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Depressive symptoms and cognitive/functional status in a sample of elderly subjects referring to a memory clinic

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Background & aims. Depression and dementia are two frequent conditions in the elderly population and are often associated; their relationship is still debated and not well understood. The aim of our study was to examine the prevalence of depressive symptoms and their possible relationship with other demographic, cognitive, and functional characteristics in a sample of elderly subjects.
Methods. We performed a cross-sectional analysis of 1142 patients (≥ 65 years) admitted to a Memory Clinic. We conducted a multidimensional evaluation including cognitive status, assessment of autonomy in Basic and Instrumental Activities of Daily Living (BADLs and IADLs) and Geriatric Depression Scale (GDS). The sample was stratified by GDS-15 score in three groups (I: < 5, n. 551, absence of depressive symptoms; II: ≥ 5 and < 10, n.442, mild-moderate depression; III: ≥ 10, n. 149, severe depression).
Results. Subjects with higher GDS score were more often women, had lower levels of education and haemoglobin ($p < 0.001$). Higher GDS scores were associated with higher score in delayed recall of Rey Auditory Verbal Learning Test (RAVLT, $p < 0.001$) and Babcock test ($p : 0.05$), and with lower performance in BADLs and IADLs ($p : 0.012$ and $p < 0.001$). In linear regression model, all the associations were confirmed.
Conclusions. Our data confirm the relationship between depressive symptoms and female gender, low level of education and greater functional impairment; moreover, we found a significant association between higher GDS score and better scores at memory tests with delayed recall. These results underline the importance of evaluating depressive symptoms as a part of multidimensional evaluation of patients with memory complaints.

Key words: depression, dementia, cognitive assessment, cognitive impairment, functional status

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INTRODUCTION

Depression and dementia are two frequent conditions in the elderly population, and their relationship is still debated and not completely understood. Regarding this topic, at least six different hypothesis have been suggested [1,2]: 1. depression could be a risk factor for dementia; 2.

depression might reduce the threshold for developing dementia; 3. cognitive impairment could be a feature of depressive syndrome; 4. depression could be a prodrome of dementia; 5. depression might be a reaction to early dementia symptoms; 6. they could belong to an "overlap syndrome", as they share common risk factors and physiopathological pathways. Although depressive symptoms have been reported in about 25% of patients with any type of dementia (prevalence significantly higher than 13% found in control subjects without cognitive decline) [3] and in more than 60% of patients with Mild Cognitive Impairment (MCI) [4,5], the prevalence of depression in people with impaired cognitive functions might differ considerably because of differences in populations, severity of dementia, and psychometric indexes used for diagnosis. Depression is generally underdiagnosed and undertreated in elderly people, especially those with dementia, and it has been associated with poorer cognition, physical function and quality of life, greater caregiver burden, and higher mortality risk [6-10]. Late-life depression may be diagnosed according to International Classification of Diseases 10th revision (ICD-10), Diagnostic and Statistical Manual of Mental Disorders (DSM)-V criteria or psychometric indexes. A useful, simple and easily reproducible tool is the Geriatric Depression Scale (GDS); also some short versions of GDS proved to be good screening instruments for depression in elderly population, also compared with standard clinical assessment [11,12]. The GDS score also has the advantages of assessing the severity of depressive symptoms and evaluating potential changes over time. In the present study we report the prevalence of depressive symptoms in a large sample of elderly individuals referring to an Italian memory clinic and analyse potential associations between depressive symptoms and demographic, cognitive, and functional variables.

MATERIAL AND METHODS

Study population

We enrolled 1142 consecutive elderly individuals (≥ 65 years) admitted from 2006 to 2017 to the Memory Clinic of the Department of Internal Medicine and Geriatrics (S. Anna University Hospital of Ferrara, Italy). The sample included:

- 115 patients with normal cognitive functions and without evidence of any functional disability due to cognitive impairment who accessed the Memory Clinic for subjective impairment or on indication of other medical physicians (no cognitive impairment);
- 66 patients with Vascular Dementia (VD) according to the National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neuroscience criteria [13];
- 244 patients with Late Onset Alzheimer Disease (LOAD) according to the NIA-AA workgroups criteria [14];
- 189 patients with "mixed" dementia. In these patients, a definite diagnosis of LOAD or VD was not possible since both the clinical characteristics of LOAD and VD were present. In particular, while brain computed tomography (CT) scan or magnetic resonance imaging (MRI) demonstrated significant cerebrovascular disease, the evolution of the symptoms was slow and progressive;
- 456 individuals with MCI [5], defined as the presence of short/long-term memory impairment, or of impairment in other single or multiple cognitive domains, in an individual who did not meet the standardized criteria for dementia and was still independent in the Instrumental Activities of Daily Living [15] (IADLs). The majority of these individuals were affected by amnestic multidomain MCI;
- 72 patients with other types of dementia (Lewy body dementia, Parkinson dementia, frontotemporal dementia, alcohol related, psychiatrics, etc.)

