obtained. The study was approved by the Ethical Committee of Santa Lucia Foundation, Rome and was conducted in accordance with the Helsinki declaration.

Analyses

First, baseline characteristics of the study population were examined, including sociodemographics, MMSE, ADL, and Instrumental-ADL. Chi-square and student t-tests were used to examine differences in baseline characteristics between MCI patients with or without a diagnosis of apathy or depression. Second, we investigated baseline differences between MCI patients who underwent follow-up examination compared to patients who visited the clinic only once. Third, patients were followed for up to four years to identify progression to AD. The positive and negative predictive values, sensitivity, and specificity, of diagnosis and symptoms of depression and apathy for identifying progression to AD in amnestic-MCI patients were calculated. Kaplan Meyer survival curves were used to show conversion to AD in amnestic-MCI patients with a diagnosis of Apathy and Depression. Cox proportional hazard models with 95% confidence intervals (CI) were used to estimate the Hazard Ratios (HR) of developing AD: i) in patients with a diagnosis of Depression or Apathy at baseline; and ii) according to baseline score on

Table 1
Baseline characteristics of 131 amnestic-MCI patients, stratified by baseline diagnosis of apathy or depression

	All patients ($n = 131$)		Patients without Apathy ($n = 117$)		Patients with Apathy ($n = 14$)		Patients without Depression ($n = 83$)		Patients with Depression ($n = 48$)	
	n	%	n	%	n	%	n	%	n	%
Gender, male	77	58.8	68	58.1	9	64.3	53	63.9	24	50.0
Education, high	80	61.1	73	62.4	7	50.0	53	63.9	27	56.3
	Mean	*SD*	Mean	*SD*	Mean	*SD*	Mean	*SD*	Mean	*SD*
Age in years	70.8	6.5	70.9	6.5	69.5	6.8	71.6	6.8	69.3	5.6
ADL[1]	6.1	0.4	6.1	0.4	6.2	0.4	6.1	0.3	6.1	0.4
I-ADL[2]	6.9	2.1	6.8	2.0	7.6	2.5	6.7	2.0	7.2	2.2
MMSE[3]	27.2	2.0	27.2	2.1	26.7	1.4	27.1	2.0	27.3	2.1

[1]ADL: Activities of Daily Living.
[2]I-ADL: Instrumental Activities of Daily Living.
[3]MMSE: Mini-Mental Status Examination.
Chi square and t-tests showed no differences between patients with or without apathy on any baseline variables at the $p < 0.05$ level.
Chi square and t-tests showed no differences between patients with or without depression on any baseline variables at the $p < 0.05$ level.

NPI depression or apathy items, entered as continuous variables. For all analyses, crude and multiple-adjusted HRs were calculated. To investigate whether the NPI symptoms of apathy predict progression to AD, rather than a clinical diagnosis of apathy, the HR of AD progression was calculated in MCI patients with NPI symptoms of apathy, adjusted for baseline diagnosis of apathy. Finally, all survival analyses were run with additional adjustment for amnestic-MCI type at baseline (single vs. multiple domain).

RESULTS

131 patients were diagnosed with amnestic-MCI (61 single and 70 multidomain amnestic-MCI). Baseline characteristics are presented in Table 1. Forty-eight (36.6%) MCI patients had a diagnosis of depression and 14 (10.7%) had apathy. Seven patients had a diagnosis of both depression and apathy. Over half the patients ($n = 76$, 58.0%) were free from depression or apathy. There were no differences in baseline characteristics of patients with or without a diagnosis of apathy, or between patients with or without a diagnosis of depression.

Patients were followed for up to four years to detect progression to dementia. Thirty-two (24.0%) patients were only examined at baseline, and they had lower mean loss of instrumental-ADL at baseline than patients with follow-up, but all other baseline characteristics were the same at the $p < 0.05$ level, as shown in Table 2, including baseline diagnosis of apathy and depression. Reasons for dropping out included death, change of medical practitioner, or refusal. Follow-up time was considered as i) the first examination point at which the patient progressed to a diagnosis of AD or ii) the last examination point in cases where patients did not convert to AD. The mean follow-up time to AD diagnosis or last examination (in patients who did not develop AD) was 16.3 months (SD=10.1); maximum 48 months. Fifteen MCI patients (15.2%) progressed to AD. No patients converted to other forms of dementia.

