Chapter 56
Predictors of Progression from Mild Cognitive Impairment to Alzheimer's Disease

Sarah Kim and Tracey Holsinger

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Objective to determine the occurrence of neuropsychiatric symptomatology and the relationship to future development of Alzheimer's disease in persons with and without mild cognitive impairment [1].

Methods Participants of this study were taken from the Kungsholmen Project, a longitudinal study initiated in 1987 which assessed the occurrence, risk factors, and

S. Kim
Duke University Department of Psychiatry and Behavioral Sciences, Durham, NC, USA
e-mail: kyung.kim@duke.edu

T. Holsinger (✉)
Duke University Department of Psychiatry and Behavioral Sciences, Durham, NC, USA

Durham VA Medical Center, Durham, NC, USA
e-mail: Tracey.holsinger@duke.edu

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evolution of dementia in individuals aged 75 years and above living in the Kungsholmen area of Stockholm, Sweden. A sample of 668 individuals who had gone through a battery of clinical assessment including a psychiatric and neurologic examination as well as neuropsychological testing were considered for this analysis.

Of the sample, 225 individuals were excluded because they met the diagnostic criteria of dementia according to Diagnostic and Statistical Manual of Mental Disorders (DSM) III-R. Another 40 individuals were excluded for scoring less than 20 on the Mini-Mental State Examination (MMSE), unknown educational level, or age over 95 years. Of the remaining, 296 individuals underwent neuropsychological testing. Sixty-four did not fulfill the criteria for amnestic or multi-domain MCI, but also did not display a normal level of cognitive functioning. Finally, a total of 232 participants (47 individuals with MCI, either amnestic or multi-domain, and 185 individuals with normal cognitive functioning) were included in this study.

For the assessment of neuropsychiatric symptoms on the 232 participants, the investigators used the Comprehensive Psychopathological Rating Scale (CPRS) [2]. This is an inventory of 40 self-reported items and 27 observed items largely surveying anxiety, depression, and paranoia symptoms on a scale from 0 to 3. The investigators in this study incorporated elements from CPRS pertinent to three categories: mood, motivation, and anxiety. They also rated each symptom on a six-point scale, with the score of 2–6 indicating a severe symptomology. Mood symptoms included dysphoria, suicidal ideation/thoughts of death, feelings of guilt, and appetite disturbances. Motivation symptoms included a lack of interest, concentration difficulties, psychomotor disturbances, and loss of energy. Anxiety symptoms included indecision, persistent worrying, anxiety, and social withdrawal.

The participants underwent neuropsychological testing assessing three specific domains: episodic memory (various word recall tasks), language fluency (category fluency for grocery items), and visuospatial functioning (block design, clock reading, and clock setting). The MCI cohort of 47 participants were divided into MCI-amnestic (impairment in episodic memory but normal functioning on language and visuospatial tasks) and MCI-multi-domain (impairment in two or more areas of the episodic memory, language, and visuospatial domains).

Subjects were reassessed 3.4 years (SD 0.6) after baseline. Nineteen subjects dropped out, and 33 subjects had died. The remaining subjects underwent a clinical examination where the dementia diagnosis was made according to DSM III-R using a three-step procedure [3]. A preliminary diagnosis was made by the examining physician and then independently reviewed by a specialist. In case of disagreement between the examining physician and the specialist, a third specialist made the final diagnosis.

Results The mean age of the study population was 84 years (SD = 5.1), 84.9% ($n = 197$) were females, and 39.2% ($n = 91$) had high education (≥8 years). Logistic regression models and chi-squared tests were used to assess differences in the neuropsychiatric symptoms between subjects with MCI and subjects without cognitive impairment, adjusting for age, sex, and education. Of the study population, 185

subjects had normal cognitive function, 17 subjects had MCI-amnestic, and 30 subjects had MCI-multi-domain at baseline.

At baseline, mood symptoms were present in 18.4% ($n = 34$) of normal subjects and 36.2% ($n = 17$) of subjects with MCI all types (35.3% in MCI-amnestic, 36.7% in MCI-multi-domains). The odds ratio (OR) of mood symptoms in MCI all types was 2.5 (95% CI, 1.2–5.0), MCI-amnestic OR was 2.3 (95% CI, 0.8–6.8), and MCI-multi-domains OR was 2.5 (95% CI, 1.1–5.7). Anxiety symptoms were present in 24.9% ($n = 46$) of normal subjects and 46.8% ($n = 22$) of subjects with MCI all types (41.2% in MCI-amnestic, 50.0% in MCI-multi-domains). The OR of anxiety symptoms in MCI all types was 2.5 (95% CI, 1.3–5.2), MCI-amnestic OR was 2.1 (95% CI, 0.7–6.0), and MCI-multi-domains OR was 2.9 (95% CI, 1.3–6.7). Motivation symptoms were present in 13.0% ($n = 24$) of normal subjects and 36.2% ($n = 17$) of subjects with MCI all types (35.3% in MCI-amnestic, 36.7% in MCI-multi-domains). The OR of motivation symptoms in MCI all types was 3.8 (95% CI, 1.8–8.0), MCI-amnestic OR was 3.9 (95% CI, 1.3–11.9), and MCI-multi-domains OR was 3.8 (95% CI, 1.6–9.0).

