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Patterns of Neuropsychiatric Symptoms in MCI and Risk of Dementia

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Abstract

Objectives—To identify clusters of patients with incident mild cognitive impairment based on their neuropsychiatric symptoms (NPS) and to examine the risk of progression to dementia, based on these clusters.

Design—Cohort study with 2 years median length follow-up. Setting: Alzheimer's disease Centers from the National Alzheimer's Coordinating Center (NACC).

Participants—Patients with MCI who were at least 60 years old with complete data and follow-up (n = 540).

Measurements—Latent class analysis was used to identify clusters of patients based on their NPS, and Cox proportional hazards models were used to examine risk of progression to dementia based on clusters. Incident MCI was defined as a participant having MCI at a current visit, but having been cognitively normal at his or her previous (yearly) visit. NPI-Q assessed presence of twelve neuropsychiatric behavioral domains.

Results—Three clusters were identified: a severe cluster (agitation, anxiety, apathy, nighttime behaviors, inhibition), an affective cluster (depression, anxiety, irritability, nighttime behaviors), and an asymptomatic cluster. The prevalence of each class was 56% for the asymptomatic class followed by the affective class (37%) and finally the severe class (7%). Compared to the asymptomatic class, the severe class had more than twice the hazard of progression to dementia (2.69, CI: 1.12–2.70) and the affective class had over one and a half times the hazard of progression to dementia (1.79, CI: 1.12–2.70).

Conclusions—Among persons with incident MCI, patterns of NPS may increase the likelihood of progression to dementia. Implications for early detection and treatment are discussed.

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Keywords

MCI; dementia; neuropsychiatric symptoms

Objective

Mild Cognitive Impairment (MCI) has been considered a transitional period between normal aging and dementia, although patients with MCI sometimes remain MCI cases or revert back to normal (1). MCI is characterized by a slight decline in cognitive function, often featuring memory loss prominently, without enough functional disability to meet criteria for a dementia (2). A substantial proportion of those with MCI, especially those with amnesic MCI, go on to develop dementia due to Alzheimer's Disease (AD) or some other form of dementia (2, 3). Although amyloid imaging, especially in combination with structural and functional imaging, shows promise, these methods are expensive and a clinical method based on observable behavior may be more cost effective and pragmatic.

Neuropsychiatric symptoms (NPS), such as depression, apathy, anxiety, irritability, and delusions, are common among patients with AD dementia (4–6) and are associated with increased likelihood of progression from mild to severe dementia (7). Four-week prevalence rates for NPS in AD dementia have been found as high as 97% (6). Four-week prevalence rates of NPS in MCI lie between those seen in cognitively normal subjects and in subjects with AD dementia, providing further support for the idea of a continuum from normal aging to AD (2). Four-week prevalence of at least one NPS in MCI can be as high as 50% (3) with the most prevalent symptoms being depression (3, 8–10), apathy (3, 8, 9, 10), irritability (3, 8, 10), anxiety (3, 4, 8, 10), and sleep disturbance (3, 10). NPS are associated with earlier institutionalization and (11) mortality (12) as well as with progression from MCI to dementia (13).

Taragano et al (14) found that MCI accompanied by NPS had a four-fold higher risk of progression to dementia when compared to MCI without NPS. These findings highlight the importance of NPS as independent prognostic indicators, as even persons with NPS without cognitive deficits appear to be at risk for dementia. Since NPS are associated with decreased time to progression from MCI to dementia, understanding which NPS or patterns of NPS predict progression may further studies of the underlying neurobiological mechanisms. This information could inform the development of effective treatments to delay the onset of dementia as well as to target those who might receive treatment of NPS. To date, limited evidence supports the idea that treating depression can reduce progression to dementia (15, 16) so further research into this area is warranted.

Exploring clusters of NPS as opposed to simply looking at the number of symptoms or total NPI score offers a chance to generate hypotheses for study of the underlying pathology of qualitatively different groups. We used data from the National Alzheimer Coordinating Center (NACC) to investigate clusters of NPS in patients with incident MCI and to examine the risk of progression to dementia, based on patterns of NPS. We employed latent class analysis to identify clusters of patients with NPS that may be associated with progression to dementia in participants with incident MCI. We hypothesized that, in addition to a class with

little or no NPS, we would identify qualitatively different clusters of patients with NPS, as have been found in AD (5, 17), specifically asymptomatic, affective, and psychotic/aggressive. Further, we hypothesized that the risk of progression from MCI to dementia would vary by class membership and that the asymptomatic class would have the lowest risk.

