

Depression in Patients With Mild Cognitive Impairment Increases the Risk of Developing Dementia of Alzheimer Type

A Prospective Cohort Study

Pedro J. Modrego, MD; Jaime Ferrández, MD

Background: Mild cognitive impairment has been regarded as a precursor to dementia of Alzheimer type, but not all patients with mild cognitive impairment develop dementia.

Objective: To determine whether depression may increase the risk of developing dementia.

Setting: The outpatient clinics of a community general hospital.

Design: Prospective cohort study.

Methods: A cohort of 114 patients with amnesic mild cognitive impairment was followed up for a mean period of 3 years. At baseline, the patients underwent memory tests, the Spanish version of the Mini-Mental State Examination, a verbal fluency test, the Geriatric Depression Scale, and the Clinical Dementia Rating Scale for staging purposes. Psychiatric examination for depression was based on structured interview and *Diagnostic and Statistical Manual of Mental Disorder, Fourth Edition* criteria. We also carried out either computed tomography or magnetic resonance imaging of the brain.

Main Outcome Measures: We carried out periodic evaluations based on the Mini-Mental State Examination,

verbal fluency test, Geriatric Depression Scale, Blessed Dementia Rating Scale, and Clinical Dementia Rating Scale. The end point was the development of probable Alzheimer disease according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association.

Results: Depression was observed in 41 patients (36%) at baseline. After a mean period of 3 years, 59 patients (51.7%) developed dementia of Alzheimer type, and 6 died. Of the depressed patients, 35 (85%) developed dementia in comparison with 24 (32%) of the nondepressed patients (relative risk, 2.6; 95% confidence interval, 1.8-3.6). The survival analysis also showed that depressed patients developed dementia earlier than the nondepressed. Most patients with depression at baseline exhibited a poor response to antidepressants.

Conclusions: We conclude that patients with mild cognitive impairment and depression are at more than twice the risk of developing dementia of Alzheimer type as those without depression. Patients with a poor response to antidepressants are at an especially increased risk of developing dementia.

Arch Neurol. 2004;61:1290-1293

Author Affiliations: Neurology Unit (Dr Modrego) and Psychiatry Unit (Dr Ferrández), Hospital de Alcañiz, Alcañiz, Spain.

MILD COGNITIVE IMPAIRMENT (MCI) has been defined as a transitional state between normal aging and dementia; patients with MCI have a memory loss greater than expected for patients with their age and educational level who have intact daily living activities but not dementia.¹ The prevalence of MCI in elderly people ranges from 3% to 20%.²

The rates of conversion to dementia vary depending on the follow-up period and conceptual definition: 12% per year for 4 years,¹ 23% to 47% across 2.6 years,² 40% across 2 years,³ 53% across 3 years,⁴

34% to 100% across 4 to 5 years,^{5,6} and 100% across 9.5 years.⁷ Currently, there is open debate on whether MCI is an independent nosologic entity at high risk of evolving into dementia or if it is a prodrome of Alzheimer disease (AD).⁸

Depression is a frequent comorbid condition in patients with AD. In a recent multicenter study, the rate of major depression in patients with AD ranged from 22.5% to 54.5% across the recruitment site.⁹ Some longitudinal studies in elderly subjects concluded that depressive symptoms might be associated with the risk of developing AD.^{10,11} Depression in patients with MCI has been rarely inves-

tigated. In a population-based epidemiological study including 320 patients with MCI, 138 (43%) exhibited neuropsychiatric symptoms, with depression in 20%.¹² A longitudinal study comparing 146 subjects with normal cognition with 19 patients who had MCI and 42 patients with AD suggests that early depressive symptoms in patients with MCI may represent a preclinical sign of dementia.¹³

The goals of our study are to evaluate longitudinally the relationship between depression and dementia in patients with MCI and to know whether depression may increase the risk of developing dementia.

METHODS

Memory complaints are a common reason for referral to our neurology unit. Most patients we see in our outpatient clinics are referred from the community by family physicians. In other instances, patients are referred from the Psychiatry Unit and other specialized units. Prior to the beginning of this study, we asked general practitioners (by telephone) to refer to us all elderly patients with recent memory complaints. Afterward, we recruited a cohort of 114 consecutive patients fulfilling the criteria of amnesic MCI proposed by Petersen et al¹: memory complaints, normal activities of daily living, normal general cognitive function, abnormal memory for age, and no dementia. In all cases, an informant (wife, husband, or relative) corroborated the memory inefficiencies of the patient. In the clinical history, we also asked for family history of dementia, vascular risk factors, depression, and other diseases. The final diagnosis was made by taking into account as much information as possible from all sources, such as general interview, neuropsychological examination, and the informant's report. The cohort was recruited from June 1999 to June 2001.