Table 3 shows the risk of progressing from MCI to AD in patients with a diagnosis of Depression or Apathy, respectively, and survival curves are show in Fig. 1. Patients with a diagnosis of Depression did not have an increased risk of AD. However, patients with a diagnosis of Apathy had an almost seven-fold risk of developing AD over follow-up than patients without Apathy, after adjustment for sociodemographics, baseline MMSE, and Depression diagnosis. For identifying which MCI patients progressed to AD, Apathy Diagnosis had a positive predictive value of 50.0 and a negative predictive value of 87.4. The sensitivity was 35.3 and the specificity was 92.7.

Table 3 also shows the hazard ratios of progressing to AD according to baseline NPI score on the items assessing depression and apathy symptoms (continuous variables). No association was found between NPI symptoms of depression and progression to AD. The risk of developing AD increased by 20% per point increase on the NPI apathy item, after multiple adjustment. The NPI apathy item score was dichotomized into no relevant symptoms (score=0−1) versus symp-

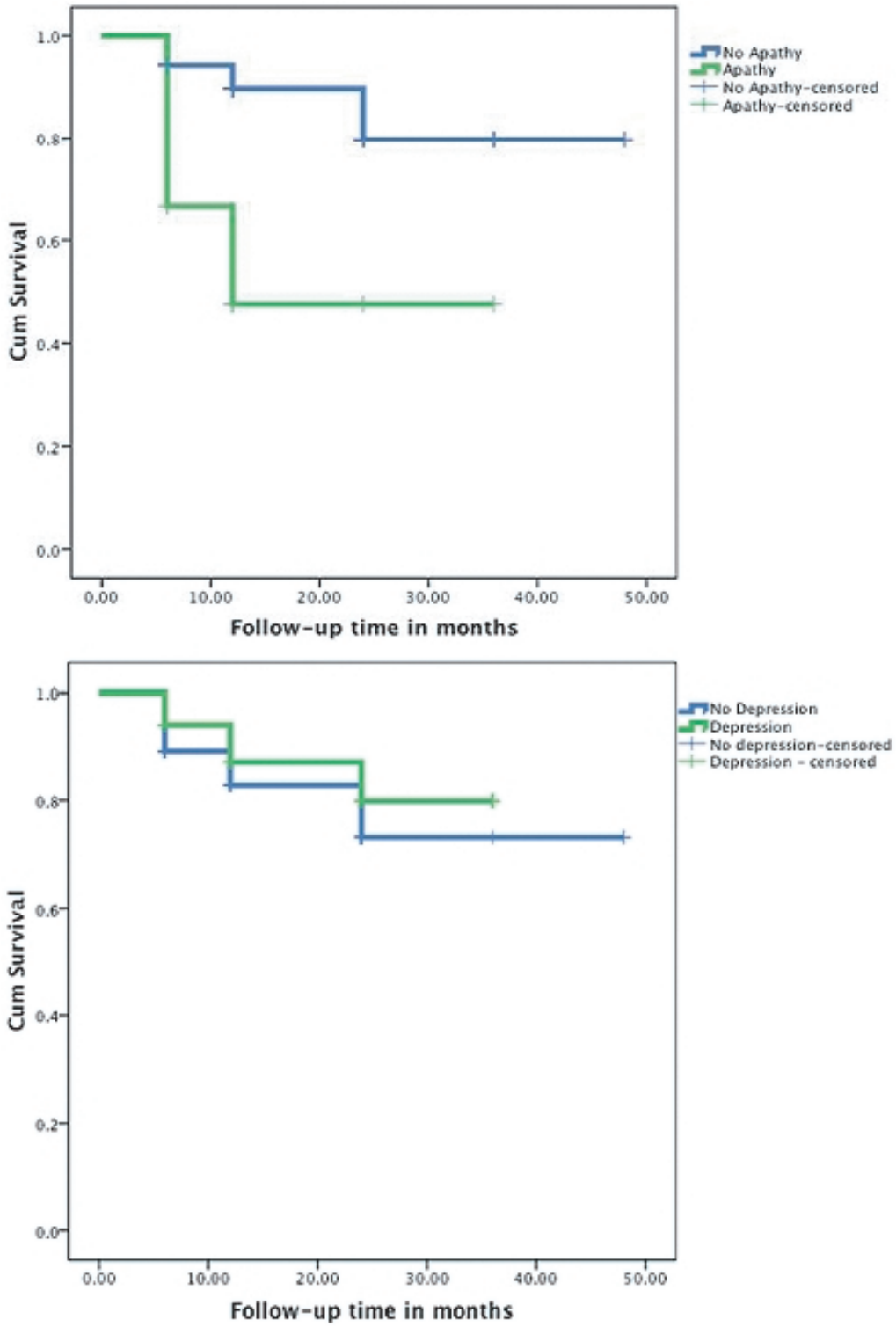

Fig. 1. Survival curve: conversion to Alzheimer's disease in Mild Cognitive Impairment patients with a diagnosis of Apathy or Depression.

Table 2
Baseline characteristics of amnestic-MCI patients who underwent follow-up compared to dropouts

	Patients with follow-up ($n = 99$)		Dropouts ($n = 32$)		
	n	%	n	%	*P value**
Gender, male	62	62.6	15	46.9	0.086
Education, high	57	57.6	23	71.9	0.149
Diagnosis of Depression	34	34.3	14	43.8	0.337
Diagnosis of Apathy	12	12.1	2	6.3	0.350
	Mean	*SD*	Mean	*SD*	
Age in years	70.5	6.6	71.4	6.2	0.613
ADL[1]	6.1	0.4	6.1	0.3	0.115
Instrumental-ADL	6.7	1.9	7.3	2.4	0.003
MMSE[2]	27.1	2.0	27.3	2.1	0.872

[1]ADL: Activities of Daily Living.
[2]MMSE: Mini-Mental Status Examination.
*Chi square and t-tests for differences between patients without or without follow-up.

Table 3
Risk of developing AD over up to four years in MCI patients with depression or apathy

