Specific memory complaints and the identification of preclinical Alzheimer's disease years before conversion to Mild Cognitive Impairment

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This work is dedicated to the late Dr Benjamin Seltzer, MD

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Abstract

Early detection of cognitive decline will become increasingly important as preventative therapies for Alzheimer's disease (AD) become available. While new imaging techniques and biomarkers have shown evidence of neuropathology in the preclinical stages of AD, most clinicians must rely on the subjective report of symptoms to identify the onset of cognitive decline. Patients often present to primary care physicians with complaints from self or family members about confusion, memory loss or personality changes. However, discriminating complaints associated with normal from abnormal aging is difficult. The identification of patient-generated specific complaints indicating prodromal or Mild Cognitive Impairment (MCI) could lead to more prompt and effective intervention strategies for future dementia patients, and could improve prognosis. This study investigated how specific subjective complaints may be related to subsequent conversion to MCI in a cohort of cognitively normal elderly subjects who have a familial and/or genetic risk for AD.

Subjects included cognitively intact participants and their informants (spouse, sibling, adult child) from a large longitudinal study of cognition in individuals with a family history of AD. Participants were further characterized by their APOE ε4 allele status. Both subjects and their informants were administered the Multidimensional Assessment of Neurodegenerative Symptoms (MANS), a questionnaire that assesses subjective changes in memory, personality, motor, vision, and speech.

Of 85 subjects who were cognitively normal at the initial MANS administration, 12 converted to MCI within 25-167 months. The participants who later converted to MCI had greater memory complaints at baseline compared to nonconverters ($\chi^2 = 5.65$, $p < 0.05$). There were no significant differences in other MANS domains. In regards to specific memory complaints, converters were significantly more likely to endorse symptoms of "losing or misplacing things" ($\chi^2 = 13.99$, $p<0.001$), having an "inability to keep events or tasks in right order," ($\chi^2 =12.06$, $p<0.001$), "forgetting names of familiar people" ($\chi^2 = 4.59$, $p < 0.05$), and "forgetting things or events from long ago," ($\chi^2 = 6.62$, $p < 0.05$). Nonconverters also endorsed some memory complaints, but no complaint or group of complaints was endorsed more than others. The APOE ε4 allele was observed in 83% of the participants who converted to MCI

compared to 52% of those who remained cognitively intact over the course of the assessment period.

In cognitively normal subjects with a family history of AD, specific memory complaints about losing or misplacing items, forgetting the order of tasks or events, forgetting names of familiar people and forgetting things or events from long ago may be useful clinical tools for identifying Preclinical AD up to eight years before conversion to MCI.

Table of Contents

List of Figures and Tables

Introduction

Early detection of cognitive decline is valuable to AD patients and caregivers, as it allows them to prepare both practically and emotionally for the future. Creating practical and easily implemented signals of early change will become increasingly important as preemptive therapies for AD become available and early treatment is able to improve prognosis.

A stage of AD termed "preclinical AD" has been introduced in which only very subtle cognitive decline exists that does not meet criteria for impairment. The diagnostic criterion for preclinical AD has been established based on several neuropathologic signs as well as subtle cognitive decline[1]. Subtle cognitive decline is defined as a change from baseline level of cognition assessed by poor performance on sensitive composite measures of cognition (such as challenging episodic memory tests), but not yet meeting criteria for MCI, where frank impairments in memory and/or other domains are evident on cognitive testing.

Detection of preclinical AD is, at present, a difficult endeavor. While comprehensive cognitive assessment, neuroimaging and other biomarkers are available, these assessments are expensive, time-consuming, and have not yet proven to be sensitive on an individual basis. Thus, clinicians still generally rely on limited screening tools and the subjective report of symptoms to detect the onset of cognitive decline in their patients. At present, there is not an established method of assessing subjective memory complaints, which can vary from patient to patient, to detect preclinical AD. While brief screening tools like the Mini Mental Status Exam (MMSE) are widely used in neurological populations, they are limited by a lack of sensitivity to subtle symptoms. In addition to being costly and time-consuming, extensive, in-depth neurocognitive testing has also demonstrated difficulties with detecting early symptoms, especially in individuals with above-average pre-morbid cognition, since performance declines from a higher level may be missed because scores are above average compared to same-age cohorts[1].