Neuropsychological examination at baseline was based on the Spanish version of the Mini-Mental State Examination (MEC, with a maximum score of 35 points), Blessed Dementia Rating Scale,¹⁴ and category fluency test (Set test).¹⁵ Memory was explored with subscales of the 144 Battery of Signoret (Spanish validated version¹⁶): (1) Immediate verbal recall of a maximum of 12 words with 3 trials, as well as delayed recall of those words. The maximum possible score is 12 points for immediate recall and 12 for delayed recall. (2) Immediate visual recall: the patient has to reproduce a complex geometric figure after 1 minute of observation. Delayed visual recall was also evaluated. The maximum possible score is 24 points for each. (3) Logical memory: immediate and delayed recall of a brief story. Maximum score: 24 points for each. (4) Digit span (number of digits recalled forward). The delay interval between immediate and delayed recall for each subscale was 15 minutes.

The patients were also evaluated with the Clinical Dementia Rating Scale (CDR) and Global Deterioration Scale (GDS)¹⁷ for staging purposes. Depression was initially assessed by means of the GDS.¹⁸ All patients scoring 10 or higher on the GDS were screened as depressed and systematically referred to the Psychiatry Unit for reassessment and treatment. The diagnosis of major depression was carried out by means of a half-hour structured interview to elicit at least 5 depressive symptoms according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* criteria.¹⁹ The patients with depressive mood but fewer than 5 required symptoms and no feelings of guilt or worthlessness were rated as mildly depressed. Patients with depressive symptoms at baseline were adequately treated and reevaluated 2 months later. By *refractory depression*, we mean the lack of changes in the number and/or intensity of depressive symptoms elicited with the struc-

tured interview after 8 weeks of treatment, with 2 different antidepressants given separately or combined.

Laboratory tests included standard blood, sedimentation rate, complete blood cell count, vitamin B₁₂, folic acid, thyrotropin levels, and proteinogram tests, as well as serologic tests for syphilis. All patients underwent either computed tomography or magnetic resonance imaging of the brain to rule out other abnormalities.

Every patient was followed up and reevaluated every 6 months or sooner. On every occasion, we repeated the following tests and scales: MEC, verbal fluency test, Blessed Dementia Rating Scale, GDS, and CDR. The main end point considered in the follow-up was the development of dementia. The diagnosis of dementia was made by consensus of the neurologist and psychiatrist with the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for AD.²⁰ The date defining onset of dementia was the date on which we diagnosed it; patients were seen every 6 months, or sooner if needed.

The demographic and clinical data were analyzed separately in depressed and nondepressed patients. Quantitative variables were compared with the 2-sided *t* test for independent samples. The proportion of patients free of dementia across time was analyzed with the Kaplan-Meier method. The survival curves for depressed and nondepressed patients were compared with the log-rank test. Statistical operations were performed with the SPSS for Windows version 10.0 statistical software (SPSS Inc, Chicago, Ill).

In this study, we obtained verbal informed consent from patients and caregivers after we explained the importance of the project. Written consent was obtained for computed tomography or magnetic resonance imaging performance.

RESULTS

A total of 114 consecutive patients with MCI were included in the study. The mean \pm SD age was 72.8 ± 5.3 years (range, 61–84 years). There were 42 men and 72 women (63%). Educational levels were as follows: 12 did not complete elementary studies, 93 completed elementary studies, 8 graduated from high school, and only 1 graduated from a university. All of them scored 0.5 on the CDR and 3 on the GDS at baseline. After a 3-year mean follow-up (range, 2–4 years), only 6 patients died, 3 of them after developing dementia, and 59 (51.7%) developed dementia of probable Alzheimer type according to NINCDS-ADRDA criteria. No patient was diagnosed with parkinsonism, falls, hallucinations, dysinhibition, or history of stroke. Only 2 patients were lost to follow-up. The mean \pm SD number of evaluations per patient in the follow-up was 5.2 ± 1.1 (range, 3–7).