The study was carried out in accordance with the Declaration of Helsinki (World Medical Association) and the guidelines/indications for Good Clinical Practice of the European Medicines Agency and of the local Ethics Committee (Ferrara, Italy). Each subject (and/or his caregiver, if demented) gave his written informed consent to the study during the first visit.

Characteristics of the study population

Sociodemographic characteristics of the study population included age and gender; years of education and history of smoking were ascertained from a baseline interview from patients and caregivers. According to protocol of our Memory Clinic, all patients underwent a general and neurological examination, blood analyses and a neuropsychological assessment, as complete as possible in relation to the patient's ability to perform and carry out the task. We conducted a multidimensional evaluation including Mini Mental State Examination (MMSE) [16], Basic Activities of Daily Living (BADLs) [17], IADLs [15], and 15-item GDS [12]. Trained geriatricians evaluated cognitive performance through a battery of tests [18,19] and made diagnosis of dementia or MCI. To rule out possible causes of secondary cognitive impairment, clinical chemistry analyses (liver and kidney function, serum folate and vitamin B12, thyroid function, blood cell count, metabolic and lipidic profile and high sensitivity C-reactive protein - hs-CRP) were performed. The prevalence of specific medical conditions

(hypertension, coronary heart disease - CHD, diabetes mellitus, stroke and hypothyroidism) was established using standardized criteria already reported elsewhere [18,19]. All patients underwent a brain CT or MR. Radiologists not informed about the clinical characteristics of the participants evaluated the acquired radiological imaging. We considered the presence of cortical ischemic lesions, single or multiple lacunar infarcts, leukoaraiosis, and signs of atrophy. Subjects affected by severe congestive heart failure, liver or kidney disease, chronic obstructive pulmonary disease, and cancer were excluded. There was no evidence of acute illnesses at the time of clinical observation and blood sampling. No subject was taking nonsteroidal anti-inflammatory drugs, antibiotics, or steroids at the time of recruitment. We had no data about psychoactive therapy, however patients of our study underwent a complete neuropsychological evaluation for the first time in our Memory Clinic and very rarely they were already taking these types of drugs.

Biochemical measures

Venous blood was sampled after a 12-h over-night fast and promptly analysed using automated techniques in S. Anna Hospital laboratory. Biochemical data were collected on plasma levels of hemoglobin (g/dL), creatinine (mg/dL), albumin (g/dL), total cholesterol (mg/dL), high-density lipoprotein cholesterol (HDL-C, mg/dL), triglycerides (mg/dL), homocysteine (µmol/L), vitamin B12 (pg/mL), folate (ng/mL), and hs-CRP (mg/dl). Low-density lipoprotein cholesterol (LDL-C, mg/dL) was calculated using the Friedewald formula [20].

Statistical analysis

The study population was divided in three groups according to GDS score (I: < 5, n. 551, absence of depressive symptoms; II: ≥ 5 and < 10, n. 442, mild-moderate depression; III: ≥ 10, n. 149, severe depression). This categorization was based on previous studies on this topic [12,21]. Clinical, cognitive, functional, neuroradiological, and biochemical characteristics of the study population were compared according to GDS groups.
Continuous variables with normal distribution were expressed as means and standard deviations (SD) and compared using the t test or ANOVA. Not normally distributed continuous variables were expressed as medians and interquartile ranges (IQR) and compared using the Kruskal-Wallis test. Categorical variables were compared by the $\chi 2$ test. Neuropsychological tests and functional indexes that resulted associated with GDS at univariate analysis were included into linear regression models, using first GDS score groups and then GSD score as continuous variable. Two models were testes; model 1 unadjusted and model 2 adjusted for potential confounders.
All analyses were performed using Stata 11.0 for Windows (Stata Corporation, College Station, TX, USA).

