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Cognitive & Behavioral Assessment

Time course of neuropsychiatric symptoms and cognitive diagnosis in National Alzheimer's Coordinating Centers volunteers

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Abstract

Introduction: Neuropsychiatric symptoms (NPSs) are nearly universal in cognitive disorders. The mild behavioral impairment construct postulates that NPS may be the first symptom of impending dementia.

Methods: Participants were cognitively normal volunteers followed up approximately annually at Alzheimer's Disease Centers, who were assessed on the Neuropsychiatric Inventory and had at least one follow-up visit during which they were diagnosed with mild cognitive impairment (MCI) or dementia. Descriptive statistics were used to determine sequencing of NPS presence with cognitive diagnoses.

Results: Data were available for 1998 participants who progressed to MCI or dementia. Over 59% developed NPS before the diagnosis of any cognitive disorder. Depression and irritability were the most common NPSs to precede cognitive diagnoses (24 and 21%, respectively).

Discussion: NPSs precede a cognitive diagnosis in most people who develop cognitive decline, both MCI and dementia. These individuals are an important group to focus clinical and research efforts.

Keywords: Neuropsychiatric symptoms; Dementia; Mild cognitive impairment; Alzheimer's and related dementias; Mild behavioral impairment

1. Introduction

Although dementia has been defined by cognitive and functional decline, neuropsychiatric symptoms (NPSs) are almost universal in persons with dementia [1,2]. Common NPSs include depression, irritability, anxiety, agitation, apathy/indifference, delusions, and hallucinations. NPSs are associated with caregiver burden, poor life quality, institutionalization, and accelerated mortality [3–6]. Even before the onset of dementia, NPSs are often present alongside mild cognitive impairment (MCI) [7–9].

Depression, in particular, has been associated with cognitive impairment and dementia. A meta-analysis estimated that depression affects overall almost one-third of persons with MCI (range: 25% in community samples to 40% in clinical samples) [10]. Depression has been associated with greater risk of progression to Alzheimer's disease, vascular dementia, and MCI of different etiologies

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[11,12], whereas subsyndromal depression has been associated with accelerated cognitive decline and frontal lobe and anterior cingulate atrophy that may reflect the underlying mechanism distinct from Alzheimer's pathology [13]. A UK cohort study of over 10,000 people found that the emergence of depressive symptoms in late life was associated with a higher risk for dementia [14]. Other studies have suggested that late-life depression is a prodromal feature of impending Alzheimer's, rather than a risk factor [14].

The construct of mild behavioral impairment (MBI) as a neuropsychiatric syndrome originated with behavioral symptoms in the setting of frontotemporal dementia (FTD). Taragano et al. [15] proposed MBI criteria that delineated a neuropsychiatric prodrome to FTD before significant memory decline [16]. In longitudinal follow-up of patients in their original study, Taragano and Allegri [17] reported that not all patients with MBI had developed FTD: 28% had Alzheimer's Disease (AD) and 18% had vascular dementia, indicating that the MBI criteria should be extended to other dementias. Consequently the International Society to Advance Alzheimer's Research and Treatment criteria for MBI were developed, which provisionally define MBI as new-onset NPSs affecting psychosocial functioning, that are present for six months or longer, in the absence of dementia [16].

With more studies demonstrating that NPSs precede cognitive changes, the construct of MBI serves as a potential way to detect earlier neurodegenerative illness, differentiate subtypes of neurodegenerative conditions, and develop specific treatments that might alter progression to dementia [10,18,19]. Early identification of individuals with neurodegenerative illness could lend itself to the earlier use of potential disease-modifying therapies that have yet to be developed, as well as the assessment of the efficacy of older treatments [16]. More effective treatment would reduce the disease burden on individuals and their caregivers and affect societal costs as well [19]. The MBI concept postulates that NPSs may be the first symptoms of prodromal dementia. Therefore, it is important to know the exact numbers of people who experience NPS before dementia, which has not previously been estimated. In this article, we try to answer the question, among those who later develop MCI or dementia, how often do NPS precede the decline? We sought to address this in a large observational cohort with extensive longitudinal follow-up. Furthermore, we will estimate rates of NPS among cognitively normal individuals who remain so for at least five additional years, to demonstrate that the presence of NPS is associated with future cognitive decline, rather than simply being prevalent among the elderly.

2. Methods

2.1. Participants

The cohort we studied were volunteers recruited with normal cognition followed up approximately annually at National Institute on Aging–funded Alzheimer's Disease Centers (ADCs) across the United States. The National Alzheimer's Coordinating Center (NACC) maintains a comprehensive clinical and neuropathologic data set collected from these ADCs [20].

