Mild Behavioral Impairment and Risk of Dementia: A Prospective Cohort Study of 358 Patients

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Background: Mild cognitive impairment (MCI) is a transitional state between normal aging and dementia, at least for some patients. Behavioral symptoms in MCI are associated with a higher risk of dementia, but their association with dementia risk in patients without MCI is unknown. Mild behavioral impairment (MBI) refers to a late-life syndrome with prominent psychiatric and related behavioral symptoms in the absence of prominent cognitive symptoms that may also be a dementia prodrome. This study sought to compare MCI and MBI patients and to estimate the risk of dementia development in these 2 groups.

Method: Between January 2001 and January 2006, a consecutive series of 358 elderly (≥ 65 years old) patients (239 with MCI and 119 with MBI) presenting to an outpatient general hospital specialty clinic were followed for up to 5 years until conversion to dementia or censoring.

Results: Thirty-four percent of MCI patients and over 70% of patients with MBI developed dementia (log-rank $p = .011$). MBI patients without cognitive symptoms were more likely to develop dementia (log-rank $p < .001$). MBI patients were more likely to develop frontotemporal dementia (FTD) than dementia of the Alzheimer's type (DAT).

Conclusion: MBI appears to be a transitional state between normal aging and dementia. MBI (specifically in those without cognitive symptoms) may confer a higher risk for dementia than MCI, and it is very likely an FTD prodrome in many cases. These findings have implications for the early detection, prevention, and treatment of patients with dementia in late life, by focusing the attention of researchers on the emergence of new behavioral symptoms.

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See also Commentary on page 582.

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Dementia is a major public health problem because of its growing prevalence and economic impact.[1–3] It is a chronic condition with global consequences that seriously impacts patients, their families, and society.[4] An understanding of the prodromal states or early clinical presentations of dementia is a significant priority, since it would aid early detection, facilitate early treatment, and could lead to effective prevention. Mild cognitive impairment (MCI) is a cognitive disturbance of older persons, more severe than that which would be expected for age and education but not of sufficient severity for a diagnosis of dementia.[5] Several operational definitions for MCI have been proposed,[5,6] and at least 2 subtypes have been described[7]: amnestic, thought to be mainly the prodrome of dementia of the Alzheimer's type (DAT), and nonamnestic, thought to be mainly a prodrome of other dementias such as frontotemporal dementia (FTD), vascular dementia (VaD), or dementia with Lewy bodies (DLB).

In the last several years, there has been growing awareness of the importance of neuropsychiatric symptoms (NPS) in dementia, given their nearly universal occurrence over the course of dementia, associated caregiver burden, and association with early institutionalization.[8–12] Whereas dementia is still defined as a cognitive disorder, neuropsychiatric symptoms are now regarded as

an intrinsic aspect of dementia and the underlying causes, usually neurodegenerative processes.

Neuropsychiatric symptoms are common in dementia,[8–12] but they have not been extensively studied in the prodromal states of dementia. In a population-based study, the most common NPS in MCI were apathy, depression, agitation, delusions, hallucinations, and sleep impairment.[13] In MCI patients, the occurrence of NPS was associated with a higher risk of dementia onset. For example, depression in MCI has been reported to double the risk of dementia.[14] Furthermore, cognitively normal elderly individuals who develop depression are at increased risk of subsequent MCI.[15] However, not all prodromal states involve prominent cognitive impairment. Many patients develop NPS as the first indicator of impending dementia. This is most common in patients with FTD, but it is also the case in patients with DAT. For example, we reported that, in 50% of a series of dementia patients who consulted our service, NPS were the first indication of change, before the occurrence of cognitive symptoms. Of the latter patients, 36% had FTD, 28% had DAT; 18% had VaD, and 18% had other types of dementia.[16] As a result, we proposed the syndrome of mild behavioral impairment (MBI), consisting of (1) persistent behavioral changes and mild psychiatric symptoms, especially disinhibition; (2) no serious cognitive complaints; (3) normal activities of daily living; and (4) absence of dementia.[16–18] MBI has been hypothesized to confer increased risk for dementia development, especially of FTD, whether or not significant cognitive symptoms are present. Here we report a validation of the MBI construct in a longitudinal study. Our aims were to compare MBI patients with MCI patients and to examine the risk of dementia development, especially FTD, in MBI patients compared to MCI patients.

