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

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Abstract

Early detection of cognitive decline will become increasingly important as preventative therapies for Alzheimer's disease (AD) become available. 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. Both subjects and their informants (spouse, sibling, adult child) 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. These "converters" had a greater number of memory complaints at baseline compared to nonconverters (χ^2=5.65, p<0.05). Converters were significantly more likely to endorse symptoms of "losing or misplacing things" (χ^2=13.99, p<0.001), having an "inability to keep events or tasks in right order" (χ^2=12.06, p<0.001), "forgetting names of familiar people" (χ^2=4.59, p<0.05), and "forgetting things or events from long ago" (χ^2=6.62, p<0.05). In cognitively normal subjects with a family history of AD, these specific memory complaints may be useful clinical tools for identifying Preclinical AD up to eight years before conversion to MCI.

Introduction

Early detection of memory or other cognitive problems may hold the key for prevention of Alzheimer's Disease. Since it is difficult and expensive to screen for subtle changes with neuroimaging, CSF or other biomarkers, finding a broad screen that can be done on routine visits would be advantageous. A previous study found that increasing numbers of memory complaints are positively associated with subjective memory impairment and the development of dementia over a short period of time (2 years), likely because patients were already impaired at the beginning of the study[1]. However, It has been unclear up to this point whether a specific complaint or group of complaints could be used as a screening tool for Pre-clinical AD in primary care settings. The aim of this study was to investigate whether subjective memory complaints in cognitively normal people indicate a pre-clinical awareness of change in cognitive function not otherwise detected. We hypothesized that cognitively intact individuals who convert to MCI or AD would endorse more subjective memory complaints than individuals whose cognition remained stable over time.

Methods

Subjects of this study were cognitively intact participants from a large longitudinal study of cognition in individuals with a family history of AD. 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. Subjects were genotyped to determine APOE ε4 status and were given a battery of cognitive tests to assess their abilities every two years. Patients were recruited, enrolled and followed from 1994 to the present[4]. We assessed individuals aged 44-81 (*M*=61.2, *SD*=7.6). 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. We assessed the cognitive outcomes for each subject, identifying those who had eventually converted to MCI or AD, labeling this group "converters." To test our hypotheses, we conducted Chi Square tests to compare the presence of specific memory complaints between converters and nonconverters.

Results

All participants:

This study consisted of 85 subjects who were cognitively normal at the baseline MANS administration. 12 of 85 subjects 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(84)= 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). 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 the 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). A variety of complaints were endorsed by nonconverters, but no complaint was endorsed more often than others. In the converter group, there was a greater percentage of complaints from subjects compared to informants in 7/9 questions. Conversely, in the nonconverters, there was a greater percentage of complaints from informants compared to subjects in 9/9 questions. 10/12 converters were APOE ε4 carriers, therefore there was no difference amongst carriers and noncarriers.

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)
ApoE4 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 Mild Cognitive Impairment or Cognitive Impairment over course of study	
Conversion to MCI	11
Conversion to Cognitive Impairment (AD)	1

Table 2: 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%

Discussion and Conclusions

To our knowledge, this is the first study to show 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 (to determine level of unawareness) or to correlate complaints with depression[1-3]. We found that participants had subjective memory complaints sometimes years before conversion to MCI. Among converters, we also found that more subjective memory complaints were endorsed by the subjects rather than the informants, suggesting that in the early stages, patients may realize changes that become less obvious as impairment increases, possibly indicating an emerging unawareness of deficit. 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. In addition, the greater number of self-reported memory complaints among converters could also be used as a screening tool. The combination of these tools could facilitate early identification of future converters and facilitate prompt interventions.

References

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Acknowledgements

This project was supported in part by the National Institute on Aging (P20-AG19610 and RO1-MH057899) and the Arizona Alzheimer's Consortium and the State of Arizona. I wish to thank my mentors Leslie Baxter, PhD and Richard Caselli, MD.