2.2. Measures

The Uniform Data Set is a standardized assessment of all ADC participants; data collected include demographics, medical history, medication use, functional and behavioral assessments, and a neuropsychological battery [21]. Using all available data, diagnoses were made by a single clinician or a formal consensus panel [22]. Participants with normal cognition were not diagnosed with either MCI or any type of dementia. Diagnoses of MCI were made using modified Petersen criteria [23], and diagnoses of AD were made using National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association criteria [24]. Consent was obtained from all participants at each ADC under local institutional review board oversight. Data included in this study were collected for Uniform Data Set visits conducted between August 2005 and January 2017. The sample was limited to cognitively normal individuals aged $\geq$60 years at their first visit, with at least one follow-up visit at which they were adjudicated to have MCI or dementia, and who did not have Down syndrome or Huntington's Disease.

Neuropsychiatric symptoms on participants were assessed approximately annually by the Neuropsychiatric Inventory Questionnaire (NPI-Q), adapted from the NPI, a widely used, validated informant-based interview [23,25,26]. The NPI-Q of individual participants was rated by a trained or certified clinician based on interview with a coparticipant or informant. NPI-Q evaluates the presence or absence of delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, motor disturbance, nighttime behaviors, and change in appetite/eating. It is important to note that NPI-Q assesses the presence or absence of NPS that are new to the person and that occurred in the months before the assessment. Consequently, long-standing or preexisting psychiatric symptoms or conditions would not ordinarily "rate" on the NPI-Q.

2.3. Statistical analysis

We generated descriptive statistics of the sample as a function of whether individuals progressed to MCI (and not dementia) or dementia (with or without MCI). Those with dementia "without MCI" were cognitively normal at one visit and then converted to dementia at a subsequent visit without having received a diagnosis of MCI. Participants were classified with regard to their cognitive diagnosis course (1: normal to MCI, 2: normal to MCI to dementia, or 3: normal to dementia). We considered diagnoses to be "sticky," meaning

Table 1
Demographics and follow-up characteristics by eventual cognitive diagnosis

Variable	MCI (N = 1345)*	Dementia (N = 653)†
Age at first visit, mean (SD)	76.9 (8.0)	80.2 (7.4)
Female, n (%)	798 (59.3)	420 (64.3)
Race, n (%)		
White	1102 (81.9)	564 (86.4)
Black/African American	202 (15.0)	80 (12.3)
Other	41 (3.0)	9 (1.4)
Family history dementia, n (%)	713 (53.0)	364 (55.7)
Years of education, mean (SD)	15.4 (3.2)	15.2 (3.2)
Number of visits, mean (SD)	5.8 (2.7)	6.5 (2.5)
Years of follow-up, mean (SD)	5.5 (2.9)	6.4 (2.5)

Abbreviations: MCI, Mild cognitive impairment; SD, standard deviation.
*Individuals have progressed to MCI but not dementia. Includes all individuals who receive an MCI diagnosis, even if they "flip" back to normal at a subsequent visit.
†Individuals may or may not have progressed through MCI before developing dementia. Includes all individuals once they have received a dementia diagnosis, even if they "flip" back to MCI or normal at a subsequent visit.

that once an individual was diagnosed with MCI, he or she was considered to have that diagnosis at subsequent visits until he or she was diagnosed with dementia. This means, for example, that a person diagnosed with MCI at visit 2 but considered cognitively normal at visit 3 was considered an MCI case. The same practice was used for dementia diagnoses. This practice greatly simplified course classification and was consistent with observations both in NACC and in the Cache County Study on Memory and Aging that individuals who had their diagnoses "downgraded," say from MCI to cognitively normal, typically were diagnosed with MCI again at a later visit [27]. In all cases, the first date on which the diagnosis was made was used as the date of diagnosis. In keeping with this approach, an individual who progressed from being cognitively normal to dementia, but was later diagnosed with MCI, was in diagnosis course 3. Participants were also classified into groups based on the timing of their onset (if any) of neuropsychiatric symptoms (1: never, 2: before MCI, 3: after MCI before dementia, 4: before dementia [no MCI], 5: after dementia). A participant was considered to have NPSs if he or she scored 1 or greater on the NPI-Q. For NPSs to be considered to have preceded a cognitive diagnosis, NPSs must have occurred on a visit before the first cognitive diagnosis. Incident NPSs that coincided at the same visit with a cognitive diagnosis were considered to have occurred with or after the cognitive diagnosis.