			Progression from MCI to AD over 4 years	
	n	%	Crude HR[1] (95% CI)	Adjusted HR[1] (95% CI)
Psychiatric diagnosis				
Depression	5	14.7	0.7 (0.2–2.0)	0.6[2] (0.2–1.8)
Apathy	6	50.0	4.6 (1.7–12.6)	6.9[3] (2.3–20.6)
NPI score (continuous)				
Depression per symptom			1.1 (0.9–1.3)	1.0[4] (0.7–1.3)
Apathy per symptom			1.3 (1.1–1.4)	1.2[4] (1.0–1.6)[5]

[1]Hazard ratio (HR) and 95% confidence intervals (95% CI) calculated with Cox proportional hazard models.
[2]Adjusted for age, gender, education, baseline MMSE, and diagnosis of apathy.
[3]Adjusted for age, gender, education, baseline MMSE, and diagnosis of depression.
[4]Adjusted for age, gender, education, baseline MMSE, and baseline diagnosis of apathy or depression.
[5]Hazard ratio statistically significant (CI=1.012–1.566, $p = 0.39$).

toms of apathy (score=2+) to investigate the role of apathy symptoms independently of an Apathy diagnosis. The risk of progressing from MCI to AD was more than four times higher in patients with NPI symptoms of apathy (HR=4.6, CI=1.3−16.2) even after multiple adjustment, including adjustment for baseline diagnosis of Apathy (26% of patients with NPI apathy score of 2+ had a baseline diagnosis of Apathy). For identifying which MCI patients progressed to AD, the NPI symptoms of apathy cutoff score (2+) had a positive predictive value of 30.0 and a negative predictive value of 91.5. The sensitivity was 70.6 and the specificity was 65.9.

Of the patients who underwent follow-up, 27 were free from symptoms and diagnoses of both apathy and depression at baseline, and only two of these patients (7.4%) developed AD, whereas 92.6% did not develop AD during follow-up. Finally, all analyses were rerun making additional adjustment for type of MCI deficit (single vs. multiple-domain MCI), and the results remained unchanged. For example, after adjustment, the HR for progressing from MCI to AD for patients with depression vs. no depression was 0.6 (0.2–1.7) and for apathy was 8.5 (2.5–28.9).

