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Neuropsychiatric Symptoms in Mild Cognitive Impairment: Differences by Subtype and Progression to Dementia

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Abstract

Background—Neuropsychiatric symptoms (NPS) are common in patients with mild cognitive impairment (MCI). Little is known, however, about how NPS vary by MCI subtype (i.e., amnesic, single domain non-memory, and multiple domain). In addition, it is unclear whether NPS increase risk of progression to dementia. We investigated the distribution of NPS across MCI subtypes and determined whether NPS increase risk of progression to dementia.

Method—Participants were 521 patients diagnosed with MCI at the Alzheimer's Research Centers of California between 1988 and 1999. At baseline, patients were classified into MCI subtypes and were assessed for NPS.

Results—The mean number of NPS was 2.3 (range 0-9.6; 74% had ≥ 1 NPS). Patients with ≥ 4 NPS had more medical comorbidities and greater functional impairment ($p \leq 0.0001$ for both). Patients with ≥ 4 NPS were more likely than patients with 0-3 NPS to have amnesic MCI (81% vs. 71%, respectively, $p = 0.03$), and patients with amnesic MCI were more likely than those with other subtypes to exhibit depressive symptoms. Patients with ≥ 4 NPS had nearly 2.5 times the odds of developing dementia at follow-up than patients with 0-3 NPS (adjusted OR = 2.44, 95% CI 1.07, 5.55).

Conclusion—NPS are common in MCI patients. Those with an elevated number of NPS may be more likely to have the amnesic subtype of MCI, and depression may be more common in amnesic MCI than in other subtypes. An elevated number of NPS may increase risk of progression to dementia for patients with MCI.

Keywords

Mild cognitive impairment; neuropsychiatric symptoms; dementia

Neuropsychiatric symptoms (NPS) such as depression, anxiety, agitation, apathy, hallucinations, and delusions often are discussed in the context of the dementias, including Alzheimer disease (AD), vascular dementia, and frontotemporal dementia. NPS occur in 60

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Key points: In the present study of older adults with MCI: (1) patients with more neuropsychiatric symptoms (NPS) were more likely than those with fewer NPS to have the amnesic subtype of mild cognitive impairment (MCI); (2) depressive symptoms were especially common in patients with the amnesic MCI subtype; and (3) an elevated number of NPS predicted progression from MCI to dementia.

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to 80% of older adults with dementia^{1, 2} and are associated with poor outcomes, including nursing home placement.^{3, 4}

Mild cognitive impairment (MCI) refers to an intermediate stage between normal cognitive aging and dementia.⁵ Increasing evidence suggests that MCI, like dementia, is a heterogeneous condition comprised of various subtypes.⁶ The *amnestic* type--characterized by memory impairment--is the most common, but other subtypes such as *single non-memory* and *multiple domain*, also are prevalent.^{7, 8}

As in dementia, an emerging literature suggests that NPS also occur frequently in patients with MCI.⁹⁻¹¹ Over 40% of MCI patients exhibit NPS in a one-month period, and 29% experience clinically significant symptoms.⁹ The distinct neuropsychological profile and divergent patterns of cortical atrophy¹² observed among individuals with different MCI subtypes suggest that the number and type of NPS might also differ by subtype. For example, individuals with MCI characterized by executive dysfunction might be more likely to demonstrate apathy than those with other patterns of cognitive deficits. Little is currently known, however, about how the patterns of specific NPS differ across the MCI subtypes,¹³ or whether the presence of NPS affects longer-term outcomes in MCI patients, such as progression to dementia.¹⁴⁻¹⁶

To address these gaps in the literature, we studied patients with MCI at 10 Alzheimer's disease Research Centers of California. We tested the hypotheses that: (a) the number and type of NPS would differ by MCI subtype; and (b) that a high number of NPS at baseline would be associated with progression to dementia at follow-up.