Then, we sought to determine if specific NPSs preceded specific cognitive diagnoses, for example, whether delusions and hallucinations generally occur only after a diagnosis of dementia. To answer this, the same five timing categories were constructed for each NPS domain assessed by NPI-Q.

Finally, to confirm that presence of NPS is associated with future risk of MCI or dementia rather than being prevalent among elderly individuals in general, we will also calculate rates of NPS at baseline among individuals who stay cognitively normal for at least five years.

Table 2
Sequencing of NPS presence with cognitive diagnosis

Diagnosis sequence		N (%)
Normal to MCI		1345 (67)
No prior NPS	289 (22%)	
NPS onset before MCI	734 (55%)	
NPS onset after MCI	322 (24%)	
Normal to MCI to dementia		375 (19)
No prior NPS	37 (10%)	
NPS onset before MCI	205 (55%)	
NPS onset after MCI, before dementia	91 (24%)	
NPS onset after dementia	42 (11%)	
Normal to dementia (no MCI)		278 (14)
No prior NPS	30 (11%)	
NPS before dementia	178 (64%)	
NPS after dementia	70 (25%)	

Abbreviations: MCI, Mild cognitive impairment; NPS, neuropsychiatric symptom.

3. Results

Table 1 contains baseline characteristics of the 1998 cognitively normal participants who progressed to MCI or dementia (with or without MCI). Most were Caucasian; women outnumbered men. They had a mean of 15 years of education. Two-thirds progressed to MCI only. Of the third who progressed to dementia, 14% did not receive an MCI diagnosis before the dementia diagnosis. The median length of time between visits was 378 days, with an interquartile range of 357-432 days. Participants had as many as 12 visits: 186 (9%) had 2 visits, 228 (11%) had 3 visits, 257 (13%) had 4 visits, 261 (13%) had 5 visits, 214 (11%) had 6 visits, 224 (11%) had 7 visits, 196 (10%) had 8 visits, 204 (10%) had 9 visits, 136 (7%) had 10 visits, and the remainder, 92 (5%), had more than 10 visits.

Table 2 shows sequencing of NPS presence by pattern of cognitive progression. Of those who developed MCI but did not progress to dementia during observation, 55% had NPSs preceding the MCI diagnosis. Less than one quarter developed NPSs after MCI. Similarly, of those who progressed from being normal to MCI to dementia, 55% had NPSs before MCI, and an additional 24% had NPSs after the MCI diagnosis but before a diagnosis of dementia. Of those who progressed from normal to dementia without receiving an MCI diagnosis, 64% had NPS before dementia compared with 25% who developed NPSs after dementia. In total, over 59% developed NPS before the diagnosis of any cognitive disorder.

To further understand the time course, we plotted NPS presence and cognitive diagnosis at each visit for participants with a long period of observation (at least nine visits) and who were diagnosed with dementia on at least one visit (N = 134) (Fig. 1). In most cases, NPSs preceded cognitive diagnosis, often by many years.

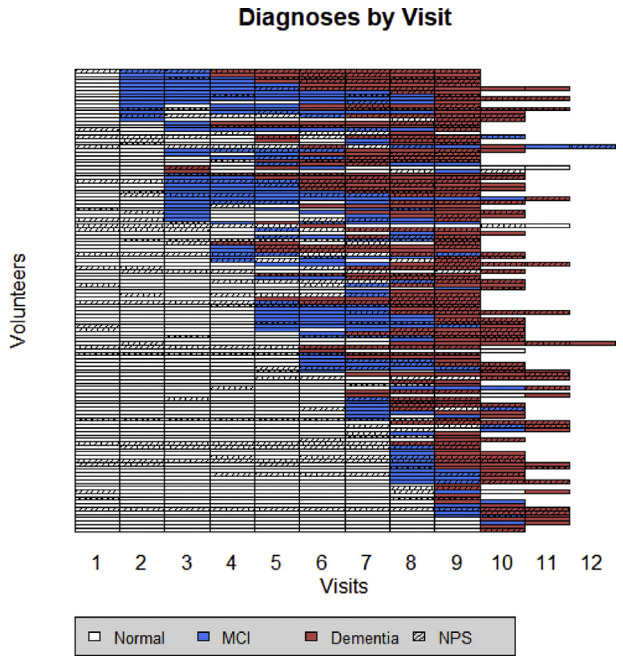

Fig. 1. Time Course of NPS presence and cognitive diagnosis for participants with at least nine annual visits. Abbreviations: MCI, Mild cognitive impairment; NPS, neuropsychiatric symptom.