Subjective complaints about memory may be a fast and efficient means to identify individuals who may meet the diagnosis of Preclinical AD. Amariglio et al investigated the relationship of subjective memory complaints and cognitive impairment in a cross-sectional study in which a large cohort of 16,964 nurses were given telephone cognitive assessments along with seven questions regarding subjective memory complaints[2]. Results showed that two subjective memory complaints (trouble following a group conversation and trouble finding one's way around familiar streets) were more highly associated than others with odds of cognitive impairment. There was also a strong, linear trend of increasingly worse scores on cognitive tests with increasing numbers of memory complaints. For each additional subjective memory complaint endorsed, the odds of cognitive impairment increased by approximately 20%.

Tobiansky et al evaluated a population of 705 independently living elderly subjects over age 65 (65-98) in a London electoral ward for the relationship between objective memory disorder, depression, and Subjective Memory Impairment (SMI)[3]. Subjects were interviewed in their homes with short-CARE, a brief version of the Comprehensive Assessment and Referral Evaluation screening tool that consists of a semi-structured interview containing indicator scales that suggest likely depression, dementia, SMI, activity limitation, sleep disorder and somatic symptoms. The SMI scale consisted of nine questions. 705 subjects were found to have SMI upon their first interview, and in follow up interviews two years later, 27% of 524 original subjects were found to have SMI. At both time points, there was a positive association between SMI, depression and dementia. Elderly with SMI at the first interview were significantly more likely to be suffering from dementia or depression two years later. Two of the nine items on the SMI scale were more associated with the development of dementia two years later: forgetting what he/she has read or heard and saying impaired memory is a problem for him/her. One item was particularly associated with depression, which was the subject being embarrassed by their memory.

Zandi et al examined the relationship between subjective memory complaints, objective memory performance and depression in a cross-sectional study of 603 elderly people who were referred to a memory clinic within a six-year timeframe[4]. Objective memory performance was assessed with the CAMDEX (Cambridge Mental Disorders in the Elderly Examination) and subjective memory complaints were assessed with four memory questions. Subjects with a greater number of subjective memory complaints scored higher on depression scales than individuals without subjective memory complaints. Also, objective memory was correlated with subjective memory and age. Age was not a predictor of subjective memory complaints, nor was subject income, living status or education.

Rabin et al investigated the independent and combined contributions of three areas of cognitive assessment upon the risk of developing AD: neuropsychological testing, self-reports and informant-reports[5]. They used a longitudinal sample composed of 627 non-demented individuals over the age of 70 and found that 48 subjects developed incident AD during a median of 3.3 years of follow-up. In models that examined the three areas of cognitive assessment simultaneously, only informant report and neuropsychological testing were associated with an increased risk of developing AD, while self-report was not.

In summary, there is a relationship with increased memory complaints in individuals who have or may soon declare as dementia. However, both normal and demented people have memory complaints. Our purpose is to determine if there are certain complaints that capture the changes that are more characteristic of impending AD. At this time, no specific subjective memory complaints have been established as effective screening tools for preclinical AD. Unlike procedural memory, controlled, or declarative episodic memory (i.e., recollection of events) has been shown to decline with age and age-related neurological conditions such as AD. Thus, episodic memory complaints have the potential to be used as preclinical AD screening tools. However, while controlled memory can be easily distinguished from procedural memory, it is nevertheless a broad category that encompasses many types of complaints. It has been unclear up to this point whether a specific complaint or group of complaints could be used as a screening tool for preclinical AD in primary care settings.