Methods

Participants were patients evaluated at the Alzheimer's Research Centers of California (ARCCs), state-supported memory disorders clinics with sites at the University of California, Davis (2 sites), Irvine, Los Angeles, San Diego, and San Francisco (UCSF) (2 sites), the University of Southern California (2 sites) and Stanford University. Patients enrolled in the ARCCs via self-referral or referral from family or physician. Data were recorded in the ARCCs Minimum Uniform Dataset (MUDS), and stored at UCSF. We reviewed records of patients evaluated over 11 years (1988-1999). Inclusion criteria were a diagnosis of MCI, a Mini-Mental State Exam¹⁷ (MMSE) score ≥ 20 , age ≥ 50 years, and having adequate existing data to determine MCI subtype. The UCSF Committee on Human Research approved this study.

Clinical Evaluation

Patients at the ARCCs received a comprehensive evaluation, including physical examination, neuropsychological testing and a review of medical records. Each patient and an informant were asked standardized questions by trained interviewers concerning demographic information, medical and psychiatric history, and family history of dementia. Functional status was determined using the Blessed-Roth Dementia Scale.¹⁸ As part of the clinical evaluation, patients or informants were asked whether the following NPS were present: hallucinations, delusions, anxiety, depression (report of ≥ 2 of 8 symptoms based on Diagnostic and Statistical Manual of Mental Disorders III-R criteria),¹⁹ apathy, disinhibition, changes in sleep, and changes in appetite. The criteria for depression did not include changes in sleep or in appetite. Additional questions concerning anger, aggression, and lability were included in the evaluation from 1992 until 1999.

The typical neuropsychological battery to determine cognitive status and MCI subtype included: Trailmaking Test, Parts A and B,²⁰ Wechsler Adult Intelligence Scale Block

Design and Digit Symbol subtests,²¹ Boston Naming Test (Kaplan EF, Goodglass H, Weintraub S. Boston Naming Test. 2nd ed. Philadelphia: Lea & Febiger; 1983) and Category Fluency Test,²² Wechsler Memory Scale Logical Memory and Visual Reproduction subtests^{23, 24} and the MMSE. Diagnoses were determined by multi-disciplinary conferences that were attended at each site by neuropsychologists, nurses, neurologists and psychiatrists. To ensure uniformity of diagnoses across sites, inter-rater reliability and consensus conferences were held. ARCC manuals described diagnostic criteria for dementia, amnestic disorder (according to the DSM III-R and DSM IV criteria),^{19, 25} other cognitive impairment not meeting criteria for dementia (CIND), no cognitive impairment, and diagnosis deferred. We defined MCI as including diagnoses of amnestic disorder and CIND.

Based on the baseline neuropsychological evaluation, clinicians rated the severity of patients' cognitive impairment (none, mild, moderate, or severe) in four domains: memory, language, visual-spatial/parietal, and executive. We classified MCI patients into one of three categories based on those with moderate to severe impairment in the memory domain only (amnestic MCI subtype), moderate to severe impairment in a single non-memory domain (single, non-memory MCI subtype), or moderate to severe impairment in two or more domains (multiple domain MCI subtype).

We collected information on progression to dementia from follow-up visits. Dementia diagnoses were determined based on follow-up ARCC evaluations, using the ARCC manual for diagnostic criteria, which closely follow DSM diagnostic guidelines. Dementia etiology also was specified (e.g., Alzheimer disease, vascular dementia, frontal, other, mixed).

Statistical Analyses

Analyses were performed using Stata, Version 9.2 SE (StataCorp, College Station, TX). We determined the baseline characteristics and the number of NPS in the patients diagnosed with MCI. Because NPS items regarding anger, aggression, and lability were added to the clinical evaluation beginning in 1992, we prorated NPS scores of participants enrolled prior to 1992. In order to make all visits comparable in an NPS summary score, we assumed that the percentage of items endorsed would have been similar if the additional questions had been asked. For example, a participant who endorsed 2 (i.e., 25%) of 8 symptoms in 1992 would be assigned a score of 2.75 (i.e., 25% of 11).