METHOD

Design and Setting

This was a prospective cohort study of outpatients with MBI and MCI. The study was performed under the oversight of the Institutional Review Board of the University Institute Center for Medical Education and Clinical Research (CEMIC). Each participant or a legal representative provided oral informed consent for participation.

Participants

Between January 2001 and January 2006, a consecutive series of 1496 new elderly (≥ 65 years old) outpatients was evaluated at the Psychogeriatric Unit of the University Institute CEMIC in Buenos Aires, Argentina. Patients were referred from 2 sources: 1133 from the CEMIC Department of Internal Medicine and 363 from community general practitioners. After a complete neuropsychiatric assessment, 425 presented with cognitive and/or behavioral symptoms; of these, 119 were found to have MBI and 239 were found to have MCI. Another 17 presented with late-onset primary psychotic disorders.

Diagnostic Criteria

MBI was defined as a behavioral disturbance not meeting DSM-IV[19] or National Institute of Neurological Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria[20] for dementia, psychosis, or another major psychiatric condition and also not meeting criteria for MCI of any type. MBI was operationalized using the following criteria for inclusion in the study: (1) the presence of a major change in patient behavior, (2) occurring later in life (> 60 years old) and persistent (> 6 months); (3) with no complaint of cognitive impairment by patient/informant; (4) normal occupational and social functioning; (5) normal activities of daily living; and (6) absence of dementia. The loss of independence criterion was crucial for ruling out dementia at baseline and follow-up, and it was operationalized as follows: cognitive deficits caused significant impairment in normal occupational and/or normal social functioning and/or normal activities of daily living.

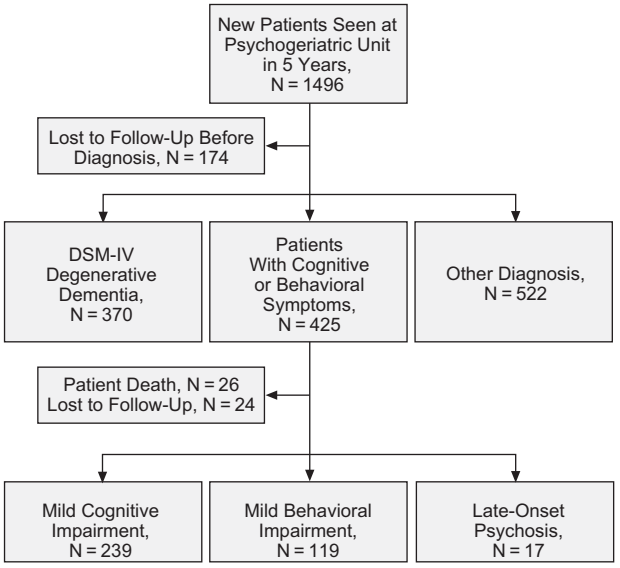
For the purpose of this study, a patient with cognitive complaints and neuropsychiatric symptoms (plus remaining criteria) was considered to have MCI. A patient with major persistent change in behavior but no cognitive complaints from either the patient or the caregiver was considered to have MBI, regardless of whether cognitive impairment was subsequently found on testing or not.

MBI was considered absent if the patient had (1) another concomitant neurological or psychiatric disorder that could better explain disturbances (e.g., epilepsy, major stroke, tumors, or schizophrenia), (2) behavioral disturbances of acute onset, and (3) alcohol or substance abuse.

Examples of major persistent changes in patient behavior that might have led to a diagnosis of MBI are as follows: agitation, anxiety symptoms, apathy, aspontaneity, delusion symptoms, depressive symptoms, disinhibition, emotional lability, euphoria, impulsivity, indifference, irritability, lack of empathy, loss of insight, loss of personal hygiene, loss of social tact, oral/dietary changes, perseverant behavior, sleep disorders.

