International Psychogeriatrics (2007), 19:1, 125–135 © 2006 International Psychogeriatric Association
doi:10.1017/S1041610206003607 Printed in the United Kingdom

Persistent mild cognitive impairment in geriatric depression

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ABSTRACT

Background: Cognitive impairment often occurs with geriatric depression and impairments may persist despite remission of depression. Although clinical definitions of mild cognitive impairment (MCI) have typically excluded depression, a neuropsychological model of MCI in depression has utility for identifying individuals whose cognitive impairments may persist or progress to dementia.

Methods: At baseline and 1-year follow-up, 67 geriatric patients with depression had a comprehensive clinical examination that included depression assessment and neuropsychological testing. We defined MCI by a neuropsychological algorithm and examined the odds of MCI classification at Year 1 for remitted depressed individuals with baseline MCI, and examined clinical, functional and genetic factors associated with MCI.

Results: Fifty-four percent of the sample had MCI at baseline. Odds of MCI classification at Year 1 were four times greater among patients with baseline MCI than those without. Instrumental activities of daily living were associated with MCI at Year 1, while age and *APOE* genotype was not.

Conclusions: These results confirm previous observations that MCI is highly prevalent among older depressed adults and that cognitive impairment occurring during acute depression may persist after depression remits. Self-reported decline in functional activities may be a marker for persistent cognitive impairment, which suggests that assessments of both neuropsychological and functional status are important prognostic factors in the evaluation of geriatric depression.

Key words: older people, cognition, longitudinal, dementia

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https://doi.org/10.1017/S1041610206003607 Published online by Cambridge University Press

Introduction

Late-life depression and cognitive impairment often occur together, suggesting a close relationship between them (Jorm, 2001). Elderly patients may have symptoms of both depression and mild cognitive deficits (Reischies and Neu, 2000). Given the heterogeneity of geriatric depression, patients may experience a wide spectrum of cognitive impairment (Lockwood *et al.*, 2000). For example, late-life depression has been associated with memory impairment (Lockwood *et al.*, 2000) and other neuropsychological deficits, including executive dysfunction (Alexopoulos *et al.* 2002; Boone *et al.*, 1995; Lesser *et al.*, 1996; Lockwood *et al.*, 2002; Steffens *et al.*, 2003), visuospatial impairment (Boone *et al.*, 1995; Lesser *et al.*, 1996), slowed mental function (Boone *et al.*, 1995; Ravnkilde *et al.*, 2002), and poor attention and concentration (Ravnkilde *et al.*, 2002).

Among depressed individuals with cognitive impairment, lack of improvement in cognition following treatment for depression may be associated with increased risk of later dementia (Devanand *et al.*, 2003). Individuals with both depression and cognitive impairment are at greater risk of developing Alzheimer's disease (AD) than those without depression (Modrego and Ferrández, 2004). Early depression symptoms among cognitively impaired individuals may represent an important pre-clinical sign, conferring increased risk for impending AD or vascular dementia among old people (Li *et al.*, 2001).

The term mild cognitive impairment (MCI) has typically been used to characterize a transitional state between normal cognition and clinically evident dementia (Petersen *et al.*, 2001). There has been controversy regarding the precise definition of MCI as a clinical entity, and MCI criteria often exclude individuals with major depression. Although one study has applied Petersen-type criteria for MCI in depression (O'Brien *et al.*, 2004), no consistent MCI criteria have been proposed for elderly people with depression even though MCI in depression may be a marker for persistent cognitive impairment. In addition, little is known about the possible course and prognosis of MCI in geriatric depression. Thus, classifying the cognitive characteristics of MCI in depression and examining change in MCI status over time is important to understanding how some depressed individuals are at greater risk for developing persistent cognitive impairment. Understanding the cognitive course of MCI in depression is key to eventually developing a broader clinical definition for this condition.

In this study, we tested an actuarial definition of amnestic MCI in depression derived from an algorithm of depressive symptomatology and objective memory test performances to examine the odds of MCI at Year 1 for geriatric depression patients, remitted by Year 1, with and without baseline MCI. We also sought to determine whether baseline functional status and apolipoprotein E (*APOE*) genotype would predict the presence of MCI at 1 year. We hypothesized

https://doi.org/10.1017/S1041610206003607 Published online by Cambridge University Press

that individuals positive for this memory-based definition of MCI at baseline would have persistent memory impairment at follow-up despite improvement in depression. We also hypothesized that individuals with MCI at 1 year would have more baseline functional impairment and a higher frequency of the *APOE ε4* allele.