We compared baseline characteristics of those with 0-3 NPS and those with ≥ 4 NPS (upper quartile of the sample) using Mann Whitney tests for continuous variables and chi-square and Fisher's exact test for dichotomous variables. We then conducted chi-square tests to determine whether the number of NPS and the distribution of specific NPS differed by MCI subtype, and performed post-hoc comparisons where appropriate.

To determine whether NPS predicted progression to dementia, we conducted unadjusted and multivariate-adjusted logistic regression analyses with number of NPS (0-3, ≥ 4) as the predictor and progression to dementia at follow-up as the outcome. Diagnostic evaluation of the final logistic model identified several patients with poor fit and high influence. We excluded the four with the poorest fit from regression analyses.

Results

11,729 patients were evaluated at the ARCCs between 1988 and 1999. 521 patients were diagnosed with MCI and met other inclusion criteria. Demographic data are presented in Table 1. Overall, 73.9% of all MCI patients or caregivers reported that patients had at least one NPS. The mean number of NPS was 2.3 ± 2.1 standard deviations (SD; range 0-9.6).

The most frequently reported NPS were anxiety (39.3%), sleep changes (35.2%) and depression (34.9%). MCI patients with ≥ 4 NPS had a higher overall number of medical co-morbidities (1.5 ± 1.1 vs. 1.1 ± 1.0 ; $p < 0.0001$), and a higher Blessed Roth score (2.3 ± 2.1 vs. 1.6 ± 1.6 ; $p = 0.0001$), indicating greater functional impairment.

Prevalence of MCI subtypes and distribution of NPS

Overall, 73.7% of patients were of the amnesic MCI subtype; 9.6% had single, non-memory MCI, and 16.7% had multiple domain MCI. The distribution of MCI subtypes differed at the trend level, depending on whether patients had high or low NPS ($\chi^2 = 5.93$, $p = 0.052$) (Table 2). Patients with high NPS were more likely than those with low NPS to have amnesic MCI (81% vs. 71%, $\chi^2 = 4.62$, $p = 0.03$), and were less likely to have single non-memory MCI (5% vs 11%; $\chi^2 = 4.55$, $p = 0.03$).

The frequency of most specific neuropsychiatric symptoms did not differ by MCI subtype (see Table 3). However, depression was twice as frequent in patients with the amnesic MCI subtype (41%) compared with the single non-memory subtype (20%) ($\chi^2 = 7.97$, $p = 0.005$) or the multiple domain subtype (18%) ($\chi^2 = 15.13$, $p < 0.001$).

Prediction of dementia at follow-up

Of the 521 patients, 270 (52%) had a follow-up evaluation (average time to follow-up = 1.6 ± 1.1 years). Availability of follow-up data did not differ by number of NPS at baseline; 51.3% of those with 0-3 NPS vs. 53.2% of those with ≥ 4 NPS returned for follow-up ($\chi^2 = 0.15$, $p = 0.70$). Overall, 64.3% of the patients with 0-3 NPS had dementia at follow-up, compared to 74.3% of the patients with ≥ 4 NPS ($\chi^2 = 2.45$, $p = 0.12$).

In an unadjusted logistic regression model, participants with ≥ 4 NPS at baseline had an 88% greater chance of dementia compared with those with 0-3 NPS (OR = 1.88, 95% CI 1.003, 3.53) (Table 4). After adjustment for age, MMSE score, number of co-morbidities, Blessed Roth score, and study site, this association increased to a nearly 2.5-fold increase in odds of progression to dementia (OR = 2.44, 95% CI 1.07-5.55).

We also conducted analyses including the four outliers. As would be expected, their inclusion attenuated associations and affected significance in unadjusted (OR = 1.61, 95% CI 0.88, 2.92) and multivariate-adjusted (OR = 1.85, 95% CI 0.87, 3.93) models, but the direction and general pattern of associations remained.

