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The role of persistent and incident major depression on rate of cognitive deterioration in newly diagnosed Alzheimer's disease patients

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ABSTRACT

Depression may potentially impair the clinical course of Alzheimer's disease (AD). Thus, the aim of this study was to investigate cognitive progression of AD patients with or without major depressive episode (MDE). In this 1-year longitudinal follow-up study conducted in three Italian memory clinics, 119 newly diagnosed probable AD patients of mild severity, who were not undergoing treatment with an acetyl-cholinesterase inhibitor (AChEI), and had not been treated with psychotropic drugs in the last 2 years, were included. Patients were assessed to investigate the effect of baseline and 1-year follow-up MDE (using modified DSM-IV diagnostic criteria for MDE in AD) on progression of global cognitive deterioration (using Mini-Mental State Examination (MMSE)), adjusted for confounding factors. Never being depressed was associated with a 3.1 (95%CI 1.0–10.1) increased risk of MMSE decline compared to recovered depression. Six times more patients with persistent depression had MMSE decline compared to patients with recovered depression. However, the largest odds (7.3; 95%CI 1.4–38.1) of cognitive decline was observed in patients who developed incident depression over follow-up. In conclusion, persistent or incident depression worsens cognitive outcome while no or recovered depression does not affect it in early AD patients.

1. Introduction

Alzheimer's disease (AD) is the most common primary degenerative dementia. The progression of the disease differs between patients, with heterogeneous rates of cognitive decline (Cummings, 2005). Although the core diagnostic criterion of AD is cognitive impairment, neuropsychiatric phenomena frequently occur during the disease (Lyketsos et al., 2002; Spalletta et al., 2010; Vilalta-Franch et al., 2010). These appear in the majority of AD patients at some point during the course of the disease and may have a different expression, ranging from affective (depression and apathy) to psychotic or behavioral disorders (Assal and Cummings, 2002; Lyketsos et al., 2002). Depression and apathy are the two most frequent clinical neuropsychiatric manifestations in AD patients (Lyketsos et al., 2002; Spalletta et al., 2004; Di Iulio et al., 2010), and depression is particularly prevalent in the early phase of the illness (Spalletta et al., 2004; Di Iulio et al., 2010).

Recent evidence suggests that apathy may negatively affect the cognitive outcome of patients, both during the preclinical AD phase of mild cognitive impairment (MCI) (Vicini Chilovi et al., 2009; Palmer et al., 2010) and in the early stages of AD itself (Starkstein et al., 2006). On the contrary, there is an open debate concerning whether depression impairs the clinical course of AD and if the effect of antidepressant treatment is positive on cognitive deterioration. There is evidence both in favor of, and contrary to, these hypotheses (Rosenberg et al., 2010). However, there is a lack of data concerning the longitudinal effect of depression on outcome of AD patients, measured with a rigorous method, and taking into account numerous potential biases that may influence these associations, such as differences in dementia severity, and the presence of psychotropic and acetyl-cholinesterase inhibitor (AChEI) treatments. Further, depression may have different courses, ranging from recovered depression (i.e., depression present at the baseline that recovers), to incident depression (i.e., depression onset at some follow-up period after the baseline) to persistent depression (i.e., depression present both at the baseline and the follow-up periods), and this may complicate its study. Thus, to further clarify the question of whether depression impairs the cognitive outcome of AD patients, we longitudinally studied a group of patients with newly diagnosed AD, who were not treated

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with psychotropic or AChEI drugs at baseline. The aim of the study was to investigate differences in the cognitive progression of AD patients with or without depression. Specifically, we aimed to investigate the effect of baseline depression, as well as depressive status after 1 year of follow-up. The a priori hypothesis was that the presence of depression 1 year after diagnosis (in different forms of incident and persistent depression) would have a larger influence on the cognitive progression of AD than the presence of depression at time of initial diagnosis, independently from confounding factors such as treatment and concurrent apathy.