DISCUSSION

In our clinical study, apathy was a strong predictor of progression from amnestic-MCI to AD. This association was found both for a diagnosis of Apathy and for NPI symptoms of apathy. No increased AD risk

was found in patients with Depression. The association between apathy symptoms or diagnosis and impending AD was independent from sociodemographic factors, cognitive and functional status, depression, or presence of single or multiple cognitive deficits. Finally, our study highlighted that patients free from depression or apathy were unlikely to progress from amnestic-MCI to AD over four years.

We found a sevenfold increased risk of AD progression in amnestic-MCI patients with a diagnosis of Apathy, in line with previous findings [12–14]. One study [14] reported an increased two-year dementia risk in MCI patients with Apathy. Almost a fifth of their dementia patients had a non-AD form, and they included also non-amnestic MCI. Another study [12], reported a difference in baseline apathy symptoms in MMSE-impaired MCI patients who developed AD over one year. Our study uniquely investigated progression specifically to AD, in patients with a thorough clinical diagnosis of amnestic-MCI. Interestingly, not only a diagnosis of Apathy, but also milder symptoms of apathy measured with the NPI were predictive of impending AD, independently from an Apathy diagnosis. Thus, in the absence of a full psychiatric diagnosis, symptoms assessed with the widely-used NPI are also of clinical value, suggesting that physicians should include a comprehensive psychiatric assessment in their evaluation. Further, physicians should consider the increased risk of progression to AD in MCI patients who exhibit mild symptoms of apathy, even if they do not fulfill diagnostic criteria for an Apathy disorder.

Although apathy is correlated to cognitive and behavioral functioning, the association between apathy and impending AD was independent from these characteristics, as it was still present after multiple adjustment. Apathy is prevalent in MCI [7,8] occurring in more than a third [8]. Hallucinations or delusions in MCI could have extremely high positive predictive value for impending AD, but their prevalence is low; 0.4% have hallucinations and 2.6% have delusions [7]. Rare symptoms have a low sensitivity for identifying large proportions of people in the preclinical AD stage. As apathy has both a high prevalence in MCI plus a good prediction for identifying impending AD, more people can be potentially identified.

Apathy is a frequent neuropsychiatric disturbance in AD [15], which may be due to frontal dysfunction. A structural MRI study in AD [22] showed an association between apathy and medial frontal region structural abnormality. In AD patients with apathy, there is neuropathological evidence of increased neurofibrillary tangle burden in the anterior cingulate cortex [23]. Attention and executive functioning may be associated specifically with functional losses in ADL, and thus, apathy may be a clinical sign of deficits in executive functioning that mark the transition from MCI to a full dementia syndrome. Alternatively, apathy could be a subjective reaction to cognitive problems. However, this hypothesis is less likely, as depression could also be a subjective response to memory problems, yet it was unrelated to impending AD in our study.

Amnestic-MCI patients with depression had no increased AD risk, supporting previous reports [9,11]. Findings suggesting depressive symptoms are frequent in MCI but are not associated with prodromal dementia are important considering the hypothesis that MCI has heterogeneous etiologies.

Our results underlie the importance of distinguishing apathy from depression, even though apathy may be a symptom of depression. Although depression and apathy often co-occur in AD, there is evidence suggesting distinct neurobiological roles and support for considering them as two distinct syndromes [15]. Depression is further complicated by the fact that it is a risk factor for other conditions, including vascular disease, diabetes, etc. We reduced bias by excluding the confounding effect of depression, vascular disease, and somatic disorders. Our adjustment for ADLs may further control for other severe diseases. Our results support the notion that depression and apathy are distinct entities, even in cognitive impairment syndromes [15], and emphasize the need for thorough psychiatric evaluation of cognitively impaired elderly, with scales differentiating depression from apathy.