Fig. 1 displays NPS presence and cognitive diagnoses at each visit for volunteers who were diagnosed with dementia at one visit and who had at least 9 visits (N = 156).

Table 3 shows sequencing of NPS presence and cognitive diagnoses as a function of later diagnosis. Individuals are only counted once in this table, using their most recent diagnosis. Amnestic and nonamnestic MCI had very similar prior NPS patterns. With regard to specific dementias, of those who ultimately developed AD, 30% developed NPSs before MCI, whereas 42% developed NPSs after MCI but before dementia. Almost two-thirds of those who developed dementia of Lewy body type had NPS before cognitive changes. Two-thirds of those who developed vascular dementia or FTD had NPSs before cognitive changes.

Table 4 shows sequences of specific NPI-Q domains and cognitive diagnoses. Depression and irritability were the most common NPSs to precede cognitive diagnoses: 24 and 21%, respectively. Nighttime behaviors and anxiety were also common before MCI. Surprisingly, rates of apathy before MCI or before dementia were relatively low (14%), as were rates of agitation before MCI or before dementia (13%). Hallucinations and delusions were rare before cognitive decline (≤3%); when they occurred, it was typically after onset of dementia.

There were 3124 participants who remained free of an MCI or dementia diagnosis for at least five years. The prevalence of NPS at baseline among this group was 24.5%. By contrast, the prevalence of any NPS in the year preceding MCI diagnosis was 45%, and the prevalence in the year preceding dementia diagnosis was 60.

4. Discussion

We report that NPS occurrence precedes dementia in most people who eventually develop cognitive decline. In fact, NPS precede MCI in most (55%) individuals. In people who progress from cognitively normal to dementia (without MCI), NPS precede dementia in almost two-thirds of cases. To emphasize this point further, over half of individuals who develop a cognitive disorder, including dementia, develop NPS *before* the cognitive disorder. To our knowledge, this is the first prospective quantification of how many people with MCI or dementia developed NPSs before the cognitive diagnosis. This finding is true for both amnestic and nonamnestic MCI, as well as AD, vascular dementia, dementia of Lewy body type, and FTD. Depression was the most frequent one occurring before MCI, whereas apathy and agitation were relatively uncommon. Delusions and hallucinations were rare and occurred most frequently after the diagnosis of dementia.

Although it is known that MBI puts individuals at risk for new-onset cognitive decline and dementia [28,29], no study has quantified in aggregate how many people with dementia actually developed NPS before cognitive changes. Based on our findings, it appears that the presence of NPS before cognitive diagnosis is the norm rather than the exception.

Strengths of this study include the large sample of individuals observed before the onset of MCI or dementia and

Table 3
Cognitive diagnosis by NPSs and cognition diagnosis sequence

Diagnosis	Never (%)	NPS before MCI (%)	NPS before dementia*	NPS after dementia (%)
Amnestic MCI	222 (22)	560 (54)	250 (24)	-
Nonamnestic MCI	67 (21)	174 (56)	72 (23)	-
AD	46 (12)	116 (30)	163 (42)	67 (17)
LBD	2 (14)	7 (50)	4 (29)	1 (7)
FTD	0	2 (67)	1 (33)	0
VaD	0	2 (67)	1 (33)	0
Mixed	8 (4)	71 (37)	77 (41)	34 (18)
Other	11 (22)	7 (14)	23 (45)	10 (20)

Abbreviations: AD, Alzheimer's disease; FTD, frontotemporal dementia; LBD, Lewy body dementia; MCI, mild cognitive impairment; NPS, neuropsychiatric symptom; VaD, vascular dementia.

*Includes those who developed NPS after MCI (normal to MCI); NPS after MCI, before dementia (normal to MCI to dementia); and NPS before dementia (normal to dementia).

Table 4
Individual NPI-Q domain by NPS and cognitive diagnosis sequence

Domain	Never (%)	NPS before MCI (%)	NPS before dementia (%)*	NPS after dementia (%)
Depression	982 (49)	484 (24)	318 (16)	214 (11)
Night time	1110 (56)	381 (19)	298 (15)	209 (10)
Irritability	1037 (52)	415 (21)	337 (17)	209 (11)
Anxiety	1164 (58)	344 (17)	312 (16)	178 (9)
Appetite/eating behaviors	1249 (63)	274 (14)	272 (14)	203 (10)
Delusions	1773 (89)	41 (2)	61 (3)	123 (6)
Hallucinations	1888 (95)	15 (1)	25 (1)	70 (4)
Agitation	1279 (64)	256 (13)	254 (13)	209 (10)
Apathy	1278 (64)	241 (12)	261 (13)	218 (11)
Disinhibition	1622 (81)	114 (6)	116 (6)	146 (7)
Motor	1769 (89)	56 (3)	61 (3)	112 (6)
Elation	1913 (96)	31 (2)	31 (2)	23 (1)