Method

Participants

The sample consisted of volunteers diagnosed with MCI at an Alzheimer's Disease Center (ADC) who were 60 years and older (18). In order to mitigate the potential for MCI severity to confound the relationship between NPS and time to dementia diagnosis, we included only individuals with "incident" MCI in our analyses. An individual was considered an incident case of MCI if he or she had MCI at a current visit, but was cognitively normal at the previous (yearly) visit. The first visit at which the individual was diagnosed with MCI was treated as his or her 'baseline', and time to dementia diagnosis or censor was measured from that point. Data collection at the ADCs took place between September 2005 and August 2013. Each ADC was overseen by its local IRB and data collection was conducted annually, in home or in clinic, by trained clinicians (19).

Measures

NPS Measures—The Neuropsychiatric Inventory Questionnaire (NPI-Q), Mini-Mental State Examination (MMSE), and the Geriatric Depression Scale (GDS) were administered at each visit. The NPI-Q is a scale measuring the following 12 behaviors associated with MCI and dementia: delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, aberrant motor behavior, sleep and nighttime behaviors, and appetite and eating disorders (20). Presence of each behavioral disturbance in the last month representing a change for that individual was measured as a dichotomous variable (present/absent). The MMSE assesses for cognitive impairment and is often used to track impairment over time. Scores for the MMSE range from 0–30 with lower scores indicating greater impairment (21). The 15 item Geriatric Depression Scale (GDS) is a self-report screening measure for depression in older adults. Scores for the GDS range from 0–15 with scores greater than 5 indicating a positive screen for depression (22). Individuals with 3 or fewer missing GDS items had scores imputed using the mean of the missing items (22).

Diagnoses—MCI was diagnosed using modified Petersen criteria (23). Possible and probable Alzheimer's disease diagnoses were made using NINCDS/ADRDA (24). Vascular dementia (VaD) was diagnosed using NINDS/AIREN criteria (25) and Frontotemporal dementia was diagnosed using consensus criteria (26). Individuals who did not meet formal criteria for MCI or dementia, but who could not be considered normal (e.g., due to reports of cognitive concerns by the subject and/or study partner or evidence of cognitive change on testing) were classified as "Impaired, not MCI" and were not included as incident MCI for this study.

Statistical Analysis

We conducted t-tests and chi-square tests to compare demographics, NPI-Q total score, and MMSE at baseline between persons who progressed to dementia and persons who did not. All tests were two-sided; t-tests assumed unequal variances and used Satterthwaite's approximation for degrees of freedom.

Latent class analysis (LCA) was conducted on the 12 dichotomous ratings for each behavioral domain to identify clusters of NPS. LCA assumes that the sample consists of a mixture of persons who have different clusters of NPS. The model provides latent class probabilities (4-week prevalence of each class) and conditional probabilities (rates of observed variables e.g. NPI symptoms, given membership in a class). Using these parameters we calculated the probability of person's membership in each cluster given an his or her reports of neuropsychiatric symptoms.

The main assumption of LCA is that after conditioning on the latent variable, the observed variables are independent of one another. Therefore, the latent variable should account for any relationship between the observed variables. We tested this assumption using standardized bivariate residuals (27) and we tested model fit by comparing observed symptom patterns with those predicted by the model. We also completed a sensitivity analysis of our imposed restrictions (only patients over 60 who had baseline NPI-Q data and subsequent follow-up data) by fitting the data to the full sample in order to show that our restrictions did not affect the estimation of the LCA model.

We fit Cox proportional hazard models where time was defined as time to diagnosis of dementia in years and the predictor was membership in each latent class. The models were adjusted for baseline age, MMSE, sex, race, and years of education. Since it is well known that treating latent class membership as an observed independent variable in subsequent regression analyses results in biased estimates and incorrect standard errors (28), we corrected for this bias using Vermunt's three-step method (28, 29). Demographics and symptom counts were completed using Stata v13 (30) and latent class analysis and survival analysis was completed using MPlus v7.1 (31).

Results

Study sample

The original data request included all visits for all 7,424 volunteers who were cognitively normal at their first ADC visit. Of those, 872 were diagnosed with MCI on at least one later visit. We excluded 48 individuals who had missing NPI-Q data at their MCI baseline visit, 264 individuals without follow-up visits, and 20 individuals who were under the age of 60 years at their first ADC visit, for a final analytic sample of 540.

Of the 540 individuals with incident MCI, 419 (78%) were not diagnosed with dementia during follow-up, 121 (22%) were diagnosed with dementia, and 167 (31%) of those who didn't progress reverted to normal. Although a substantial number of participants reverted to normal cognition we chose to include these people because it is fairly typical for a considerable number to revert back to normal. Our goal was to predict survival based on

incident MCI and to exclude them would overestimate the risk of conversion among patients with incident MCI and we want the results to be applicable to individuals at their time of diagnosis when it is not known if they will progress or revert. Median length of follow-up was approximately 2 years (sd = 1.26).