The mean scores on the MEC, verbal fluency test, Blessed Dementia Rating Scale, and GDS are reported in **Table 1**, and memory subscales for depressed and nondepressed patients are reported in **Table 2**. The mean \pm SD GDS score was 12.2 ± 5.5 for converters and 6.8 ± 2.7 for nonconverters, which was significant ($P < .001$).

According to the *DSM-IV* criteria, the number of depressed patients at baseline was 41 (36%); 31 were mildly depressed, 10 had major depression, and 73 were not depressed. All patients with major depression had depressive mood, and 7 had feelings of guilt and worthlessness. The first-line antidepressant was a selective serotonin

Table 1. Descriptive Statistics of the Main Variables*

Variable	Depressed Patients (n = 41)	Nondepressed Patients (n = 73)
Age, y	73.4 ± 4.5	72.3 ± 5.6
MEC score	26.3 ± 3.1	28.6 ± 3.7
Set test score	32.6 ± 3.2	35.6 ± 3.6†
Blessed Dementia Rating Scale score	3.1 ± 1.2	2.2 ± 0.8
GDS score	15.34 ± 3.4	6.12 ± 1.43†

Abbreviations: GDS, Geriatric Depression Scale; MEC, Spanish version of Mini-Mental State Examination; Set test, verbal fluency test.

*Data are presented as mean ± SD.

† $P < .05$ using the t test.

Table 2. Memory Scores for Depressed and Nondepressed Patients*

Subscale	Depressed Patients (n = 41)	Nondepressed Patients (n = 73)
Immediate verbal recall	8.1 ± 3.2	8.7 ± 2.4
Delayed verbal recall	2.6 ± 2.2	4.5 ± 1.6
Immediate visual recall	8.2 ± 4.4	12.3 ± 3.8†
Delayed visual recall	4.6 ± 3.3	7.2 ± 3.1
Immediate logical memory	8.4 ± 4.3	11.6 ± 3.9†
Delayed logical memory	6.6 ± 5.4	7.7 ± 4.3
Digit forward	5.5 ± 2.2	5.8 ± 2.0

*Data are presented as mean ± SD. Subscales are from the 144 Battery of Signoret (Spanish validated version¹⁶).

† $P < .05$ using the t test.

reuptake inhibitor. Usually we do not use tricyclic antidepressants in elderly patients. The depressed patients were initially treated as follows: 20 to 40 mg of citalopram hydrobromide, 50 mg of sertraline hydrochloride, or 20 to 40 mg of paroxetine hydrochloride or fluoxetine hydrochloride daily in 33 patients; 30 mg of mianserin hydrochloride daily in 5 patients; and 100 mg of trazodone hydrochloride daily in 3 patients. In the cases of major depression, a single antidepressant was not efficacious, and we had to use combined therapy: 40 mg of paroxetine hydrochloride plus 30 mg of mianserin hydrochloride daily in 4 patients, 50 mg of sertraline hydrochloride plus 30 mg of mianserin hydrochloride in 2 patients, and 40 mg of citalopram hydrobromide plus 100 mg of trazodone hydrochloride in 4 patients.

Of the nondepressed patients, 24 (32%) converted to dementia, and 49 (67%) did not. Of the depressed patients, 35 (85%) converted to dementia, and 6 (15%) did not (relative risk, 2.6; 95% confidence interval, 1.8-3.6). The difference between survival curves for depressed and nondepressed patients was also significant using the log-rank test (see **Figure**). Among converters, dementia appeared earlier in depressed patients than in nondepressed patients. We observed a poor response to antidepressants in 23 of the 35 patients with dementia who were diagnosed as having depression at baseline, but in none of the 6 depressed patients who did not convert to dementia. All 10 patients with major depression developed dementia. Despite the poor response, treat-