In this study, we utilized the MANS, a multidimensional questionnaire of symptoms associated with neurodegenerative disorders which contains a set of questions about subjective memory complaints. It is an informant and patient-based questionnaire that assesses subtle changes over time in the domains of memory, Activities of Daily Living (ADLs), personality, visual recognition, speech and motor functioning. Factor and reliability analyses showed excellent internal consistency for both the self-report and the informant-report versions of the MANS, while correlational analyses supported the construct validity of the MANS. This validation is consistent with a study of subjects with preclinical AD and MCI in which self and informant reports of cognitive impairment were shown to correlate with performance on cognitive tests, suggesting that subjective complaints of cognitive impairment are a reliable indicator of cognitive decline[6].

The aim of this study was to investigate how subjective memory complaints in cognitively normal people can differ for individuals who convert to MCI compared to those who remain cognitively stable. We hypothesized that particular subjective memory complaints would be predictive of cognitive decline occurring years later, indicating a preclinical stage of AD.

Research Materials & Methods

Subjects of this study were cognitively intact participants with informants (spouse, sibling, adult child) from a large longitudinal study of cognition in individuals with a family history of AD. Criteria for entry into the longitudinal study included a score of >26 on the MMSE, a score of <10 on the Hamilton Depression Rating Scale (Ham-D), and no impairment documented on both the Functional Activities Questionnaire (FAQ) and the Instrumental Activities of Daily Living Questionnaire (IADLQ). In addition, none of the subjects had confounding medical, neurologic or psychiatric problems, and none of them met the criteria for MCI, AD, Major Depressive Disorder or dementia.

In order to assess individuals who were likely to convert to MCI/AD within a reasonable time of the baseline MANS, we assessed individuals aged 44-81 (M = 61.2, SD = 7.6). Subjects of the study were initially genotyped for APOE allelic status using a polymerase chain reaction based assay. There was an enrichment of APOE ε4 participants by recruiting in groups of four, with each group consisting of two APOE ε4 carriers (either heterogenous or homozygous) and two noncarriers. Subjects were given the following battery of cognitive tests to assess their abilities every two years: Full neurologic examination, MMSE, HAM-D, IADLQ, and the Structured Clinical Interview from the third revised edition of the Diagnostic and Statistical Manual of Mental Disorders. A panel of neurologists determined the cognitive status of patients at entry and at each two-year follow up. Patients were recruited, enrolled and followed from 1994 to the present.

Table 1: Demographics of subjects at baseline MANS completion

Total number of subjects	85
Age	61.2(7.6)
Male	35
Female	50
Years of education	15.8(2.8)
APOE ε4 carriers	43
Non-carriers	42
AVLT total words learned	46.9(9.1)
Folstein MMSE	29.6(0.78)
CFT recall	16.8(6.5)
Study participation (from completion of baseline MANS)	
0-24 months	3
25-48 months	7
49-72 months	12
Over 72 months	63
Conversion to MCI or Cognitive Impairment over course of study	
Conversion to MCI	11
Conversion to Cognitive Impairment (AD)	1

We identified our subjects by searching for patients who had completed multiple MANS questionnaires. For these subjects, we obtained MANS data from all domains, for each individual question. Each domain section on the MANS begins with, "to the best of your knowledge, over the past year, have you noticed a change in x domain?" Followed by the questions for that domain. Each question can be answered as 0 (never), 1 (once), 2 (occasionally), 3 (more than monthly) or 4 (routinely). We took these numerical responses and converted them to either 0; representing the absence of a complaint, or 1; representing the presence of a complaint. Original responses of 1-4 were assigned to 1 (presence of complaint), while original responses of 0 were assigned to 0 (absence of complaint). We assessed the cognitive outcomes for each subject. Those who had eventually converted to MCI or AD based on diagnostic criteria were labeled "converters." For statistical analyses, we conducted Chi Square tests to compare the presence of specific memory complaints from either subjects or informants, between converters and nonconverters.

Table 2: MANS Memory Questions

1. In the past year, how often have you forgotten recent events?
2. In the past year, how often have you forgotten the names of familiar people?
3. In the past year, how often have you lost or misplaced things?
4. In the past year, how often have you forgotten things or events from long ago?
5. In the past year, how often have you forgotten about planned activities or appointments?
6. In the past year, how often have you been unable to keep events or tasks in the right order?
7. In the past year, how often have you become lost or asked for directions in familiar places?
8. In the past year, how often have you become mixed up about time of day, date or year?
9. In the past year, how often have you not known where you are?