2. Methods

2.1. Participants

Patients with a diagnosis of probable AD of mild severity, recruited from three outpatient memory clinics in Rome, were considered for the current study. Patients were diagnosed with probable AD by trained neurologists according to NINCDS-ADRDA criteria (McKhann et al., 1984). We included only patients with a new diagnosis of AD, who were not undergoing treatment with AChEI, and had not been treated with psychotropic drugs (i.e. antidepressants, antipsychotics or anxiolytics) in the last 2 years.

Exclusion criteria were: a) global cognitive impairment of moderate-severe level defined as MMSE (Folstein et al., 1975) score <18 and CDR (Hughes et al., 1982) score >1; b) vision and hearing insufficient for compliance with testing procedures; c) major medical illnesses, e.g., diabetes (not stabilized), obstructive pulmonary disease, or asthma; hematologic/oncologic disorders; vitamin B_{12} or folate deficiency as evidenced by blood concentrations below the lower limits of the reference intervals; pernicious anemia; clinically significant and unstable active gastrointestinal, renal, hepatic, endocrine, or cardiovascular system disease; newly treated hypothyroidism; d) past (in the last 5 years) or present comorbidity of primary psychiatric or neurological disorders (e.g., schizophrenia, major depression, stroke, Parkinson disease, seizure disorder, head injury with loss of consciousness) and any other significant mental or neurological disorder; e) known or suspected history of alcoholism or drug dependence and abuse during lifetime; f) Magnetic Resonance Imaging (MRI) evidence of focal parenchymal abnormalities or neoplasm and; g) lack of a "reliable" caregiver, defined as someone able to ensure the patient's compliance with assessment procedures and to contact the patient at least twice weekly, with one contact being a personal visit.

Based on the inclusion criteria, 133 patients were recruited. At 1, 3, and 6 months after baseline, patients were clinically examined by the respective physicians for care purposes. After 1 year, patients underwent follow-up examinations to investigate progression of global cognitive deterioration, performance in functional and basic activities of daily living (ADL), and neuropsychiatric disorder severity. One-hundred nineteen patients completed the follow-up procedure and were included in this study. Table 1 shows characteristics of the study population. There were no significant differences between patients who completed ($n=119$) the follow-up and those who did not complete ($n=14$) the follow-up period concerning sociodemographic and clinical variables at baseline, apart from the MMSE score, which was higher in drop-out subjects.

2.2. Diagnostic and cognitive examination

Prior to the beginning of the study, the interviewers (neurologists and psychologists) had been trained by means of didactic instruction, live interviews, and a review of diagnostic rating. The nature and purposes of this study were presented to both patients and their responsible caregivers, and written informed consent was obtained prior to beginning detailed screening activities. Trained clinical neurologists ($n=3$) interviewed patients and caregivers using the NINCDS-ARDRA (McKhann et al., 1984) criteria for the diagnosis of AD. Trained PhD level clinical psychologists ($n=3$) with an expertise in neuropsychology interviewed patients and caregivers using the cognitive, neuropsychiatric, and functional clinical battery which has been described below. Acceptable inter-rater reliability for the present study was defined as $k \geq 0.80$. All interviewers achieved this level between them. In order to confirm cognitive deficits required for AD diagnosis, an extensive neuropsychological battery was used.

To assess performance in specific cognitive domains, we administered the Mental Deterioration Battery (MDB) (Carlesimo et al., 1996), a standardized and validated neuropsychological battery. This included assessment of: verbal memory (MDB Rey's 15-word immediate and delayed recall); short term visual memory (MDB Immediate Visual Memory); logical reasoning (MDB Raven's Progressive Matrices' 47); language (MDB Phonological Verbal Fluency and MDB Sentence Construction); simple constructional praxis (MDB Copying Drawings), and planning ability (MDB Copying Drawings with Landmarks).

Global cognitive functioning was assessed with the MMSE (Folstein et al., 1975), which is a widely used neurocognitive screening test measuring orientation, language, verbal memory, attention, visuospatial function and mental control. It is composed of 16 items, with scores ranging from 30 (no impairment) to 0 (maximum impairment). Global cognitive functioning was assessed both at baseline and at 1-year follow-up.

Table 1
Baseline characteristics of the included and drop-out AD subjects, and clinical outcomes after 1 year of follow-up.