MCI[21] was defined as cognitive decline not meeting DSM-IV criteria for dementia. It was operationalized using results of neuropsychological testing in 2 groups as follows, with both groups considered as one in this study: (1) Patients were considered to have MCI amnestic-type if they met the following criteria: memory complaint, normal activities of daily living, normal general cognitive function, abnormal memory function for age (defined as a score on a standardized test that was 1.5 SD below the mean compared with individuals of the same age and level of education); and (2) Patients were considered to

Figure 1. Patient Recruitment Flow



have nonamnestic MCI if they met the following criteria: cognitive complaints, normal activities of daily living, abnormal cognitive function for age (defined as a deterioration in at least 1 cognitive domain not including memory or 1 abnormal test 1.5 SD below the mean adjusted for age and education in at least 2 other domains).

Follow-Up and Outcome Assessment

Patients were assessed at baseline and every 4 months or when necessary using a comprehensive approach, for up to 5 years. The median follow-up for MBI was 30 months and for MCI was 24 months. Loss to follow-up was < 12%: 26 patients died, and 24 were lost to follow up for other reasons (Figure 1).

Data collected at baseline included sociodemographic and clinical variables such as age at assessment, years of education, sex, marital and retirement state, socioeconomic level, and number of times patients were seen by psychiatrists during the study. Physical examination and laboratory analysis were performed as clinically appropriate for each patient. Neuroimaging examinations using brain CT, and as appropriate magnetic resonance imaging (MRI) or single-photon emission computed tomography (SPECT) were assessed. At each visit, neurological examination findings, such as primitive reflexes, were assessed, as were medical history, blood pressure, medications, physical function, and social support. The following cognitive assessment battery was also administered by blinded raters to the group using validated translated versions: Signoret memory tests,[22] the Wechsler Abbreviated Scale of Intelligence,[23] the Buenos Aires adaptation of the Spanish version of the Boston Naming Test,[24] the Mini-Mental State Examination (MMSE),[25] and the Trail Making Test.[26] At each examination, we used the Neuropsychiatric Inventory (NPI)[27] to assess the occurrence and severity of NPS. The NPI has wide acceptance as a measure of NPS associated with cognitive disorders. It is a fully structured interview, which obtains its information from an informant knowledgeable about the participant. It focuses on observable symptoms and behaviors. Depressive symptoms were assessed using the Beck Depression Inventory.[28] Two of the authors (F.E.T., R.F.A.) reviewed the data from each visit to determine at each time point whether a given patient had converted to dementia using the baseline DSM-IV or NINCS-ADRDA criteria.[19,29–31]

Statistical Analysis

Initially, analyses were performed to compare the MCI and MBI patients at baseline. Categorical variables were expressed as percentages; for continuous variables, means and standard deviations were estimated, while for non–normally distributed variables, medians and percentiles were considered. When frequency differences were compared by diagnosis, univariate analyses were carried out using χ^2 tests. Student t tests were used to compare groups on continuous variables, while the nonparametric Wilcoxon rank sum test was applied to compare groups on non–normally distributed variables. Survival analyses were then conducted to compare groups on time to onset of dementia. The main outcome was diagnosis of dementia. The time to dementia was considered the outcome of interest. The follow-up period was from the initial observation to dementia conversion or to the end of the study. Cox proportional hazards models were also estimated to test multivariate associations between multiple explanatory variables and dementia conversion in patients with MBI compared to MCI. Effects are shown as hazard ratios (HRs), with 95% CIs. For all analyses, the Stata 8.0 statistical software package was used (StataCorp LP, College Station, Tex.).

RESULTS

Comparison of the MBI and MCI Groups at Baseline

Table 1 shows demographic characteristics of the study groups. There were no differences between the MBI and MCI groups on demographic characteristics. The MBI participants were followed up longer by 6 months at the median but had a similar median number of follow-up visits.

Table 2 compares the groups on baseline clinical and laboratory characteristics. The MCI group was more likely to have dyslipidemia,[32,33] or hypothyroidism,[34] found on questioning of past medical history but not in the lab screening for altered thyroid gland by the determination of serum thyroid-stimulating hormone levels (data

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Table 1. Demographic Characteristics at Baseline