Discussion

Our results suggest that NPS are common among MCI patients. Approximately 75% of MCI patients referred to the California Alzheimer's Centers experienced at least one NPS. Patients with an elevated number of NPS had more medical co-morbidities and lower functional status, and were more likely to be of the amnesic MCI subtype. In addition, patients with amnesic MCI were twice as likely to have depressive symptoms, compared to patients with the other MCI subtypes. Of particular interest is our finding that patients with an elevated number of NPS at baseline were almost 2.5 times more likely to have dementia at follow-up.

Our results are consistent with those of other studies that have shown that NPS are common in MCI. Lyketsos et. al found that among patients with MCI in the community-based Cardiovascular Health Study (CHS), 43% had NPS, with 29% being rated as being clinically significant.⁹ The fact that our sample was clinically-based and not community-based may account for the higher prevalence observed among our participants. Anxiety, sleep changes, and depression were the most frequently reported NPS in our cohort and this is consistent

with relative frequencies in previous studies. Depression, apathy, anxiety, and sleep changes were among the most frequently reported in the CHS.⁹ Similarly, other studies have found that frontally mediated behaviors (apathy and executive dysfunction) were reported most often.²⁶

Most demographic variables did not differ among the NPS groups. For example, we did not find a relationship between race and NPS. Chan et al, found, however, that non-white MCI patients were at an increased risk for NPS, compared to whites.²⁷ In the present study, participants with ≥ 4 NPS also experienced more co-morbid illness than those with 0-3 NPS. It is not surprising that burden of illness is related to NPS in MCI; patients with a greater number of medical illnesses might experience symptoms of depression or anxiety as a result of stress related to the symptoms of these comorbidities and their management. Similarly, those with greater functional impairment may be experiencing more NPS as a result of lower function, or *vice versa*. A study by Feldman et al. found that MCI patients with NPS exhibit greater functional impairment,²⁸ and NPS have been associated with functional impairment in dementia patients as well.²⁹ We also observed a trend-level association between MMSE and NPS, and this is consistent with prior findings.²⁸ Given that a higher number of NPS is associated with greater comorbidity, functional impairment, and cognitive impairment, it is possible that NPS could serve as a marker for overall disease severity and burden in the setting of MCI.

Consistent with our hypothesis that NPS would differ by MCI subtype, patients with elevated NPS were more likely to have the amnesic MCI subtype, and depressive symptoms were especially common among participants with the amnesic subtype. It may be that those with amnesic MCI are more likely to develop depressive symptoms, or it may be that depression is a risk factor for amnesic MCI. Previous research in amnesic MCI patients has shown high prevalence of depressive symptoms, as well as increased risk for Alzheimer disease (AD) for those with depressive symptoms.³⁰ Indeed, depressive symptoms have been shown to be a risk factor for AD in multiple studies.³¹⁻³³

We also hypothesized that those with a higher number of NPS would be more likely to progress to dementia. We found that an elevated number of NPS at baseline was associated with a greater likelihood of receiving a dementia diagnosis at follow-up, even after adjusting for age, baseline MMSE score, functional status and co-morbidities. Although a surveillance bias might account for this observation if patients with more NPS are more closely followed than those with fewer NPS, this is unlikely because follow-up was similar in our cohort for patients with high and low numbers of NPS. Our findings beg the question of whether treatment of NPS in MCI might delay or even prevent progression to dementia. Further research is needed to address this possibility.

Some limitations in our study design warrant consideration. First, although a clinician administered the MUDS questionnaire to ascertain the presence of NPS, no validated scale such as the Neuropsychiatric Inventory³⁴ was used. In addition, a lack of data on the duration of participants' NPS precluded us from investigating whether NPS duration predicted progression to dementia. Furthermore, follow-up data was incomplete in the present study, raising the possibility of selection bias. Finally, because patients were seen at university-based referral centers, results may not be generalizable to patients seen at clinics without an academic affiliation.

Conclusion

In conclusion, our findings suggest that patients with elevated NPS are more likely to have the amnesic subtype of MCI, and that depressive symptoms are especially common in patients with amnesic MCI. Our results also indicate that patients with MCI who have an

elevated number of NPS may have more than twice the odds of progression to dementia than those with fewer NPS. Additional studies are needed to determine the extent to which NPS duration and severity predict progression from MCI to dementia.