Methods

Participants

Participants included 142 individuals enrolled in the National Institute of Mental Health (NIMH)-sponsored Conte Center for the Study of Neuroscience of Depression in Late Life at Duke University Medical Center (DUMC). All participants met DSM-IV criteria for major depression and were at least 60 years of age at the time of baseline enrollment. Exclusion criteria for the Conte study were: (1) another major psychiatric illness; (2) alcohol or drug abuse or dependence; and (3) clinically diagnosed primary neurological illness, including dementia (see below). Patients recruited into the Conte Center were referred from either from primary-care physicians, psychotherapists or psychiatrists at Duke or in the community.

Procedures and measures

At baseline, a trained interviewer administered the Duke Depression Evaluation Schedule (DDES; Landerman *et al.*, 1989), a computer-assisted standardized interview that assesses criteria for major depression as well as symptoms of mania, psychosis, anxiety and substance abuse using the NIMH Diagnostic Interview Schedule (Robins *et al.*, 1981). The DDES also contains questions on Instrumental Activities of Daily Living (IADL; Steffens *et al.*, 1999). A study geriatric psychiatrist met with each patient and completed a comprehensive clinical examination as well as standardized clinical assessments of depression, including the Montgomery–Åsberg Depression Rating Scale (MADRS; Montgomery and Åsberg, 1979), a 10-item measure of depression severity. All participants had a MADRS score at study entry of 15 or greater. Subjects completed the neuropsychological testing either at study entry or at the 2-week return visit (see details below). All subjects in the present study had a MADRS score of 10 or greater at the time of the neuropsychological testing. Patients were seen by the study geriatric psychiatrist at least quarterly for clinical evaluation and MADRS assessment.

At baseline and 1 year later, participants completed a neuropsychological test battery that assessed multiple domains of neurocognitive function. The battery in its entirety is discussed elsewhere (Steffens *et al.*, 2004). Memory measures in the

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battery used as part of the current study were: (1) the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) word-list learning, (2) delayed recall, (3) true positive recognition and (4) true negative recognition (Morris *et al.*, 1989); (5) Logical Memory I (immediate recall) and (6) Logical Memory II (delayed recall) from the Wechsler Memory Scale-Revised (WMS-R; Wechsler, 1987); (7) the Benton Visual Retention Test-Revised (BVRT; Benton, 1974); and (8) delayed recall of CERAD Constructional Praxis drawings (Yuspeh *et al.*, 1998). The Mini-mental State Examination (MMSE; Folstein *et al.*, 2001) was part of the neuropsychological battery and was used in the current study as a measure of global cognitive function.

Baseline cognitive screen to rule out dementia

Conte Center geriatric psychiatrists examined all participants, reviewed medical records, and conferred with referring physicians for all patients, which was one level of exclusion for indications of progressive cognitive impairment. Patients were excluded if they had dementia or suspected dementia at baseline. In addition, individuals entering the Conte Center with a baseline MMSE score below 25 were followed through an acute (8-week) phase of treatment to determine whether cognition improved. Participants whose MMSE scores remained below 25 were not followed longitudinally in the Conte Center. Thus, in the clinical judgment of the study geriatric psychiatrist and by established Conte Center protocol, dementia was effectively excluded at or close to baseline in all elderly depressed Conte Center subjects.

Mild cognitive impairment (MCI)

Our purpose in this study was to explore a definition of amnestic MCI based on objective neuropsychological performance. To this end, MCI was defined as a performance of 1.5 standard deviations or more below mean levels on one or more of the eight memory measures from the neuropsychological battery. Means and standard deviations were based on the published norms for each specific test. To eliminate confounding of neuropsychological performance by depression at Year 1 follow-up, we restricted analyses to participants with Year 1 MADRS scores less than 9, reflecting remitted depression (Forlenza *et al.*, 2001).

Determination of *APOE* genotype

After signing informed consent forms for genetic testing, patients provided a blood sample for *APOE* genotyping. White blood cells were processed and *APOE* genotypes determined using a method described by Saunders *et al.* (1993).

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Analytic methods

To ensure that we were accounting for level of depression at time of follow-up cognitive testing, subjects whose MADRS assessment and neuropsychological assessment differed by more than 2 weeks were excluded from the Year 1 analysis. Thirteen participants whose Year 1 MADRS fell outside this window were excluded, leaving 129 subjects.