Characteristic	MCI (N = 239)	MBI (N = 119)	Comparison
Age at evaluation, mean (SD), y	72.3 (7.8)	72.91 (8.9)	t = 0.626, p = .531[a]
Sex, male, N (%)	98 (41)	56 (47)	χ^2 = 1.188, df = 1, p = .276[b]
Married, N (%)	159 (67)	84 (7)	χ^2 = 0.600, df = 1, p = .438[b]
Education, median, y	12	12	z = 1.187, p = .235[c]
Retired, N (%)	182 (76)	109 (92)	χ^2 = 2.350, df = 1, p = .125[b]
Follow-up in study			
Median, mo	24.15	30.00	z = –4.213, p < .001[c]
10th percentile	9.00	12.00	
90th percentile	51.89	60.00	
Median visits, no.	7	8	z = –2.723, p = .006[c]
10th percentile	2	4	
90th percentile	21	21	

[a]t test.
[b]Pearson χ^2.
[c]Wilcoxon rank sum test.
Abbreviations: MBI = mild behavioral impairment, MCI = mild cognitive impairment.

Table 2. Baseline Clinical and Laboratory Characteristics

Characteristic	MCI (N = 239), N (%)	MBI (N = 119), N (%)	Comparison
Arterial hypertension	79 (33.1)	45 (37.8)	χ^2 = 0.795, df = 1, p = .372[a]
Diabetes	19 (7.9)	7 (5.9)	χ^2 = 0.504, df = 1, p = .478[a]
Dyslipidemia	72 (30.1)	13 (10.9)	χ^2 = 16.177, df = 1, p < .001[a]
Mild hypothyroidism	35 (14.6)	8 (6.7)	χ^2 = 4.717, df = 1, p = .030[a]
Psychiatric medication			
Antidepressant	99 (41.4)	21 (17.6)	χ^2 = 20.152, df = 1, p < .001[a]
Antipsychotic	33 (13.8)	26 (21.8)	χ^2 = 3.732, df = 1, p = .053[a]
Benzodiazepine	85 (35.6)	23 (19.3)	χ^2 = 9.942, df = 1, p = .002[a]
Family history of dementia	40 (16.7)	26 (21.8)	χ^2 = 1.380, df = 1, p = .240[a]
Pyramidal signs on examination	28 (11.7)	26 (21.8)	χ^2 = 6.368, df = 1, p = .012[a]
Extrapyramidal signs on examination	22 (9.2)	40 (33.6)	χ^2 = 33.054, df = 1, p < .001[a]
Primitive reflexes	38 (15.9)	59 (49.6)	χ^2 = 45.621, df = 1, p < .001[a]
Altered hematocrit	2 (0.8)	5 (4.2)	0.043[b]
Hypercholesterolemia	23 (9.6)	4 (3.4)	0.035[b]

[a]Pearson χ^2.
[b]Fisher exact.
Abbreviations: MBI = mild behavioral impairment, MCI = mild cognitive impairment.

not shown). The MCI group was also more likely to be taking antidepressants and benzodiazepines (substance-induced persisting amnestic disorder patients were already excluded at baseline), which might explain their relatively low anxiety and depression scores on the NPI (below). In contrast, the MBI group was more likely to have neurologic signs and primitive reflexes.[35,36] Altered hematocrit and hypercholesterolemia were the laboratory values with significant differences between groups.

Table 3 compares the groups on baseline cognitive complaints and test results. By definition, all MCI patients had memory complaints. In the MBI group, we found that 49.6% of patients had cognitive symptoms discovered by raters, even though these symptoms were not a complaint for either the patient or the family. MCI patients had lower scores on memory tests, while MBI patients had lower scores on tests of executive function and IQ domains.

Table 4 compares the groups on NPS. Because of the inclusion criteria, all MBI patients had persistent changes in behavior. While 85 MCI patients (35.6%) had behavioral disturbances reported by relatives on the NPI (χ^2 = 134.562, df = 1, p < .001), a smaller group of 23 (9.6%) showed a persistent major change in patient behavior occurring later in life (χ^2 = 271.1424, df = 1, p < .001). The 2 groups differed on a number of NPS. Depression and anxiety scores were lower in the MCI group, possibly related to their more frequent use of antidepressants. Although change in behavior was an inclusion criterion for MBI, no patients had a psychosis-specific disorder.

Table 5 compares the groups on neuroimaging characteristics. Most MBI patients had brain imaging carried out for clinical reasons. While there were no major differences in CT or MRI findings, the MBI group was more likely to show decreased perfusion in frontal or temporal lobes on SPECT.