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Table 1

Characteristics of patients by number of neuropsychiatric symptoms.

Characteristic (Mean ($\pm$ SD) or %)	0-3 NPS <i>n</i> = 382	$\geq$ 4 NPS <i>n</i> = 139	<i>p</i> -value*
Age (years)	73.2 $\pm$ 8.4	71.7 $\pm$ 10.1	0.27
Education (years)	13.0 $\pm$ 4.1	12.8 $\pm$ 4.3	0.37
Female (%)	51.1	54.0	0.56
Race (%)			0.47
White	74.5	76.8	
African-American	7.1	5.8	
Hispanic	12.1	8.0	
Asian	4.5	7.3	
Other	1.8	2.2	
Income < \$10K (%)	33.7	37.9	0.61
Comorbidities (Current or Past)			
Hypertension	38.4	45.3	0.16
Myocardial infarction	11.4	8.0	0.26
Diabetes	12.7	13.7	0.76
Parkinson's disease	3.2	5.0	0.32
Stroke	11.1	14.6	0.28
# Comorbidities (0-5)	1.1 (1.0)	1.5 (1.1)	<0.0001
Alcohol use >1 times/day	3.7	2.0	0.96
Current Smoker	4.1	2.9	0.61
Family Hx Dementia	29.3	26.0	0.50
Mini-Mental State Exam (0-30)	26.4 $\pm$ 2.7	26.0 $\pm$ 2.7	0.09
Blessed-Roth (0-17)	1.6 $\pm$ 1.6	2.3 $\pm$ 2.1	0.0001

N = 521.

* Mann Whitney tests for continuous variables, chi-square and Fisher's exact test for dichotomous variables

Table 2

Prevalence of particular MCI subtypes among patients with 0-3 vs. ≥ 4 neuropsychiatric symptoms.

MCI Subtype	Number of NPS		Chi-square	<i>p</i> -value
	0-3	≥ 4		
Amnesic	71.2	80.6	4.62	0.03
Single domain, non-memory	11.3	5.0	4.55	0.03
Multiple domain	17.5	14.4	0.73	0.39
Total	100	100	--	--

Note: $N = 521$. MCI = mild cognitive impairment; NPS = neuropsychiatric symptoms. Overall $\chi^2 = 5.93$, $p = 0.052$.

Table 3

Proportion (%) of patients with specific neuropsychiatric symptoms in each MCI subtype.

Neuropsychiatric Symptom	MCI Subtype			<i>p</i> -value*
	Amnesic (<i>n</i> = 384)	Single, Non-Memory (<i>n</i> = 50)	Multiple Domain (<i>n</i> = 87)	
Delusions	10.2	8.0	14.1	0.48
Hallucinations	5.8	6.0	3.6	0.80
Disinhibition	6.0	10.0	6.9	0.51
Depression	40.6	20.0**	18.4**	<0.001
Anxiety	41.3	26.0	38.4	0.11
Lability	15.5	14.6	11.5	0.71
Apathy	22.9	20.4	15.1	0.28
Aggression	14.7	12.0	11.5	0.78
Anger	29.3	18.4	20.7	0.21
Sleep changes	33.3	49.0	36.1	0.09
Appetite changes	17.8	20.8	23.3	0.48

Note: *N* = 521.* For all NPS, *p*-value displayed is for overall χ^2 .** *p* < 0.05 compared with amnesic MCI subtype.

Table 4

Association between number of neuropsychiatric symptoms and progression to dementia.

Number of Neuropsychiatric Symptoms	Unadjusted OR (95% CI) N = 266	Multivariate-adjusted* OR (95% CI) N = 238
0-3 (ref)	1.00	1.00
≥ 4	1.88 (1.003, 3.53)	2.44 (1.07, 5.55)

* Adjusted for age, MMSE score, number of co-morbidities, Blessed Roth score, and study site.