RESULTS

Mean age of the sample was 78.3 ± 5.4 years; females were 730 (63.9%). The median GDS score was 5 (IQR: 2-7), and 591 (51.8%) patients presented depressive symptoms (GDS ≥ 5).
The principal characteristics of the population according to GDS score are reported in Table I. Subjects with higher GDS score were more often women, had a lower level of education, and lower haemoglobin levels; a greater prevalence of hypertension was also noted in patients with mild-moderate depression (GDS score 5-9).
In Table II are described the cognitive, functional, and neuroradiological characteristics of the sample, according to GDS score. No relationship was found between MMSE and GDS score. In contrast, higher GDS scores were associated with higher scores in delayed recall of Rey Auditory Verbal Learning Test (RAVLT), as well as delayed recall in Babcock test. Subjects with more depressive symptoms also displayed a lower functional autonomy in BADL and IADL. In particular, a loss of autonomy in all basic activities (except for feeding), and in all instrumental activities (except for using the phone) was associated with higher GDS score (data not shown). No association was found between GDS score and neuroimaging findings.
In Table III are reported the results of linear regression models for the relationship between GDS score groups and selected neurocognitive and functional tests. All the associations were confirmed, except for delayed recall of RAVLT (associated only with the group GDS 5-9), after adjustment for age, gender, years of education, and MMSE score.
As reported in Table IV, when GDS score was considered as a continuous variable, the associations with delayed recall of RAVLT and of Babcock test and with BADLs and IADLs were demonstrated. As regards the Token test, its association with GDS was not confirmed after adjustment for confounding factors.
We further analysed the relationships between GDS score and cognitive/functional tests stratifying the sample based on diagnosis (no cognitive impairment, MCI and dementia) (data not shown). Compared with the result described above, no differences emerged in patients without cognitive impairment. Among MCI, GDS score was associated with delayed recall of RAVLT, BADLs and IADLs but not with delayed Babcock test. Among patients with dementia, GDS score was associated with delayed Babcock test and IADLs but not with delayed recall of RAVLT and BADLs.

Table I. Demographic, biochemical, and clinical characteristics of study population according to Geriatric Depression Scale (GDS) score.

Characteristics	GDS < 5 (n = 551, 48.2%)	GDS 5-9 (n = 442, 38.7%)	GDS ≥ 10 (n = 149, 13.1%)	*P*
Age (years), mean ± SD	78.3 ± 5.4	78.5 ± 5.6	77.8 ± 4.9	0.430
Female sex, n (%)	311 (56.4)	299 (67.7)	120 (80.5)	**< 0.001**
Education (years), mean ± SD	6.6 ± 4.0	6.4 ± 3.5	5.2 ± 3.3	**< 0.001**
Smoking (past or current), n (%)	234 (42.5)	174 (39.4)	66 (44.3)	0.581
Biochemical parameters, mean ± SD				
Hemoglobin (g/dl)	13.4 ± 1.5	13.0 ± 1.5	12.8 ± 1.5	**< 0.001**
Creatinine (mg/dl)	0.98 ± 0.36	0.99 ± 0.43	0.97 ± 0.52	0.923
Albumin (g/dl)	4.0 ± 0.4	4.0 ± 0.3	4.0 ± 0.4	0.931
Total cholesterol (mg/dl)	205.8 ± 39.8	209.3 ± 44.0	211.9 ± 38.7	0.192
Triglycerides (mg/dl)	110.3 ± 48.0	117.2 ± 56.7	117.4 ± 51.2	0.077
LDL cholesterol (mg/dl)	122.9 ± 34.2	126.2 ± 38.6	127.0 ± 33.8	0.256
Hs-CRP (mg/dl)*	0.16 (0.08-0.38)	0.18 (0.09-0.38)	0.2 (0.1-0.4)	0.609
Homocysteine (µmol/l)	18.5 ± 10.5	18.3 ± 11.1	19.7 ± 16.4	0.632
Vitamin B12 (pg/ml)*	305 (212-421)	316 (242-453)	346.5 (238-469)	0.06
Folate (ng/ml)	6.7 ± 3.4	7.0 ± 4.1	6.8 ± 3.7	0.373
Medical conditions, n (%)				
Hypertension	345 (62.6)	313 (70.8)	93 (62.4)	0.02
Coronary heart disease	73 (13.3)	64 (14.5)	27 (18.1)	0.310
Diabetes	77 (14)	79 (17.9)	26 (17.5)	0.216
Stroke	17 (3.1)	21 (4.8)	9 (6)	0.353
Hypothyroidism	67 (12.2)	48 (10.9)	17 (11.4)	0.811
Cognitive status, n (%)				
No cognitive impairment	44 (8)	53 (12)	18 (12.1)	
Vascular dementia	31 (5.6)	24 (5.4)	11 (7.4)	
Late onset Alzheimer's disease	131 (23.8)	85 (19.2)	28 (18.8)	
"Mixed" dementia	95 (17.2)	68 (15.4)	26 (17.4)	
Mild cognitive impairment	221 (40.1)	182 (41.2)	53 (35.6)	
Other types of dementia	29 (5.3)	30 (6.8)	13 (8.7)	0.269

* value expressed as median (IQR)

DISCUSSION

Demographic, biochemical, and functional characteristics

We investigated the prevalence of depressive symptoms (measured by GDS) and their possible relationship with demographic, cognitive, and functional characteristics in a large sample of elderly people referring to an Italian memory clinic.