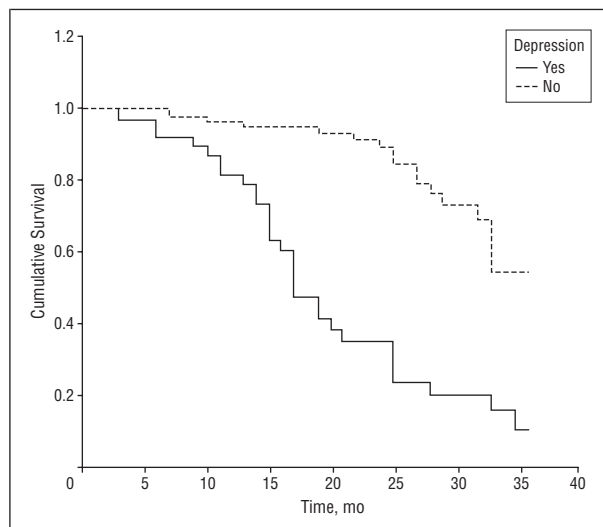


Figure. Survival curves for depressed patients (lower curve) and nondepressed patients (upper curve). The curves represent the proportion of patients free of dementia across time. Log-rank test: 32.7; $P < .001$. Hazard ratio: 4.1; 95% confidence interval, 2.4-6.9.

ment for depression was maintained indefinitely for all patients, but we did not observe long-term significant improvement in those patients who did not improve within the first 2 months.

COMMENT

Depression is a frequent symptom in patients with AD, and it has negative consequences for patients and caregivers.²¹ However, few reports address the natural history of depression in these patients. In a large survey in 1953 of patients with AD and 2093 of their unaffected relatives, it was concluded that depression was a risk factor for AD, especially for families in whom depressive symptoms occurred within 1 year of the onset of AD.²² It has been suggested that the increased incidence of depression in patients with AD points to a common neurobiological basis for both diseases.²³

An important finding in our work is that most patients with MCI and depression responded poorly to antidepressants and developed dementia; this may help to individualize the risk of dementia more accurately. A cohort of 112 patients with MCI was followed up for 3 years, and depression at baseline was associated with conversion to AD but not with a more rapid cognitive decline.²⁴ Although we cannot rule out a negative influence of antidepressants on cognitive deterioration, a randomized placebo-controlled trial showed that sertraline improved depression and activities of daily living in more than 70% of patients with AD. A major drawback was the small sample (44 patients) and the short period of follow-up (12 weeks).²⁵ Another small trial (50 patients) showed that citalopram improved depression and quality of life in patients with AD after 1 year of follow-up.²⁶ However, in a previous longitudinal study, depressive symptoms in patients with MCI and vascular dementia tended to be more persistent and refractory to treatment than in patients with AD.¹³ Thus, the poor re-

sponse to antidepressants in patients with MCI who develop dementia suggests that depression in the early stages of AD could have a different pathophysiological basis from that appearing in later stages of AD. The lack of responsiveness to treatment also indicates that depression in patients with MCI could be the beginning of AD rather than the product of mood disturbance.

We are aware of the shortcomings of our study. It is difficult to distinguish MCI from early AD on clinical grounds alone because some studies indicate that 100% of patients with MCI develop dementia when they are followed up for long periods.^{6,7} The overlapping of symptoms makes it sometimes difficult to distinguish a major depression from dementia or MCI. In addition, we cannot rule out the possibility that some patients developed a dementia other than AD; the NINCDS-ADRDA criteria have a high sensitivity but a moderate specificity.

In conclusion, depression in patients with MCI greatly increases the risk of developing dementia and predicts a faster cognitive deterioration. We think that patients with depression and MCI deserve more attention and should be closely observed.

Accepted for Publication: December 5, 2003.

Correspondence: Pedro J. Modrego, MD, Avda Juan Carlos I, 21, 50009 Zaragoza, Spain (med009626@saludalia.com).

Author Contributions: Study concept and design: Modrego and Ferrández. Acquisition of data: Modrego and Ferrández. Analysis and interpretation of data: Modrego. Drafting of the manuscript: Modrego. Critical revision of the manuscript for important intellectual content: Ferrández. Statistical expertise: Modrego. Administrative, technical, and material support: Ferrández.