Demographics, baseline assessments, and follow-up time by progression status are shown in Table 1. Compared to persons who did not progress to dementia, persons who progressed to dementia were older at baseline (82.7 years, SD=7.7 vs. 79.4 years, SD=8.1), more likely to be female (74% vs. 58%), and had lower MMSE scores (26.8, SD=2.0 vs. 27.9 SD= 2.0). NPI-Q scores were significantly higher for persons who progressed (2.4, SD=3.2) than for persons who did not (1.5, SD= 2.6) ($t = 2.81$, $p=0.01$) and those who progressed had a higher GDS score than those who did not progress (3.90, SD=11.35 vs. 2.12, SD=2.46). Those who progressed had a slightly greater number of visits than those who did not progress (3.53 vs. 3.11) whereas those who did not progress had marginally more follow-up years than those who did progress (2.31 vs. 2.00).

Four-week prevalence of neuropsychiatric symptoms

Depression was the most commonly endorsed NPI-Q symptom among the analytic sample (22%) followed by irritability (21%), anxiety (18%), nighttime behaviors (17%), apathy (12%), agitation (12%), and eating behaviors (11%). All other domains (delusions, hallucinations, elation, disinhibition, and motor) had 4-week prevalences of 5% or less. We fit the models with 1 to 5 classes. We tested model fit using bootstrapped likelihood ratio tests (32) and found that a 3-class model was the best fit. A 4-class model did not fit significantly better than a 3 class model ($-2LL$ difference: 1749.276, $df=13$, $p=0.154$). A 2-class model fit significantly better than a 1-class model ($-2LL$ difference: 1958.039, $df=13$, $p<0.001$) but a 3-class model fit significantly better than a 2-class model ($-2LL$ difference: 1775.276, $df=13$, $p<0.001$) so we chose a 3-class model.

Model Checking

We tested the conditional independence assumption by looking at the 264 standardized bivariate residuals. We found only one (hallucinations and delusions) to be related after conditioning on class membership and since there was such a low rate of endorsement for hallucinations (<1%), we did not consider this justification to change the model. We found that standardized residuals comparing observed and expected counts of pattern frequencies showed satisfactory fit. For example the observed versus expected counts for most common symptoms was no symptoms (252 vs. 251), followed by only irritability (23 vs. 22), and only anxiety (23 vs. 21).

NPS Classes

The conditional probability estimates for each NPI-Q domain for each class are shown in Figure 1. We labeled class 1 (7% of the sample) as “severe” because it features high rates of almost all of the symptoms including agitation (84%), anxiety (52%), apathy (51%), nighttime behaviors (48%), and disinhibition (44%). We labeled class 2 (27% of the sample) as “affective” since it is characterized by high rates of depression (41%), anxiety (31%), irritability (32%), and nighttime behaviors (35%). Class 3 (56% of the sample) was labeled

as “asymptomatic” because all of the symptoms were endorsed at less than 5%. Of those who reverted to normal, 15% were in the severe class, 28% were in the affective class, and 33% were in the asymptomatic class.

Individuals in the asymptomatic class tended to have only one symptom (24%) or no symptoms (76%), excluding depression and nighttime behaviors. The symptom patterns of those in the affective class included mainly affective symptoms as well as motor problems (e.g. pacing, repetitive activities, fidgeting), in the absence of disinhibition or agitation. Individuals with this symptom pattern were included in the severe class. The symptom patterns for the severe class were more extensive however the majority of individuals in that class endorsed agitation and depression, or agitation and either disinhibition or motor problems. Although delusions were not highly prevalent in the sample, agitation plus delusions was the difference between being placed in the severe class versus the affective class. Since it would be unwieldy to list modal class assignment by every possible pattern, a calculator for modal class assignment as a function of pattern of NPI domains can be found at <http://www.hopkinsmedicine.org/psychiatry/bayview/research/Leoutsakos.html>.