We found that depressive symptoms were more frequent in female sex. This finding confirms previous data from literature, since several studies found that depressive disorders are approximately twice as common in women compared to men [22,23]. Noble suggested the involvement of several biological processes (genetically determined vulnerability, hormonal fluctuations, and a hormonal sensitivity in brain systems) and environmental factors in the predisposition of women to depression [24].

The association between depressive symptoms and lower formal education might be linked to the "resource substitution theory" [25,26]; education would improve well-being more for women than for men. Indeed, previous studies demonstrated that the negative relationship between levels of education and depression is much more stronger in women compared with men.

Depressive symptoms were also associated with lower haemoglobin levels, although within the normal range. Previous studies found that anaemia is associated with depressive symptoms [27-31]; anaemia could be the expression of other diseases (e.g. cancer, renal failure, infectious disease, malnutrition) which in turn can worsen the quality of life and lead to depressive symptoms [32].

A greater functional impairment was found in patients with severe depressive symptoms, and this underlines the importance of evaluating/managing functional status and depressive symptoms in patients with cognitive

Table II. Cognitive, functional, and neuroradiological characteristics of study population according to Geriatric Depression Scale (GDS) score.

Characteristics	GDS < 5 (n = 551, 48.2%)	GDS 5-9 (n = 442, 38.7%)	GDS ≥ 10 (n = 149, 13.1%)	*P*
Neurocognitive tests, mean ± SD				
Mini Mental State Examination (/30)	22.9 ± 4.1	23.0 ± 3.9	22.3 ± 4.1	0.167
Rey Auditory Verbal Learning test, immediate recall (/75)	28.7 ± 9.9	29.8 ± 9.5	29.4 ± 9.4	0.284
Rey Auditory Verbal Learning test, delayed recall (/15)	3.8 ± 3.2	4.5 ± 2.9	4.6 ± 3.2	**< 0.001***
Raven matrix test (/36)	22.5 ± 6.2	22.3 ± 5.9	22.2 ± 5.2	0.810
Trail Making test A (sec)	123.9 ± 78.4	142 ± 89.7	134.7 ± 71.2	0.144*
Trail Making test B (sec)	235.3 ± 133.4	218.5 ± 101	233 ± 117.3	0.826*
Token test (/36)	29.1 ± 4.3	28.5 ± 4.2	28.1 ± 4.1	0.172
Verbal fluency test per letter (n)	12.6 ± 8.6	13.4 ± 9.8	11.5 ± 8.2	0.195*
Verbal fluency test per category (n)	18.3 ± 15	18.4 ± 14.3	16.0 ± 12.9	0.269*
Babcock test, immediate recall (/8)	3.3 ± 2.3	3.6 ± 2.2	3.4 ± 2.2	0.167
Babcock test, delayed recall (/8)	3.2 ± 2.8	3.6 ± 2.5	3.7 ± 2.7	**0.05**
Frontal assessment battery (/18)	11.9 ± 3.5	11.6 ± 3.6	11.5 ± 3.8	0.605^
Functional tests, mean ± SD				
Barthel index (/100)	92.0 ± 16.0	86.6 ± 22.8	85.1 ± 22.2	**0.015^**
Lawton-Brody scale (/19)	15.4 ± 3.8	14.1 ± 4.3	13.2 ± 4.2	**< 0.001^**
Radiological characteristics, n (%)				
Cortical ischemic lesions	52 (9.4)	52 (11.8)	16 (10.7)	0.481
Single lacunar lesion	40 (7.3)	34 (7.7)	5 (3.4)	0.143
Multiple lacunar lesions	165 (30)	126 (28.5)	40 (26.9)	0.576
Leukoaraiosis	223 (40.5)	185 (41.9)	65 (43.6)	0.88
Atrophy	310 (56.3)	243 (55)	86 (57.7)	0.945

*significance calculated with normalized variables with their square root. ^ significance calculated with normalized variables with their exponential value.

Table III. Linear regression models (not adjusted and adjusted for potential confounders) for the relationship between Geriatric Depression Scale (GDS) score groups and selected cognitive and functional tests.