Abbreviations: MCI, Mild cognitive impairment; NPI-Q, Neuropsychiatric Inventory Questionnaire; NPS, neuropsychiatric symptom.
*Includes those who developed NPS after MCI (normal to MCI); NPS after MCI (normal to MCI to dementia); and NPS before dementia (normal to dementia).

followed up for over five years on average. We acknowledge several limitations to our data. One limitation is that individuals comprise a nonrandom volunteer sample. As volunteers, their family history and educational history differ from the general population. Almost 40-50% of volunteers have a family history of dementia, which is higher than the proportion of people in the general population with a family history of dementia. However, because these individuals were recruited as healthy controls, it is possible that this volunteer effect is less biasing than it would be for participants who first join the NACC after a dementia diagnosis or due to cognitive concerns. As in any longitudinal study, particularly of the elderly, individuals are lost to follow up. As such, many of the individuals who were observed to progress to MCI, but not beyond, may well progress in the future. Such an occurrence, however, would not negate the finding that a substantial portion developed NPS before their MCI diagnosis. In the case of individuals who did not receive an MCI diagnosis before dementia, it is possible that many did, in fact, have MCI in between study visits. In those cases, the estimate of the proportion of individuals experiencing NPS before cognitive changes would be biased downward. Because volunteers are only seen yearly and NPS may fluctuate, it is quite possible that the NPI-Q, which refers only to the previous 30 days, may fail to identify NPSs that occur between visits. Again, in such a case, the proportion of individuals experiencing NPSs before cognitive changes would actually be underestimated.

We considered one who develops MCI or dementia at a visit his or her "final" diagnosis. Individuals who develop MCI and then return to normal cognition are often subsequently diagnosed with MCI again; the same is true for individuals with dementia [27]. Moreover, this simplifies our classification scheme, and by moving the bar for cognitive diagnosis to the earliest possible time, we are, if anything, underestimating the proportion of people who experience NPSs before diagnosis.

Our findings suggest that older adults with new-onset NPSs, but without a cognitive diagnosis, are at increased risk of developing a cognitive disorder and thus an important target group for clinical and research efforts. These individuals have typically been labeled as "psychiatric patients" and excluded from trials of disease-modifying interventions [30]. We suggest that they represent a target population for observational and interventional studies in the secondary prevention of dementia. Intervening at this stage, before cognitive diagnosis, could delay the onset of dementia, alter the disease course, and reduce its severity and impact [16,31]. Specifically, the enrollment of this population in interventional studies, for instance with antiamyloid agents, or in neuroimaging studies to identify biomarkers might shift the ethical balance and enhances study power because there is a higher likelihood they will develop the disease in question, and patients once considered "psychiatric" patients excluded from trials might now participate. Awareness of the association between NPSs and onset of MCI and dementia can minimize delays in dementia diagnosis so that individuals are not severely advanced by the time they are detected and formally assessed [30,32]. Therapy development should also include clinical trials and reimbursement of nonpharmacologic and psychosocial interventions in treating NPSs [33]. Future treatment studies of NPSs may identify ways to forestall disease trajectory and reduce overall disease burden.

Moreover, studying these individuals may help us identify the causal pathway between anxiety, depression, and other affective symptoms and cognitive impairment [34]. Future studies should examine how severity and particular patterns of symptoms relate to progression of neurodegenerative disease and the underlying pathology.

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RESEARCH IN CONTEXT

1. Systematic review: The authors reviewed the literature using traditional (i.e., PubMed) sources and meeting abstracts and presentations. The presence of neuropsychiatric symptoms (NPSs) alongside neurodegenerative disorders has been widely accepted, and more recently, the concept of mild behavioral impairment, or a neuropsychiatric syndrome preceding dementia, has been described, but exact numbers of people who experience NPSs before dementia are unknown. Relevant citations are included.
2. Interpretation: Our findings demonstrated that most people who develop a cognitive disorder develop NPSs before their cognitive diagnosis.
3. Future directions: The manuscript lays the foundation for further studies of individuals with NPSs before the onset of a cognitive disorder. Examples include (1) observational studies to see how severity and pattern of symptoms relate to progression of disease; (2) interventional studies in the secondary prevention of dementia; and (3) neuroimaging and biomarkers of individuals to elucidate underlying pathology.

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