Table 3: Demographics of converters and nonconverters at baseline MANS completion

	Converters	Nonconverters
Number of subjects	12	73
Age	63.8(7.1)	59.7(7.7)
Education	15.6(2.1)	15.8(2.9)
Folstein MMSE (at baseline)	29.2(1.0)	29.6(0.7)
AVLT	42.8(9.0)	47.5(9.0)
CFT recall	14.0(7.0)	17.1(6.3)
Months in study	85.1(34.0)	96.2(40.0)
Range of months to conversion	25-167	---

Results

This study consisted of 85 subjects who were cognitively normal at the baseline MANS administration. Out of that 85, 12 people converted to MCI within 25-167 months. There were no significant differences at baseline between converters and nonconverters in age (*M* = 63.8 and 60.8 respectively, t(184) = 1.31, p = 0.21), years of education (*M* =15.8 and 15.9, t(84) = 0.17, p = 0.87), months in study (*M* = 85.7 and 96.1, t(84) = 0.96, p = 0.35), or neurocognitive test scores (MMSE: *M* = 29.2 and 29.6, t(84) = 1.5, p< 0.17; AVLT: *M* = 42.8 and 47.5, t(84) = 1.67, p< 0.12, CFT Recall: *M* = 14.6 and 17.1, t(84) = 1.2, p<0.27). The MMSE, Auditory Verbal Learning Test (AVLT) and Complex Figure Test Recall (CFT Recall) were analyzed in order to avoid any confounding objective evidence of converters having worse memory than nonconverters at baseline. In this cohort of cognitively intact individuals, there were very few endorsements of complaints in the domains of personality, motor, vision, and speech; thus not allowing for further group analyses.

There were 12 participants who converted to MCI or AD in the range of 25-167 months from baseline MANS completion. Comparing converters and nonconverters, the converters had significantly more memory complaints at baseline than nonconverters (χ^2(1, *N* = 85) = 5.65, p<0.05). There were four specific memory complaints that were endorsed significantly more often by converters: losing or misplacing things (χ^2 = 13.99(1, *N* = 85), p<0.001), inability to recall events or tasks in right order (χ^2(1, *N* = 85) = 12.06, p<0.001), forgetting the names of familiar people (χ^2(1, *N* = 85) = 4.59, p<0.05) and forgetting things or events from long ago (χ^2(1, *N* = 85) = 6.62, p<0.05). The nonconverters did endorse a variety of complaints, but there was no pattern to the complaints as none were endorsed more often than others.

In the converter group, there was a greater percentage of subject complaints compared to informant complaints in 7/9 questions. Conversely, in the nonconverters, there was a greater percentage of informant complaints compared to subject complaints in 9/9 questions.

Table 4: Specific memory complaints of converters and nonconverters

Memory complaints	Converters	Nonconverters
Subject and/or informant complained	83.3% (χ^2 = 5.65, p < 0.05)	49.3%
Subjects only complained	33.3%	5.5%
Informants only complained	16.7%	24.7%
Both complained	33.3%	19.2%
Specific memory complaints		
1. Subject and/or informant complained about forgetting recent events	75%	37%
2. Subject and/or informant complained about forgetting names of familiar people	58% (χ^2 = 4.59, p < 0.05)	30%
3. Subject and/or informant complained about losing or misplacing things	91% (χ^2 = 13.99, p < 0.001)	39%
4. Subject and/or informant complained about forgetting things or events from long ago	67% (χ^2 = 6.62, p < 0.05)	32%
5. Subject and/or informant complained about forgetting planned activities or appointments	50%	30%
6. Subject and/or informant complained about inability to keep events or tasks in right order	58% (χ^2 = 12.06, p < 0.001)	19%
7. Subject and/or informant complained about getting lost or asking for directions in familiar places	25%	9.5%
8. Subject and/or informant complained about forgetting the day, date or year	41%	28%
9. Subject and/or informant complained about not knowing where they are	16%	16%