Risk of progression according to NPS class

As shown in Table 2, relative to the reference asymptomatic class both the severe class and the affective class had a higher hazard of dementia diagnosis with the severe class having more than twice the risk of the asymptomatic class (2.69, CI: 1.65–4.37) and the affective class having more than one and half times the hazard of the asymptomatic class (1.75, CI: 1.12–2.70). We tested the proportional hazards assumption using Schoenfeld residuals (33) and found no evidence that the assumption was violated ($\chi^2 = 5.54$, $df=6$, $p=0.477$). Mean years of follow-up were similar for each class (Class 1 = 3.03, Class 2 = 3.11, Class 3 = 3.27). The number of cases for each contact visit 1–7 are 540, 532, 328, 188, 89, 33, and 4, respectively. Figure 2 shows a Kaplan-Meier survival plot of progression to dementia for each class as a function of time. We ran a model that included medications (antidepressants, antipsychotics, and benzodiazepines) and a model that included all neuropsychological tests. The model with medications resulted in increased hazard ratios and the model with neuropsychological tests did not result in significantly different hazard ratios than the originally model.

Type of dementia

Of persons who progressed to dementia, more than two-thirds were diagnosed as possible or probable AD (68%) with VaD being the second most prevalent at 5%. The majority of those who progressed to dementia had amnesic type MCI at baseline (88%). NPS prevalences did not differ statistically significantly by type of MCI. In all classes the most common dementia diagnosis was AD and the percentage of those who converted to AD from each class shows a similar gradient as the survival analysis by class with the severe class having the highest progression percentage and the asymptomatic class having the lowest percentage.

Conclusion

We identified three clusters of individuals based on patterns of NPS in MCI – a large asymptomatic cluster, an affective cluster, and a severe cluster. Further, consistent with our initial hypothesis, we found that the asymptomatic cluster had the lowest hazard of progression whereas the severe cluster had a significantly higher hazard of dementia diagnosis on follow-up, with the affective cluster falling in between the severe and asymptomatic cluster.

Our aim in this study was to elucidate clusters of patients with NPS, using latent class analysis, that are predictive of an eventual dementia diagnosis. Latent class analysis has been used to detect clusters of NPS in patients with dementia (5, 17). One study done in Cache County found three classes of NPS symptoms in patients with AD dementia. The first and largest class was asymptomatic (e.g., those with no NPS symptoms), the second class was mainly affective symptoms (e.g., depression, irritability, or anxiety), and the third class was largely psychotic symptoms (e.g., hallucinations and delusions) (5). A later study found a similar three-class structure, in this instance they were: asymptomatic, anxious/depressive, and aggressive symptoms (17).

Understanding the relationship between patterns of NPS and progression to dementia may make it possible to predict which patients will eventually be diagnosed with dementia and to estimate how long it will take. For example, a patient who endorsed agitation, depression, anxiety, and irritability would be included in the affective cluster but a patient with the same symptoms in addition to disinhibition would be included in the severe cluster. Similarly, a patient with disinhibition, irritability, and nighttime behaviors would be included in the affective cluster, but if a patient had agitation rather than nighttime behaviors they would be included in the severe cluster. Classifying patients based on their symptom profiles might allow for better understanding of how the addition of certain symptoms may change risk of dementia diagnosis as well as shorten time to diagnosis. Lyketsos and colleagues (34) proposed treatment for dementia based on NPS advocating examination of symptom clusters that have the potential to become treatment targets. They note that in the past NPS have been treated as individual symptoms in clinical trials and that this approach has been largely unsuccessful due to symptom overlap. They therefore advocated studying treatment for empirically derived clusters of symptoms. Although this research was specific to those with dementia, a similar idea could be employed for those with MCI.

Apathy and depression were common in both the affective and severe classes. These symptoms may prove to be part of NPS clusters that are most predictive of progression. Apathy and depression have been shown to increase the likelihood of progression from MCI to dementia as well as decrease time to dementia progression (9). Palmer and colleagues found a 7-fold increased risk of AD progression in those with MCI and apathy compared to those with MCI and no apathy (9). Our results are in line with these studies in that apathy was most prevalent in the class with the highest hazard of progression, was found in addition to depression in nearly everyone in the severe cluster, and no one in the cluster with the lowest hazard of progression endorsed depression.

Our study derives advantages from the use of a large dataset from multiple ADCs and the use of latent class analysis to identify subtypes of NPS in MCI. Our study also has some limitations. There are currently no reliability studies on the NACC clinical diagnoses among the different sites nor are there any reliability studies on the identification of psychiatric symptoms in NACC. And, although the NPI is reliable in dementia, reliability in MCI has not been established. The sample was composed of volunteers who may be presenting due to increased concerns about their cognitive functioning and so may not be representative of the population. They may also be more likely to have a family history of AD. Since we only included participants with “incident MCI” based on diagnosis of MCI at a subsequent visit after at least one visit where they were considered cognitively normal we may have failed to include some of the more severe cases of MCI so are results may not be generalizable to those with late MCI. As is the case for all survival analysis, our analysis is subject to right-censoring; that is, the time to progression to dementia is unknown for persons who did not progress during the follow-up interval. Our model assumes that censorship is not related to failure however there is no explicit way to test this without further contact. In our analysis some misclassification of cluster membership may have occurred. The advantage of the latent class model is that it is based on a statistical model with good fit to the data, and is person-centered. The classes derived were qualitatively different from one another, with a separate class with affective symptoms that would not be captured by the total score. As in all research, the patterns need to be assessed in other samples.