Conversion to Dementia

Figure 2 compares time to dementia onset between the 2 groups on Kaplan-Meier plots, adjusted for age. Demen-

Table 3. Cognitive Complaints and Test Results at Baseline

Results	MCI (N = 239)	MBI (N = 119)	Comparison
Cognitive symptoms, N (%)	239 (100)	59 (49.6)	$\chi^2 = 141.878$, df = 1, $p < .001$[a]
Mini-Mental State Examination score, mean (SD)	27.4 (1.8)	26.1 (2.1)	$t = 4.420$, $p < .001$[b]
Signoret Memory Battery			
Paragraph recall, median	5	7	$z = -7.064$, $p < .001$[c]
Paragraph delay recall, median	4	5	$z = -3.781$, $p < .001$[c]
List of words, median	7	8	$z = -5.099$, $p < .001$[c]
Retention, median	4	6	$z = -5.305$, $p < .001$[c]
Recall with clues, median	7	8	$z = -1.607$, $p = .108$[c]
Recognition, median	11	10	$z = 2.790$, $p = .005$[c]
Boston Naming Test, mean (SD)	49.6 (0.43)	47.9 (0.64)	$t = 2.2663$, $p = .024$[b]
Semantic fluency, median	15	14	$z = 2.169$, $p = .030$[c]
Phonological fluency, median	12	11	$z = 0.433$, $p = .665$[c]
Digit Span, median	8	6	$z = 6.760$, $p < .001$[c]
Trail Making B, mean (SD)	125.7 (8.37)	158.9 (8.50)	$t = -2.616$, $p = .009$[b]
Wechsler Abbreviated Scale of Intelligence			
Vocabulary, median	55	50	$z = -0.359$, $p = .719$[c]
Similarities, median	48	37	$z = -0.359$, $p = .719$[c]
Block Design, median	42	32	$z = -4.707$, $p < .001$[c]
Matrix Reasoning, median	40	36.5	$z = -3.856$, $p < .001$[c]
Verbal IQ, mean (SD)	107.8 (1.88)	96.7 (1.03)	$t = 4.3335$, $p < .001$[b]
Performance Scale IQ, mean (SD)	95.5 (1.04)	88.9 (0.91)	$t = 4.3467$, $p < .001$[b]
Global IQ, mean (SD)	101.1 (0.96)	92.3 (0.85)	$t = 6.2819$, $p < .001$[b]

[a]Pearson χ^2.
[b]t test.
[c]Wilcoxon rank sum test.

Table 4. Neuropsychiatric Characteristics at Baseline

Characteristic	MCI (N = 239), N (%)	MBI (N = 119), N (%)	Comparison
Neuropsychiatric symptoms as assessed on the NPI	85 (35.6)	119 (100)	$\chi^2 = 134.562$, df = 1, $p < .001$[a]
Delusions	22 (9.2)	67 (56)	$\chi^2 = 94.3368$, df = 1, $p < .001$[a]
Hallucinations	9 (3.8)	22 (18.5)	$\chi^2 = 21.7688$, df = 1, $p < .001$[a]
Agitation	22 (9.2)	31 (26.1)	$\chi^2 = 17.8737$, df = 1, $p < .001$[a]
Depression	40 (16.7)	57 (47.9)	$\chi^2 = 39.0560$, df = 1, $p < .001$[a]
Anxiety	40 (16.7)	54 (45.4)	$\chi^2 = 33.6585$, df = 1, $p < .001$[a]
Euphoria/negation	6 (2.5)	9 (7.6)	$\chi^2 = 5.0520$, df = 1, $p < .001$[a]
Apathy/indifference	28 (11.7)	35 (29.4)	$\chi^2 = 17.1565$, df = 1, $p < .001$[a]
Disinhibition	26 (10.9)	58 (48.7)	$\chi^2 = 63.4130$, df = 1, $p < .001$[a]
Irritability	41 (17.2)	55 (46.2)	$\chi^2 = 34.1945$, df = 1, $p < .001$[a]
Aberrant motor behavior	10 (4.2)	26 (21.8)	$\chi^2 = 27.4081$, df = 1, $p < .001$[a]
Sleep	23 (9.6)	60 (50.4)	$\chi^2 = 74.2451$, df = 1, $p < .001$[a]
Appetite and eating disorders	19 (7.9)	32 (26.9)	$\chi^2 = 23.3305$, df = 1, $p < .001$[a]
Beck Depression Inventory score, median	9	12	$z = -4.583$, df = 1, $p < .001$[b]
Complaint of a major change in patient behavior occurring later in life and persistent	23 (9.6)	119 (100)	$\chi^2 = 271.1424$, df = 1, $p < .001$[a]