Table 5: ApoEε4 carrier status in converters and nonconverters

	Converters	Nonconverters
Subjects	12	73
ApoE4 carriers (homo or hetereozygotes)	10 (83.3%) (χ^2 = 4.74, $p < 0.05$)	38 (52.1%)

Discussion

In this study, we investigated how specific memory complaints in individuals who have no evidence of cognitive problems are related to subsequent conversion to MCI/AD. We found that 10/12 persons who converted to MCI/AD within 25-106 months were significantly more likely than nonconverters to endorse the following memory complaints *before any signs of MCI/AD were present on cognitive or other functional assessments*: losing or misplacing items, forgetting the order of tasks or events, forgetting the names of familiar people and forgetting things or events from long ago. In contrast, complaints regarding forgetting recent events, forgetting planned activities or appointments, getting lost or asking for directions in familiar places, forgetting the day, date or year and not knowing one's location were not associated with subsequent development of MCI/AD. In addition, nearly every memory complaint in the converter group had a greater proportion of self-reported complaints compared to informant-reported complaints, while this pattern was reversed for nonconverters.

The four memory complaints endorsed by the converter group may indicate subtle cognitive change in the preclinical AD period, thereby having the potential to serve as an efficient screening tool in the identification of patients who may later develop MCI/AD. In addition, the greater number of self-reported memory complaints amongst converters during the preclinical AD period could also be used as a screening tool. The combination of these two tools could allow for the early identification of future converters and facilitate prompt interventions.

To our knowledge, this is the first study that determines that subjective memory complaints are present even in individuals known to be cognitively intact based on cognitive, functional and medical criteria. Many of the previous studies related to subjective complaints have focused on correlating subjective complaints with current problems of individuals who are already experiencing memory problems[5].

We found that participants had subjective memory complaints sometimes years before the conversion to MCI. We found overlap with other studies with narrower time to conversion, or subjective complaints in MCI patients, but there were some unique complaints that may indicate an evolving picture of complaints or subtle deficits that can occur.

We found more subjective memory complaints being endorsed by the subjects rather than the informants, which may suggest that in the early stages, patients may realize changes that may become less obvious as impairment increases, which may be indicative of emerging unawareness of deficit.

In a cross-sectional study which investigated the relationship between subjective memory complaints and cognitive impairment, Amariglio et al used a list of memory complaints to assess subjective memory which contained two items that were very similar to memory complaints used in our study: trouble finding one's way around familiar streets and having trouble remembering recent events[2]. While having trouble finding one's way around familiar streets was associated with cognitive impairment in Amariglio's study, virtually the same complaint of becoming lost or asking for directions in familiar places was NOT endorsed by those who converted to MCI/AD in our study. This may suggest that this complaint is indicative of cognitive impairment but not of preclinical AD.

In examining the relationship between objective memory disorder, depression, and SMI, Tobiansky et al assessed whether subjective memory complaints were predictive of dementia[3]. Two particular complaints were found most likely to predict the development of dementia two years after an initial interview: forgetting what he/she has read or heard and saying impaired memory is a problem for him/her. These two items were not included in our study. However, one of the questions used by Tobiansky that was not found to predict the development of dementia two years later; forgetting where one has placed things, was one of the four complaints endorsed by converters in our study. This discrepancy may reflect the different timeframes in which subjects were followed. While Tobiansky's subjects were followed-up once after only two years, the subjects in our study were interviewed up to eight years after their initial interview. The complaint of losing or misplacing things may be an earlier indicator of preclinical AD, thus explaining why it was endorsed by converters in our study but not by converters in Tobiansky's study.

The Zandi study used four memory complaints to evaluate SMI in its analysis of the relationships between subjective memory complaints, objective memory performance and depression[4]. Unlike our study, the memory complaints were summed and categorized as low versus high SMI, and were not examined individually. However, two of the Zandi study complaints were very similar to memory complaints endorsed by our converters: “Do you forget where you have left things more than you used to?” and “Have you been in your town and neighborhood and forgotten your way?” This study found that subjects with a greater number of subjective memory complaints scored higher on depression scales than individuals without subjective memory complaints, thus highlighting the importance of correcting for depression in our study.