Our results have implications for early detection and treatment of dementia in those with NPS. Since patients with more NPS and specific NPS are more likely to progress to dementia diagnosis preventing NPS earlier in life may be an avenue for prevention of MCI and dementia. Our results may also have implications for understanding the underlying etiology of MCI with NPS. Hanfelt and colleagues (38) found that those MCI phenotypes that showed prominent functional and neuropsychiatric features were more likely to have cerebrovascular disease (CVD) suggesting a possible etiology for MCI with NPS. NPS are likely to be associated with great neurochemical deficits and neuropathology, as we have reviewed recently (39). We would hypothesize that greater severity of NPS and increased risk of cognitive decline are associated with greater monoaminergic and glutamatergic deficits, as well as AD pathology in cortical-limbic circuits implicated in mood and impulse control symptoms. Neurobiological studies to test specific hypotheses using molecular imaging and analyses of neuropathological data are future directions to this work. Future research into the etiology of MCI may benefit from the understanding of NPS profiles in MCI.

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Figure 1.

This figure shows the conditional probabilities (y-axis) for each NPI-Q domain (x-axis). The solid lines are the point estimates and the dotted lines are the 95% confidence intervals. National Alzheimer's Disease Coordinating Center data (2005–2013).

Figure 2. Kaplan Meier Plot for progression to dementia as a function of class. National Alzheimer's Disease Coordinating Center data (2005–2013).

Table 1

Volunteer Characteristics at Baseline

	Non Converters (N = 419)	Converters (N=121)	T or χ^2 Statistic ^a
Age (yrs)	79.41 (8.13) ^b	82.66 (7.72)	T ₅₃₈ = 3.92, p <0.001
Female	241 (58%) ^c	90 (74%)	χ^2_1 = 11.25, p = 0.001
Education (yrs)	15.39 (5.34)	16.28 (11.13)	T ₅₃₈ = 1.22, p = 0.22
Race			
White	109 (90%)	358 (86%)	χ^2_1 = 1.60, p=0.21
MMSE	31.65 (15.92)	28.60 (11.17)	T ₅₂₇ = -1.95, p = 0.05
NPI-Q	1.54 (2.63)	2.35 (3.16)	T ₅₃₈ = 2.82, p=0.005
GDS	2.12 (2.46)	(3.90)	T ₅₂₈ = 2.94, p = 0.003
Depression (last two years)	110 (26%)	33 (27%)	χ^2_1 = 0.62, p =0.74)
Depression (past)	75 (18%)	24 (20%)	χ^2_1 = 0.79, p=0.67
Number of visits	3.11 (1.22)	3.53 (1.25)	T ₅₃₈ = 3.39 (p<0.001)
Follow-up (yrs)	2.31 (1.31)	2.00 (1.03)	T ₅₃₈ = -2.42, p = 0.02

Abbreviations: MMSE – Mini-Mental Status Examination; NPI-Q – Neuropsychiatric Inventory Questionnaire; GDS – Geriatric Depression Scale (15-item)

^a χ^2 test statistics are presented for categorical variables, *t* test statistics for continuous variables.

^b Continuous variables are described with mean (SD).

^c Categorical variables are described with number (%).

Table 2

Risk of dementia for persons with incident MCI based on National Alzheimer's Disease Coordinating Center data (2005–2013). Hazard ratios are estimated from Cox proportional hazard models adjusted for age, sex, education, race, and MMSE score.

	Hazard Ratio (95% Confidence Interval)	<i>p</i> -value ^d
Severe Class	2.69 (1.65–4.37)	<0.001
Affective Class	1.74 (1.12–2.70)	0.014
Asymptomatic Class	1.00 (reference)	
Age (years)^a	1.03 (1.01–1.05)	0.009
Female	2.04 (1.37–3.03)	<0.001
Education (years)^b	1.03 (0.98–1.08)	0.316
White	1.36 (0.79–2.32)	0.260
MMSE^c	0.81 (0.76–0.87)	<0.001

Abbreviations: MMSE – Mini Mental Status Exam

^a Hazard ratio for each additional year of age

^b Hazard ratio for each additional year of education

^c Hazard ratio per additional point

^d *p*-value calculated using Wald z-test