Depression and Alzheimer disease: a risk factor or a prodrome

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Background
The number of elderly individuals in the population is steadily increasing. One of the well known problems in the elderly is cognitive impairment. Alzheimer disease is the most common cause of cognitive impairment. Another health problem in this age group that can present with cognitive impairment is depression. Several controversies exist regarding the relationship between depression and Alzheimer disease.

Aim
This work aims at studying whether depression can be a risk factor for future development of Alzheimer disease.

Patients and methods
Twenty patients with Alzheimer disease in the outpatient clinic were asked about their history of depression and the presence of depression at the onset of illness.

Results
One unmarried woman (5%) had a history of depression. Seven patients (35%) had depression at the onset of illness.

Conclusion
The current study supports the hypothesis that depressed mood is not a risk factor for future development of Alzheimer disease. Further studies are needed to assess the relationship between cognitive symptoms of depression and future development of Alzheimer disease.

Keywords:
Alzheimer disease risk factor, depression, prodrome

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Introduction

The number of elderly people in the population is steadily increasing. In 1900, the percentage of elderly individuals older than 65 years was 5%. In 2003, the percentage increased to 15%, and it is expected to be about 24% in 2030. Elderly individuals suffer from several social and medical problems. One of the most common medical problems suffered by them and faced by physicians dealing with them is cognitive decline (Steffens *et al.*, 2009).

One of the most well-known causes of progressive cognitive decline in the elderly is dementia. Dementia has a serious impact on the affected person, his/her caregiver(s), and on the community as a whole. The most common cause for dementia is Alzheimer disease (AD). Five percent of elderly individuals above 65 years suffer from AD. This percentage increases to 30% in those above 85 years. It is expected that 81 million people will suffer from AD in 2040 (Alzheimer's Association, 2009).

Anticholinesterases were introduced as a pharmacological treatment for dementia with an evidenced efficacy in delaying the progress and sometimes improving the course of the disease (Dickerson *et al.*, 2007; Traykov *et al.*, 2007; Wu *et al.*, 2009). Therefore, early detection and treatment of dementia is of considerable importance (Milisen *et al.*, 2006; Belleville *et al.*, 2008). This has led to the recognition of mild cognitive impairment (MCI) (Dierckx *et al.*, 2007). MCI is the intervening zone between normal aging and dementia. MCI is considered by many authors as the prodrome of dementia (Brodaty *et al.*, 2003; Rosenberg and Lyketsos, 2008; Werner and Korczyn, 2008).

There are several causes for cognitive decline in the elderly other than dementia. Examples for these causes are systemic illness, previous psychotic illness, intake of medications, and depression (Steffens *et al.*, 2009).

Depression is a very common problem among the elderly population. Prevalence of clinically significant depression among them is about 10%, which means that depression is more common than dementia (Potter and Steffens *et al.*, 2007; Hattori, 2008, 2009). Depression and dementia have serious consequences; yet, their treatment and prognosis are totally different. Therefore, differentiation between depression and dementia is of considerable importance (Chertkow *et al.*, 2008; Steffens, 2008; Thomas and O'Brien, 2008).

In the real clinical practice, this differentiation is sometimes very difficult. This difficulty is due to the following reasons:

(1) Cognitive decline is a common presentation for depression in the elderly (known as pseudodementia).
(2) Depressive symptoms are common in actual dementia.
(3) Sometimes, depression is the prodrome of dementia.

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Treating depression with antidepressants markedly improves cognitive decline, but the cognition rarely becomes normalized (Wright and Persad, 2007; Gagliardi, 2008; Steffens and Potter, 2008).

The question now is can we consider depression as a risk factor for future development of AD?

Aim

This work aims at studying whether depression can be a risk factor for future development of AD.

Patients

This study included 20 patients with AD in the outpatient clinic. They were chosen according to the following inclusion and exclusion criteria:

Inclusion criterion:

(1) Age above 60 years.

Exclusion criteria:

(1) Presence of previous psychotic illness.
(2) Mental subnormality.
(3) Presence of severe systemic illness (e.g. chronic advanced liver disease, chronic advanced renal disease).
(4) Presence of previous neurological disease (e.g. stroke, infection, and epilepsy).

Methods

Written consent was taken from the patients (or their relatives) before participation in the study.

Clinical assessment was performed with special emphasis on the following:

(1) Age.
(2) Sex.
(3) Main presenting manifestations.
(4) Previous history of depression.
(5) Depression at onset of illness.

Results

The present study was carried on 20 patients with AD. The number of women was 12 (60%), whereas the number of men was eight (40%). The mean age of the studied group (in years) was 79.65 ± 3.13.