To avoid confounding between depression and cognitive impairment, subsequent analyses were restricted to 67 subjects who met the definition for remission of depression at Year 1 (MADRS < 9). Association between baseline MCI and Year 1 MCI was assessed in this cohort using standard χ^2 procedures. To evaluate putative predictive factors, each factor was regressed on a four-level proxy variable denoting the four possible MCI conditions: (1) baseline MCI $= 0$ and Year 1 MCI $= 0$; (2) baseline MCI $= 0$ and Year 1 MCI $= 1$; (3) baseline MCI $= 1$ and Year 1 MCI $= 0$; (4) baseline MCI $= 1$ and Year 1 MCI $= 1$. Subsequently, for each model a pre-specified contrast between levels 3 and 4 (above) was estimated and the subsequent *t*-statistic calculated using SAS PROC GLIMMIX (SAS Institute, 2003). Factors included: (1) demographic covariates for age, race and gender; (2) MADRS severity; (3) global cognition (MMSE); (4) IADL; and (5) *APOE* genotype (dichotomized at any *versus* no *APOE*-4). Each variable was regressed on a model including a four-level proxy denoting group status as follows: (A) participants with no memory impairment at baseline or Year 1; (B) participants with no memory impairment at baseline but who were classified as MCI at Year 1; (C) participants classified as MCI at baseline but not at Year 1; and (D) participants classified as MCI at both baseline and Year 1. Our assumption was that impairment at Year 1 was not affected by acute mood disturbance because of the inclusion of remitted individuals only. Contrasts were restricted to comparisons between participants who were MCI at baseline but not at Year 1 against participants who were MCI at both time points. Models were estimated using generalized linear models (SAS PROC GLIMMIX). Dichotomous outcomes were estimated assuming a binomial distribution with a logistic link (logistic regression).

Results

We present baseline data on 67 patients with depression who were remitted at 1-year follow-up. At baseline, 52.2% were female and 89.4% were Caucasian, and the mean age of the sample was 68.0 (S.D. $= 6.4$) years. The mean baseline MADRS was 20.7 (S.D. $= 6.8$), consistent with a mild to moderate level of depression symptomatology, and the mean MMSE score was 27.7 (S.D. $= 2.1$). The mean number of reported IADL impairments was 2.8 (S.D. $= 3.7$). Among

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Table 1. Relationship of baseline MCI to MCI at Year 1 for 67 participants remitted at Year 1

	YEAR 1	
BASELINE	MCI-NO	MCI-YES
MCI-No	22	8
MCI-Yes	15	22
Odds ratio (confidence interval)		4.03 (1.42–11.43)

39 individuals with *APOE* genotype, 33.3% had at least one *APOE* $\varepsilon 4$ allele. Mean MADRS score at the 1-year follow-up was 2.9 (S.D. = 2.5).

Table 1 shows that 55.2% of the sample were classified as MCI at the baseline assessment, while 44.8% had MCI at Year 1. Of the initial 37 participants classified as MCI at baseline, 22 remained cognitively impaired at Year 1 (59.4%). By contrast, of the 30 subjects not meeting MCI criteria at baseline, only eight were classified as MCI at Year 1 (26.7%). In an age- and education-adjusted logistic regression analysis, MCI at baseline was significantly associated with MCI at 1 year [odds ratio = 4.03, χ^2 (1 d.f.) = 7.20, $p \leq 0.007$], with a relatively large confidence interval around the odds ratio estimate (Table 1).

In a set of contrasts designed to identify baseline factors associated with cognitive impairment at Year 1, female gender (59% *vs.* 41%, $t = -2.14$, d.f. = 63, $p = 0.0359$), education (13.0 ± 2.4 *vs.* 15.3 ± 3.7 years, $t = 2.49$, d.f. = 63, $p = 0.0154$) and number of IADL impairments (3.7 ± 4.1 *vs.* 2.2 ± 3.1, $t = -2.18$, d.f. = 48, $p = 0.0344$) significantly distinguished between persistent MCI and non-MCI subjects at Year 1. Age, race, baseline MADRS, baseline MMSE and *APOE* genotype were not associated with impairment.

Discussion

We investigated MCI status in geriatric depression over a 1-year period as defined by neuropsychological performance. Fifty-five percent of geriatric depression patients who were remitted at 1-year follow-up were classified as having MCI at baseline assessment. This rate of MCI is broadly consistent with a rate reported among depressed individuals based on clinical and neuropsychological criteria (Adler *et al.*, 2004) and confirms previous observations that mild memory impairments are prevalent among depressed elderly adults (Lockwood *et al.*, 2000). In addition, depressed individuals classified as MCI at baseline in the current study were approximately four times more likely to be classified as MCI 1 year later relative to subjects not meeting MCI criteria at baseline, despite

https://doi.org/10.1017/S1041610206003607 Published online by Cambridge University Press

remission of depression. These results are consistent with previous reports that the extent of memory impairment in depressed elderly adults prior to treatment is associated with persisting cognitive impairment (Adler *et al.*, 2004; Butters *et al.*, 2000). Persistent memory deficits in the context of depression may be an indicator of underlying structural changes that present an elevated risk of converting to AD (Butters *et al.*, 2000) or another dementia.