	Included subjects ($n=119$)		Drop-out subjects ($n=14$)			
Baseline	*n*	%	*n*	%	χ^2	*p* Value
Gender female	67	56.3	8	57.1	0.004	0.9522
Major depression in AD (modified DSM-IV criteria)	51	42.9	5	35.7	0.262	0.6086
Apathy disorder	55	46.2	6	42.9	0.057	0.8113
Lifetime frequency of mood disorders (DSM-IV)	16	13.5	2	14.3	0.008	0.9307
	Mean	S.D.	Mean	S.D.	*t*	*p* Value
Age (years)	74.7	6.3	76.5	7.1	−0.985	0.3266
Education (years)	7.2	3.7	9.3	4.8	−1.865	0.0644
Age at onset (years)	72.3	6.6	74.1	7.6	−0.949	0.3443
Duration of disease (years)	2.4	1.9	2.4	1.6	0.039	0.9692
ADL	5.6	0.8	5.4	1.2	0.758	0.4499
IADL	4.3	1.9	4.5	2.1	−0.388	0.6987
MMSE*	20.7	3.2	23.3	3.4	−2.826	0.0054
Follow-up	*n*	%				
Major depression in AD (modified DSM-IV criteria)	44	37.9				
Antidepressant therapy	18	15.1				
Decline on MMSE	67	56.3				
Stable MMSE	11	9.2				
Improvement on MMSE	41	34.5				

AD=Alzheimer's disease; ADL=Activities of Daily Living; IADL=Instrumental Activities of Daily Living; MMSE=Mini Mental State Examination.
* Statistically significant difference.

2.3. Sociodemographic and functional variables

Information on age, education, and sex was collected at baseline, and verified by the patient's informant. Education was calculated in years as the maximum level achieved. Age at onset was defined as the age at the onset of cognitive symptoms severe enough to compromise patient functioning, and was assessed through an interview with the patients and caregivers. Basic ADLs were assessed using the Katz scale (Katz, 1983). Instrumental ADL (I-ADL) was assessed with Lawton and Brody's I-ADL scale (Lawton and Brody, 1969). Both ADL and I-ADL were treated as continuous variables.

2.4. Drug treatment

After the baseline diagnostic evaluation, patients' medical care was performed by clinicians who were blind to the aims of the study. These clinicians used AChEI or psychotropic agents at any dosage according to the guidelines for the treatment of AD of the Italian Neurological Society and international guidelines (Cummings, 2004). For the current analysis, antidepressant medication use initiated at baseline was considered as a dichotomous variable.

2.5. Neuropsychiatric assessment

Patients underwent a structured interview that included modified DSM-IV diagnostic criteria for Major Depressive Episode (MDE) in AD (Olin et al., 2002) and diagnostic criteria for apathy (Jeste and Finkel, 2000) in AD. Modified criteria for MDE in AD require the presence of three (as opposed to five in the DSM-IV) or more symptoms not required to be present "most of the day, nearly every day," distinguishing social isolation or withdrawal from anhedonia, and adding irritability as a symptom (Olin et al., 2002). These criteria are based on the identification of individual symptoms by an expert consensus conference. They have face validity (Vilalta-Franch et al., 2006), and may be applicable clinically as demonstrated in a series of cases (Rosenberg et al., 2005). Among the various methods for diagnosing depression in AD, the highest percentage of agreement (43.6%; $k=0.52$, 95% CI=0.43–0.61) has been described between DSM-IV and Olin criteria for MDE (Vilalta-Franch et al., 2006). An important reason why these criteria were developed is to make clear the distinction between MDE in AD and primary depression. Indeed, primary depression may cause pseudodementia (which is not AD, but reversible dementia caused by depressive symptoms) and this may generate diagnostic confusion. Specifically, the Olin's criterion B for MDE in AD requires that "all criteria are met for Dementia of the Alzheimer Type (DSM-IV-TR)". Thus, the diagnosis of AD has to be present in patients diagnosed with MDE in AD and researchers, during the diagnostic process, have to verify if cognitive symptoms