	RAVLT, delayed recall (*P*)		Babcock test, delayed recall (*P*)		Barthel index (*P*)		Lawton-Brody scale (*P*)	
	Coeff (M1)	Coeff (M2)	Coeff (M1)	Coeff (M2)	Coeff (M1)	Coeff (M2)*	Coeff (M1)	Coeff (M2)*
GDS < 5	-	-	-	-	-	-	-	-
GDS 5-9	0.66 (0.002)	**0.82 (< 0.001)**	0.37 (0.044)	**0.50 (0.009)**	-5.5 (0.024)	**-4.24 (0.05)**	-1.30 (0.001)	**-1.26 (< 0.001)**
GDS ≥ 10	0.81 (0.011)	0.57 (0.073)	0.53 (0.057)	**0.59 (0.035)**	-6.91 (0.026)	**-8.09 (0.005)**	-2.19 (< 0.001)	**-1.76 (< 0.001)**

Coefficient indicates the variation of the variable in each group compared to the reference group (GDS score < 5). M1: not adjusted model; M2: model adjusted for age, gender and years of education; M2*: model adjusted for age, gender, years of education, and MMSE score.

impairment. The relationship between depressive symptoms and functional performance has been already reported in previous studies [33-37]. Functional dependence is a risk factor for depression and vice versa [38]; moreover, among depressed people, dependence in IADLs has been associated with a greater cognitive impairment [39], and with the persistence of cognitive impairment after depression remission [40].

Neurocognitive characteristics

By analysing the association between depressive symptoms and cognitive performance, we expanded the results of previous studies. We found an interesting relationship between depressive symptoms and higher score in delayed memory recall of RAVLT and Babcock tests. In case of a pure depressive disorder, there is

Table IV. Linear regression models (not adjusted and adjusted for potential confounders) between Geriatric Depression Scale (GDS) score, as continuous variable, and selected neurocognitive and functional tests.

	Coeff (*P*)	Coeff (*P*)
Rey Auditory Verbal Learning test, delayed recall	0.10 (**0.004**)	0.11 (**0.008**)*
Token test	-0.097 (**0.014**)	-0.056 (0.196)*
Babcock test, delayed recall	0.10 (**0.017**)	0.13 (**0.004**)*
Barthel index	-0.025 (**0.011**)	-0.033 (**0.003**)#
Lawton-Brody scale	-0.203 (**< 0.001**)	-0.246 (**< 0.001**)#

*adjusted for age, gender and years of education; # adjusted for age, gender, years of education, and MMSE score

no memory storage deficit, at the expense of attention difficulties. Memory may appear compromised, but depressed people can often find the correct solution with additional thinking time or mnemonic cues. In AD, instead, the ability to store new information is damaged and information can be difficultly retrieved [41].

Previous studies demonstrated as a normal recall is typically found in major depression, whereas a flat learning curve and a rapid forgetting are typical for AD [42-44]. Indeed, as demonstrated by Dannenbaum et al. [45], subjects with depression perform better than AD patients in all initial learning and recall, as well as in delayed recall measures. Niederehe et al. [46] found that depressed and mildly demented patients displayed similar performance in psychomotor speed, but the recall of symbols was significantly better in depressed than in mild AD. From the neurobiological point of view, these deficits could be explained by a general cognitive inefficiency and attention problem in depressed patients, rather than a to structural deficits.

Despite some strengths (high sample size, detailed neuropsychological characterization of participants, adjustment for potential confounders), important limitations of our study should be acknowledged. First, the analyses are based on cross-sectional data, limiting any causal interpretation of our results. Second, we do not have detailed information about possible antidepressant drug treatments or information on the onset and duration of depressive symptoms. Third, the categorization of people according to depressive symptoms is based on the GDS scale and not on ICD-10 or DSM-V clinical criteria.

In conclusion, in a large sample of elderly people referring to an Italian memory clinic, individuals with depressive symptoms were more often women, had a lower level of education, presented a greater functional impairment, and better scores at memory tests with delayed recall. These results underline the importance of evaluating depressive symptoms as part of a complete multidimensional evaluation of patients with memory loss in order to improve diagnosis, safeguard functional autonomy and possibly start a target therapy.

Ethical consideration

The study was carried out in accordance with the Declaration of Helsinki (World Medical Association) and the guidelines/indications for Good Clinical Practice of the European Medicines Agency and of the local Ethics Committee (Ferrara, Italy).

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Everyone who contributed significantly to the work appears in the list of authors.

Conflict of interest

The Authors declare no conflict of interest.

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