[a]Pearson χ^2.
[b]Wilcoxon rank sum test.
Abbreviations: MBI = mild behavioral impairment, MCI = mild cognitive impairment, NPI = Neuropsychiatric Inventory.

tia onset was faster in MBI patients (log-rank test for equality of survivor functions: p = .0114). Cox proportional hazards model estimation revealed that the risk of onset was 43% higher in MBI than in MCI (HR = 1.43, 95% CI = 1.01 to 2.03). After adjusting for age at diagnosis, this HR was essentially unchanged (HR = 1.48, 95% CI = 1.04 to 2.11).

MBI Participants With and Without Cognitive Symptoms, and MCI Participants With and Without Psychiatric Symptoms

As shown in Table 3, when the clinician examiners evaluated specifically for cognitive symptoms in MBI patients, 49.6% reported such symptoms. Also, as shown in Table 4, when they investigated specifically for psych-

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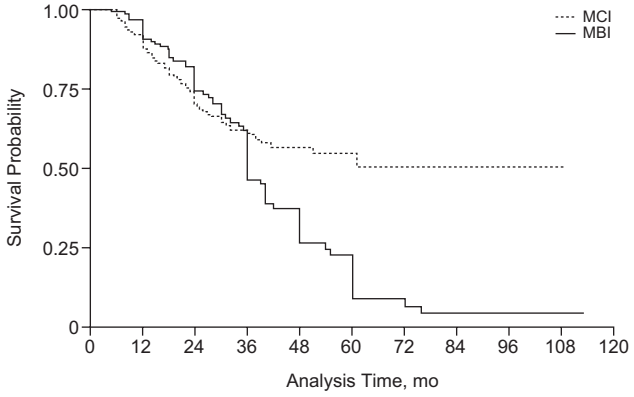
Table 5. Neuroimaging Comparison at Baseline

Results	MCI (N = 239), N (%)	MBI (N = 119), N (%)	Comparison
CT or MRI			
No image	87 (36.4)	5 (4.2)	$\chi^2 = 44.147$, df = 7, $p < .001$[a]
Normal	30 (12.6)	18 (15.1)	
(1) mild generalized atrophy	45 (18.8)	22 (18.5)	
(2) leucoareosis	34 (14.2)	10 (8.4)	
(3) mild focal atrophy	21 (8.8)	22 (18.5)	
(1) + (2)	11 (4.6)	4 (3.4)	
(1) + (3)	2 (0.8)	2 (1.7)	
(2) + (3)	9 (3.8)	0 (0.0%)	
SPECT			
No image	178 (74.5)	6 (5.0)	$\chi^2 = 141.870$, df = 4, $p < .001$[a]
Normal	22 (9.2)	7 (5.9)	
Decreased perfusion in parietal or temporal parietal lobes	18 (7.5)	15 (12.6)	
Decreased perfusion in several areas	1 (0.4)	4 (3.4)	
Decreased perfusion in frontal or frontal temporal lobes	20 (8.4)	51 (42.9)	

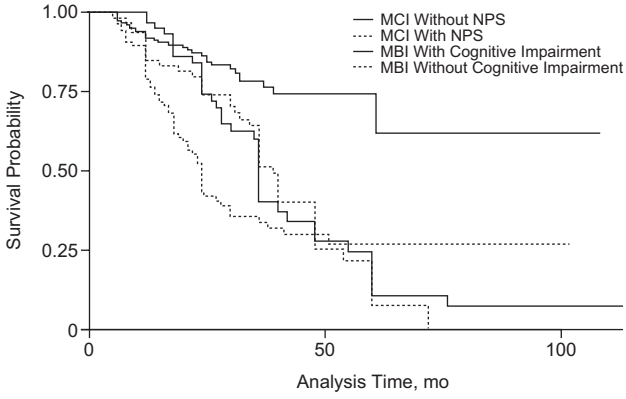
[a]Pearson χ^2.
Abbreviations: CT = computed tomography, MBI = mild behavioral impairment, MCI = mild cognitive impairment, MRI = magnetic resonance imaging, SPECT = single-photon emission computed tomography.