Although previous studies have identified persistent cognitive impairment in depression (Adler *et al.*, 2004; Butters *et al.*, 2000) and others have presented a definition of MCI in depression (Brassen *et al.*, 2004), few studies characterize MCI in depression based exclusively on objective neuropsychological performance (see O'Brien *et al.*, 2004). Other studies have used neuropsychologically based algorithms to diagnose dementia, as opposed to clinical assessment (Pittman *et al.*, 1992; Tschanz *et al.*, 2000). We elected to focus on tests of memory rather than a multidomain algorithm of neuropsychological performance based on the suggestion by Petersen *et al.* (2001) that MCI represents a transition stage to AD. Prevalence rates of clinically defined MCI in depression are considerably higher than amnestic MCI rates in non-depressed samples, which range from approximately 3% to 6% (Ganguli *et al.*, 2004; Lopez *et al.*, 2003). Longitudinal research will be needed to determine if the conversion rate to AD among depressed individuals with neuropsychologically defined amnestic MCI is considerably higher as well. Finally, it will be important to assess how well the current memory-based definition predicts conversion to types of dementia other than AD.

In contrast with earlier studies examining MCI in non-depressed individuals, we did not find the *APOE* $\varepsilon 4$ genotype to be associated with MCI status. Our finding, however, is consistent with studies reporting no association between the *APOE* $\varepsilon 4$ allele and cognitive functioning in late-life depression (Butters *et al.*, 2003; Schweitzer *et al.*, 2002). In the former report, the *APOE* genotype did not explain variance in any cognitive domain, including memory function, suggesting that increased risk of AD among depressed individuals may be mediated by other non-*APOE*-4-related factors (Butters *et al.*, 2004).

Self-reported impairment in IADL at baseline was significantly associated with MCI status at Year 1. Other studies have found self-rated impairments in ADL to be associated with higher levels of apathy in depression, and with greater overall cognitive impairment (Steffens *et al.*, 1999). Alexopoulos *et al.* (1996) found that interviewer-rated impairment in functional activities was associated with greater cognitive impairment, older age at depression onset, and a higher burden of medical illness. In non-depressed samples, impairment in daily activities has been found to predict conversion from MCI to AD (Tabert *et al.*, 2002). These results suggest that report of functional impairments in the context of depression may be a sensitive indicator of persistent cognitive impairment.

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The current study has limitations. The large confidence interval around the odds ratio estimate predicting persistent MCI (Table 1) may limit the reliability of the estimate, while restricted sample size at Year 1 may have limited our ability to detect significant associations between MCI and *APOE* genotype. In *post hoc* analyses, we re-examined the data with a larger sample ($n = 129$) in which subjects were included regardless of the Year 1 MADRS score. Our results were similar, both for the main effects of female sex, education, baseline MCI and IADL predicting MCI at follow-up and for the negative association with *APOE* genotype. Another potential concern is that previous research has shown that demographic factors can bias the prediction of neurocognitive impairment based on a neuropsychological algorithm (Pittman *et al.*, 1992). We addressed this issue by using age- and education-adjusted normative values and including age and education as covariates in our analyses. However, this was a largely Caucasian sample, and additional research would be needed to understand how the current results might generalize to other ethnic groups. Another limitation is lack of a non-depressed control group. Finally, this study was also performed in the context of a longitudinal study in which treatment was not limited to a single pharmacological agent; however, based on the treatment protocol, many individuals were treated with the same single agent or an agent from the same drug class (see Steffens *et al.*, 2002). We cannot rule out the possibility that different treatments had differential effects on neurocognitive performance.

The results of this study show the importance of memory impairment as a stable feature in elderly depressed patients that is associated with self-reported difficulties with ADL and may reflect an increased risk for the development of dementia. Patients with geriatric depression and MCI based on cognitive testing may need comprehensive clinical follow-up to detect further cognitive decline and need for intervention. The further course of cognitive outcome in these patients is currently being assessed.

Conflict of interest

None.

Description of authors' roles

Dr. Lee formulated the hypotheses for this analysis and had a major role in writing the paper; Dr. Potter designed the neuropsychological algorithm and was involved in data collection and manuscript revision; Dr. Wagner conducted the statistical analyses and assisted in manuscript revision; Dr. Welsh-Bohmer

https://doi.org/10.1017/S1041610206003607 Published online by Cambridge University Press

designed the neuropsychological battery and was involved in data collection and manuscript revision; Dr. Steffens was principal study investigator and helped revise the paper.

Acknowledgments

We thank Karee Powers for her role in the collection of neuropsychological data and preparation of data sets. This study was supported by NIMH grants P50MH60451, R01 MH54846 and K24 MH70027. Dr. Lee was a visiting scholar at Duke University Medical Center supported by Yong-In Mental Hospital.

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