At 3-year follow-up, 77.1% ($n = 131$) of cognitively normal subjects were alive without dementia; 12.9% ($n = 22$) were dead without dementia; 5.9% ($n = 10$) had been diagnosed with Alzheimer's disease (AD) and 4.1% ($n = 7$) with other dementias. For the subjects with baseline MCI, 18.6% ($n = 8$) were alive without dementia; 18.6% ($n = 8$) were dead without dementia. A total of 56.2% ($n = 24$) had been diagnosed with AD and 7.0% ($n = 3$) with other dementias. The relative risk (RR) for each neuropsychiatric symptom was assessed for progression to AD in subjects with MCI and in subjects with no cognitive impairment at baseline. There was no statistically significant increased risk for mood symptoms increasing progression from MCI to AD (RR = 0.9 [95% CI, 0.6–1.5]). Anxiety symptoms almost doubled the risk of progression to AD in subjects with MCI (RR = 1.8 [95% CI, 1.2–2.7]). Motivation symptoms did not show statistically significant increased risk of progression to AD in MCI subjects (RR = 1.1 [95% CI, 0.7–1.8]). For cognitively normal subjects, there was increased risk of developing AD when mood symptoms were present at baseline (RR = 1.9 [95% CI, 1.0–3.6]). Motivation symptoms at baseline also increased risk (RR = 1.9 [95% CI, 0.5–7.4]), but baseline anxiety symptoms did not (RR = 1.1 [95% CI, 0.5–2.3]).

Conclusions Neuropsychiatric symptoms such as mood (depression), anxiety, and motivation symptoms were more common in participants with MCI (66.0%) when compared to the population without cognitive impairment (38.9%). Among the symptoms examined, anxiety showed highest prevalence (46.8%) in participants with MCI, followed by mood (36.2%) and motivation (36.2%) symptoms. At 3-year follow-up, baseline anxiety symptoms were associated with an increased risk of progression to AD in MCI subjects (RR = 1.8), but not a significantly increased risk of developing AD in subjects who were cognitively normal at baseline (RR = 1.1). Mood and motivation symptoms did not show a statistically significant increase in risk of progression to AD in MCI subjects (RR = 0.9, RR = 1.1, respectively) but

showed an increased risk of developing AD in subjects with normal cognition at baseline (RR = 1.9 for both).

Strengths of the Study

1. Longitudinal population-based cohort study.
2. This study not only assessed the effect of neuropsychiatric symptoms on progression or development of AD but also evaluated the prevalence of such symptoms in MCI population.
3. There was separation and comparison of general "mood" symptoms into depression, anxiety, and motivation.
4. The length of follow-up period (3 years).
5. The diagnosis of dementia through a three-step procedure.

Limitations of the Study

1. Small sample size in the final MCI groups.
2. Large female to male ratio (84.9% female) which can be a confounding factor for prevalence of disorders such as depression and anxiety.
3. Unclear assessment in making cognitive diagnoses of patients who had died.

Take-Home Points

Neuropsychiatric symptoms are more common in individuals with MCI. Neuropsychiatric symptoms not only increase the risk of progression of MCI to AD but also increase the risk of incidence of AD in individuals without cognitive impairment at baseline. Among the various neuropsychiatric symptoms, anxiety increases the risk of progression to AD in participants who have a MCI by twofold, and depression increases the risk of development of AD by twofold in subjects who were cognitively normal at baseline.

Practical Applications of the Take-Home Points

These findings suggest that anxiety symptoms may reflect the neuropathological changes responsible for the progression from MCI to AD. It could also be that anxiety is a subjective reaction to the neurodegenerative process in progress. Whether it be reflective of actual changes or a subjective reaction, anxiety is common in cognitive impairment, and behavioral agitation is also common in later stages of dementia. Many studies have looked at the impact of depression on dementia, but fewer have examined the effect of anxiety. This study proposes that the role of anxiety in dementia may be greater than previously known.

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