Figure 2. Kaplan-Meier Survival Estimates, Adjusted for Age, by Initial Diagnosis[a]



[a]Stratified log-rank test for equality of survivor functions: $\chi^2 = 8.94$, df = 2, Pr > $\chi^2 = 0.0114$.
Abbreviations: MBI = mild behavioral impairment, MCI = mild cognitive impairment, Pr = probability.

Figure 3. Kaplan-Meier Survival Estimates, Adjusted for Age, by Initial Diagnosis[a]



[a]Stratified log-rank test for equality of survivor functions: $\chi^2 = 42.87$, df = 3, Pr > $\chi^2 < 0.001$.
Abbreviations: MBI = mild behavioral impairment, MCI = mild cognitive impairment, NPS = neuropsychiatric symptoms, Pr = probability.

iatric symptoms in MCI patients, 35.5% reported such symptoms. Consequently, an analysis was performed to compare rates of conversion to dementia in the following groups: (1) MCI patients without neuropsychiatric symptoms, (2) MCI patients with neuropsychiatric symptoms, (3) MBI patients with cognitive symptoms, and (4) MBI patients without cognitive symptoms. MCI patients with psychiatric symptoms differed from MCI patients with no psychiatric symptoms, as they had a 4-fold increased risk of conversion to dementia (HR = 4.01, 95% CI = 2.5 to 6.3). Their risk was similar to that of MBI patients with cognitive symptoms ($\chi^2 = 2.46$, df = 1, p = .116). We also found, as shown in Figure 3, that MCI patients without NPS and MBI patients without cognitive symptoms were quite different in the time to dementia onset, which was much faster for MBI patients without cognitive symptoms than for MCI patients without NPS (log-rank test $\chi^2 = 42.87$, df = 3, $p < .001$). Table 6 displays data regarding dementia conversion rates and the type of dementia to which patients converted. While MCI patients without NPS converted mainly to DAT, and MBI patients without cognitive symptoms mainly converted to FTD,

Table 6. Comparison of Groups on Dementia Conversion

Patients Converted, N (%)	MCI Without NPS (N = 154)	MCI With NPS (N = 85)	MBI With Cognitive Symptoms (N = 59)	MBI Without Cognitive Symptoms (N = 60)	Comparison
To any dementia	29 (18.8)	54 (63.5)	41 (69.4)	44 (73.3)	$\chi^2 = 42.87$, df = 3, $p < .001$[a] $\chi^2 = 142.38$, df = 6, $p < .001$[b]
To FTD	0 (0)	15 (17.6)	12 (20.3)	41 (68.3)	
To DAT	28 (18.2)	37 (43.5)	25 (42.4)	2 (3.3)	
To DLB	1 (0.6)	2 (2.4)	4 (6.8)	1 (1.6)	

[a]Log-rank test for equality of survivor functions.
[b]Pearson χ^2.
Abbreviations: DAT = dementia of the Alzheimer's type, DLB = dementia with Lewy bodies, FTD = frontotemporal dementia, MBI = mild behavioral impairment, MCI = mild cognitive impairment, NPS = neuropsychiatric symptoms.

MCI patients with NPS and MBI patients with cognitive symptoms showed conversion risks similar to one another. Overall, there were 68 incident cases of FTD compared to 92 of DAT, and the highest risk of conversion for all types of dementia was seen in the MBI group without cognitive symptoms.

DISCUSSION

We examined conversion to dementia in 358 patients, 239 with MCI and 119 with MBI, over a 5-year period. We were specifically interested in the construct of MBI, which, as with MCI, has been proposed to represent a transitional state between normal aging and dementia. An obstacle to research progress in this area has been the lack of agreement on what constitutes behavioral impairment. In this study, MBI was defined using criteria first proposed in 2003. NPS were consistently and robustly associated with faster time to dementia conversion across groups. Although this outcome has previously been reported,[37–40] since the MBI group without cognitive complaints converted to dementia faster than the MCI group without psychiatric complaints, this study emphasizes the importance of NPS *even in the absence of cognitive symptoms*. Rates of dementia conversion in the MBI group with cognitive complaints were comparable to those in the MCI group with neuropsychiatric symptoms, suggesting that these 2 groups could probably be considered a single one. Finally, the presence of MBI was associated with clinical and neuroimaging evidence of abnormalities in the frontal regions of the brain and with a greater risk of conversion to FTD than to DAT. Hence, MBI, specifically in the absence of cognitive symptoms, probably represents an FTD prodrome, at least in about one half of cases.