REFERENCES

- Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol*. 1999; 56:303-308.
- Busse A, Bischof J, Riedel-Heller SG, Angermeyer MC. Mild cognitive impairment: prevalence and incidence according to different diagnostic criteria: results of the Leipzig Longitudinal Study of the Aged (LEILA75+). *Br J Psychiatry*. 2003;182:449-454.
- Johnson KA, Jones K, Holman BL. Preclinical prediction of Alzheimer's disease using SPECT. *Neurology*. 1998;50:1563-1572.
- McKelvey R, Bergman H, Stern J. Lack of prognostic significance of SPECT abnormalities in elderly subjects with a mild memory loss. *Can J Neurol Sci*. 1999; 26:23-28.
- Bennet DA, Wilson RS, Schneider JA, et al. Natural history of mild cognitive impairment in elderly persons. *Neurology*. 2002;59:198-205.
- Krasuki JS, Alexander GE, Horwitz B, et al. Volumes of medial temporal lobe structures in patients with Alzheimer's disease and mild cognitive impairment (and in healthy controls). *Biol Psychiatry*. 1998;43:60-68.
- Morris JC, Storandt M, Miller JP, et al. Mild cognitive impairment represents early-stage Alzheimer's disease. *Arch Neurol*. 2001;58:397-405.
- Ritchie K, Touchon J. Mild cognitive impairment: conceptual basis and current nosological status. *Lancet*. 2000;355:225-228.
- Zubenko GS, Zubenko WN, McPherson S, et al. A collaborative study of the emergence and clinical features of the major depressive syndrome of Alzheimer's disease. *Am J Psychiatry*. 2003;160:857-866.
- Berger AK, Fratiglioni L, Forsell Y, Winblad B, Bäckman L. The occurrence of depressive symptoms in the preclinical phase of AD: a population based study. *Neurology*. 1999;53:1998-2002.
- Wilson RS, Barnes LL, Mendes de Leon CF, et al. Depressive symptoms, cognitive decline, and risk of AD in older persons. *Neurology*. 2002;59:364-370.
- Lyketsos CG, Lopez O, Jones B, Fitzpatrick AL, Breitner J, DeKosky S. Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment: results from the cardiovascular health study. *JAMA*. 2002;288:1475-1483.
- Li YS, Meyer JS, Thornby J. Longitudinal follow-up of depressive symptoms among normal versus cognitively impaired elderly. *Int J Geriatr Psychiatry*. 2001;16: 718-727.
- Blessed G, Tomlinson BE, Roth M. The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects. *Br J Psychiatry*. 1968;114:797-811.
- Isaacs B, Akhtar AJ. The set test: a rapid test of mental function in old people. *Age Ageing*. 1972;1:222-226.
- González Torres M. Batería 144 para el estudio de las funciones mnésicas y de aprendizaje. In: Peña Casanova J, ed. *La exploración neuropsicológica*. Barcelona, Spain: MCR; 1988:177-192.
- Reisberg B, Ferris SH, de Leon MJ, Crook T. The Global Deterioration Scale for assessment of primary degenerative dementia. *Am J Psychiatry*. 1982;139: 1136-1139.
- Spreen O, Strauss E. Geriatric depression scale (GDS). In: Spreen O, Strauss E, eds. *A Compendium of Neuropsychological Tests*. New York, NY: Oxford University Press; 1998:612-616.
- American Psychiatric Association. *Manual diagnóstico y estadístico de los trastornos mentales (DSM-IV)*. Barcelona, Spain: Masson; 1995. [*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. Washington, DC: American Psychiatric Association; 1994.].
- McKhan G, Drachman D, Folstein M, Katzman R, Price D, Stadlan E. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group. *Neurology*. 1984;34:939-944.
- Lee HB, Lyketsos CG. Depression in Alzheimer's disease: heterogeneity and related issues. *Biol Psychiatry*. 2003;54:353-362.
- Green R, Cupples LA, Kurz A, et al. Depression as a risk factor for Alzheimer's disease: the MIRAGE study. *Arch Neurol*. 2003;60:753-759.
- Heun R, Kockler M, Ptak U. Depression in Alzheimer's disease: is there a temporal relationship between the onset of depression and the onset of dementia? *Eur Psychiatry*. 2002;17:254-258.
- Copeland MP, Daly E, Hines V, et al. Psychiatric symptomatology and prodromal Alzheimer's disease. *Alzheimer Dis Assoc Disord*. 2003;17:1-8.
- Lyketsos CG, DelCampo L, Steinberg M, et al. Treating depression in Alzheimer's disease: efficacy and safety of sertraline therapy, and the benefits of depression reduction. *Arch Gen Psychiatry*. 2003;60:737-746.
- Moretti R, Torre P, Antonello RM, Cazzato G, Bava A. Depression and Alzheimer's disease: symptom or comorbidity? *Am J Alzheimers Dis Other Dement*. 2002;17:338-344.