Rabin et al found that informant reports of memory complaints and episodic memory tests were associated with a risk of developing AD, while self-reports of memory complaints were not[5]. Our study results differed, in that we found a greater number of self-reported complaints in the group of subjects who converted to MCI/AD.

Future Directions

One challenge to our study is the question of whether the subjective complaints of our converters were merely a sign of cognitive decline associated with normal aging. However, the four complaints endorsed by our converters differ from the nature of complaints associated with Age Associated Cognitive Decline (AACD), which have been shown to primarily involve neuroticism and gender.

Another challenge to our study is the low number of subjects. Our results should ideally be replicated in a study with a larger subject pool.

In addition, we selected subjects from a pool based on completion of multiple MANS forms. Perhaps there is a significant difference between subjects who did and did not complete the MANS questionnaires at each two year interval, making our group of subjects not representative of cognitively normal elderly persons at risk of developing AD. Willingness to complete the MANS could be driven by neurocognitive problems and could be related to age, sex, or education.

The MANS memory questions have a few limitations. The questions are asked in the format of "in the past year," which may cause subjects or informants to not account for changes occurring during the entire two-year interval between filling out each MANS. There is a degree of ambiguity in some of the memory questions, such as, "In the past year, how often have you forgotten things or events from long ago?" Long ago may be perceived by some as 1-2 years ago, and by others as 20 years ago. Similarly, "recent events" is not clarified as recent events in the subject's personal life versus news events.

Conclusions

In cognitively normal subjects with a family history of AD, specific memory complaints about losing or misplacing items, forgetting the order of tasks or events, forgetting names of familiar people and forgetting things or events from long ago may be useful clinical tools for identifying preclinical AD up to eight years before conversion to MCI. The identification of patient-generated specific complaints indicating prodromal AD or MCI could lead to more prompt and effective intervention strategies for future dementia patients, and could improve prognosis.

References

1. Sperling, RA. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging: Alzheimer's association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011;(3):280-92.

2. Amariglio, RE. Specific subjective memory complaints in older persons may indicate poor cognitive function. *J Am Geriatr Soc* 2011;(59):1612-1617.

3. Tobiansky R, Blizard R, Livingston G, Mann A. The Gospel Oak Study stage IV: the clinical relevance of subjective memory impairment in older people. *Psychol Med* 1995;25(4):779-86.

4. Zandi, T. Relationship between subjective memory complaints, objective memory performance, and depression among older adults. *American Journal of Alzheimer's Disease and Other Dementias* 2004;19(6): 353-360.

5. Rabin, LA. Predicting Alzheimer's disease: neuropsychological tests, self-reports, and informant reports of cognitive difficulties. *J Am Geriatr Soc* 2012;60(6):1128-34.

6. Locke, D. Assessment of Patient and Caregiver Experiences of Dementia-Related Symptoms: Development of the Multidimensional Assessment of Neurodegenerative Symptoms Questionnaire. *Dement Geriatr Cogn Disord* 2009;27(3): 260–272.

7. Caselli RJ, Reiman EM, Osborne D, et al. Longitudinal changes in cognition and behavior in asymptomatic carriers of the APOE e4 allele. *Neurology* 2004;62:1990-5.

8. Caselli RJ, Reiman EM, Locke DE, et al. Cognitive domain decline in healthy apolipoprotein E epsilon4 homozygotes before the diagnosis of mild cognitive impairment. *Arch Neurol* 2007;64:1306-11.

9. Caselli RJ, Chen K, Lee W, Alexander GE, Reiman EM. Correlating cerebral hypometabolism

with future memory decline in subsequent converters to amnestic pre mild cognitive impairment. *Arch Neurol* 2008;65:1231-6.

10. Caselli RJ, Dueck A, Osborne D. Longitudinal modeling of age-related memory decline and the APOE ε4 effect. *N Engl J Med* 2009;361:255-63.