Another relevant finding was that few amnestic-MCI patients who were free from diagnoses and symptoms of depression and apathy developed AD. This suggests that memory impairment, without accompanying affective disorders, has a low likelihood of being caused by an ongoing AD-related neurodegenerative etiology. Although it is important to inform a patient of potential AD-related disease progression prognosis, it is of equal importance to discuss with a patient when their risk of developing AD is not very high. The information also enables the physician to focus investigation on alternative potential causes of the memory disturbances.

Some limitations deserve mention. First, our patients were referred to the clinics by general practioners and may not represent the general population. Nevertheless, this may have increased the homogeneity of our sample, and consequently the clinical relevance of our findings. Second, we were unable to investigate dif-

ferences in patients with both depression and apathy as opposed to apathy alone, as we did not have a sufficient subsample size. However, the study was sufficiently powered for all the other multivariate analyses, and the results remained unchanged after adjustment for presence of apathy or depression. Third, we included both single- and multiple-domain amnestic-MCI. However, all results remained the same after adjustment for single- or multi-domain subtype. Fourth, although our aim was to investigate the role of depression and apathy, there may be other relevant risk factors that predict conversion from MCI to AD that will be of interest to investigate in future studies. Finally, there was a difference in instrumental-ADL functioning between patients who participated in the follow-up and dropouts, which may have affected the results. However, all other baseline characteristics were the same between the two groups, including the frequency of baseline diagnoses of apathy and depression. The strengths of our study include the large number of patients, assessment of psychiatric diagnoses as well as symptoms, and extensive examination at all follow-ups. A unique aspect of our study was the diagnostic procedure. We specifically investigated potential concurrent disorders that may be etiologically associated, including MCI secondary to Major Depressive Disorder, vascular disease, and other somatic disorders, to select a homogenous group of amnestic-MCI patients with a special focus on progression to AD-type dementia, to increased understanding of the mechanisms underlying the evolution of AD.

Although patients were followed for up to four years, some patients had shorter follow-up times, due to the inclusion of recently-diagnosed patients. Caution should be taken when interpreting our mean follow-up of less than two years. Follow-up time was considered to be the last clinical examination or the first examination point at which the patient converted to AD. All analyses were conducted with survival analyses taking into account time of follow-up.

The progression rate from MCI to AD in our study seems lower than commonly-reported figures. However, a recent meta-analysis [5] showed that annual conversion is greatly variable among studies, and lower than previously expected (8.1% in clinical settings, and 6.8% in community settings). Pooled-analyses [4] showed that the proportion of MCI patients converting to dementia decreases with increasing follow-up periods, suggesting that initial reports of conversion of 10–15% per year are only valid for short observation periods. All our patients underwent thorough clinical examination to diagnose AD at all follow-ups. These points support our results and suggest that our conversion rates are accurate.

The use of diagnostic criteria for apathy and depression specific for AD patients is both a limitation and a strength. The criteria for depression in AD [19] differ from DSM criteria, as they require the presence of only three symptoms; they include two additional types of symptoms, and although symptoms should be present for a two-week period, they do not need to be stable. This may account for the relatively high prevalence of depression among the MCI patients in our study. However, these criteria are more sensitive for detecting depression in patients with AD, and thus, may be more sensitive in patients with other types of cognitive impairment such as MCI.

Our results have implications for patients, caregivers, and healthcare providers. Early detection of AD is valuable for individuals' planning care and finances. Although current clinical trials of pharmaceutical treatment in MCI have limited success [24,25], early AD identification can help to target future interventions and may identify suitable candidates for clinical trials or cognitive rehabilitation [26,27]. Identifying markers that are less evasive, quicker, and cheaper than neuroimaging or biomarkers has relevant implications. Psychiatric evaluation is part of routine clinical practice in memory clinics. Thus, our findings identify convenient markers of AD that can easily be incorporated into routine patient assessment.

Our study provides evidence of a role of apathy in the progression from amnestic-MCI to AD. Apathy may be a convenient, simple marker to use in clinical settings to identify patients who later develop AD. These findings may also help to understand the ongoing degeneration in AD, and identify regions that may degenerate at earlier phases of the disease. Patients with amnestic-MCI who have a concurrent diagnosis or symptoms of apathy should be closely monitored in the clinical setting.

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