Confidence in these findings is supported by several factors. First, the clinical definition of MBI was based on a standardized clinical examination, supplemented by the administration of widely used neuropsychiatric scales by experienced physicians. Second, the effect of NPS on conversion to dementia was observed with both dementia types (DAT and FTD), reducing the likelihood that diagnostic imprecision affected results. Third, the availability of 119 subjects with MBI with high follow-up participation over 5 years improved power to estimate associations between behavior, cognitive tests, clinical findings, brain imaging findings, and dementia incidence.

There are several limitations to consider in this study. One is the relatively short median follow-up of 30 months. Another is that the results were based on a selected group of patients referred for consultation to a psychogeriatric service. The fact that participants were referred by general practitioners is a strength that indicates the growing importance these practitioners are giving to NPS in late life. Nevertheless, they might have been biased to prescribe fewer psychiatric medications to MBI patients with apathy/indifference, which might in part explain the heterogeneous distribution of medications. While we cannot be entirely sure that MCI patients, who were more likely to be taking antidepressants and benzodiazepines, did not have MBI at some point before this study was started, we certainly looked for that possibility by searching records and questioning patients and family about a change in behavior.

Another limitation of this study is the possibility that lack of insight might have affected the reporting of both cognitive and behavioral complaints, which affected whether a diagnosis of MCI or MBI was made. Many patients lack insight into their own cognitive changes, and often family members and patients do not recognize behavioral changes. For this reason, the presence of specific complaints in either the cognitive or behavioral area is of great clinical significance: these complaints are typically the reason for which care is sought. The point is further reinforced by the analyses' showing strong associations between MBI without cognitive complaints and dementia conversion. In light of this evidence, we believe that the groups of MBI and MCI patients, defined in this way, are different enough to think of them as 2 separate groups for the purposes of this report. We are aware that there is overlap between the MCI with NPS and MBI with cognitive impairment groups. Therefore, the *no cognitive complaints* criterion of the MBI diagnosis should be

improved in future investigations to better differentiate these groups.

One more limitation of this study is the lack of an investigation of conversion *from MBI to MCI*. We know that the mean (SD) MMSE score of the MBI group without cognitive symptoms was 26.9 (1.42), while the mean (SD) score for the MBI group with cognitive symptoms was 25.7 (1.67), $t = 3.761$, $p < .001$. We are conscious that many patients might have converted from MBI to MCI, but we did not investigate this possibility in the study. This possibility would seem to be an important aspect of future research. While some of these limitations may affect the external validity (generalizability) of the study, they should not affect its internal validity. Nevertheless, it is important to replicate this study in other settings.

We conclude that MBI, specifically in the absence of cognitive symptoms, as with MCI, is a transitional state between normal aging and dementia, at least for some patients. MBI confers a higher risk of dementia conversion than MCI, with or without NPS, especially to FTD. These findings emphasize the importance of the emergence of NPS in later life as worrisome. Early detection of dementia and targeting of therapies, possibly even prevention, will very likely be served well by a better understanding of these observations. Further, it is possible that targeted treatment for MBI using available psychopharmacology might delay conversion to dementia.

Authors' contributions: **Drs. Taragano**, **Allegri**, **Krupitzki**, and **Lyketsos** were responsible for study concept and design, for analysis and interpretation of data, for drafting of the manuscript, for critical revision of the manuscript for important intellectual content, and for obtaining funding. **Drs. Taragano** and **Allegri** were responsible for acquisition of data and study supervision. **Dr. Krupitzki** provided statistical expertise. **Drs. Serrano**, **Sarasola**, and **Loñ** served as raters. **Drs. Serrano**, **Sarasola**, and **Loñ** provided administrative, technical, or material support.

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Alzheimer's Disease and Related Disorders section. Please contact Eric M. Reiman, M.D., at ereiman@psychiatrist.com.

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