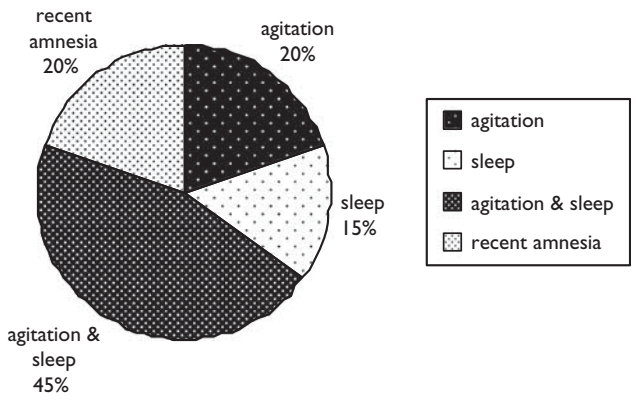
Recent amnesia was the first symptom that propelled the caregivers of the patient to seek medical advice in four cases (20%), whereas agitation alone was responsible for another four cases (20%) to start to seek medical advice; sleep problems alone were responsible for three cases. The majority (nine cases; 45%) sought medical advice for both agitation and sleep problems (Fig. 1).

Only one female patient (5%) reported a history of depression (Fig. 2). Of the 20 patients, seven (35%) reported suffering from depression at the onset of illness (Fig. 3).

Discussion

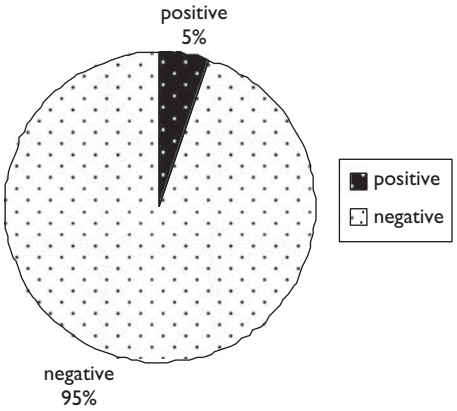
Is depression a risk factor for developing future dementia (including AD) or is depression a prodrome of AD?

Figure 1



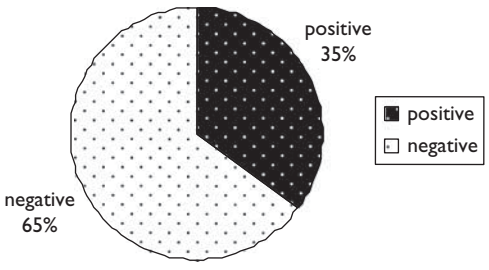
First symptom for seeking medical advice.

Figure 2



History of depression.

Figure 3



Depression at onset of disease.

Answering this question is important because if depression is a risk factor for AD, effective treatment of depression can, theoretically, decrease the probability of developing AD in the future.

The number of women in the studied group was 12 (60%), whereas the number of men was eight (40%). The mean age was 79.65 ± 3.13 years. These findings were consistent with that of Benson *et al.* (2005).

According to the current study on AD patients, only one unmarried woman (5%) reported a history of depression (Fig. 2). Also, in this group, seven patients (35%) reported suffering from depression at the onset of illness (Fig. 3). These findings support the fact that depression is not a risk factor for AD. Also, these findings support the theory of considering depression as a prodrome of AD under some, but not all, conditions. Accordingly, we can see cases of depression alone, cases of depression at the start that culminate in AD, and finally we can see AD that did not start from depression. Thus, we can see depression and dementia from a dimensional perspective.

Several cross-sectional and longitudinal epidemiological studies have found an association between late-life depressive symptoms and subsequent cognitive decline, including MCI and probable dementia (Barnes, *et al.*, 2006; Geda *et al.*, 2006), but it remains uncertain whether the presence of depressive symptoms is a risk factor or a prodrome or a consequence of a pathological cognitive decline or a part of the pathological process.

A meta-analysis (Ownby *et al.*, 2006) has suggested that a history of depression approximately doubles the risk of developing AD, supporting the fact that depression can indicate a risk of future occurrence of AD. However, recent large prospective cohort studies (Panza *et al.*, 2008a, 2008b; Becker *et al.*, 2009) have failed to show that depressed mood is a risk factor for MCI and dementia.

In the Baltimore Longitudinal Study of Aging and the Personnes Agée QUID study, the presence of premorbid depressive symptoms increased the risk of later development of dementia, especially AD, but only in men, suggesting a predisposition based on sex (Fuhrer *et al.*, 2003; Dal Forno *et al.*, 2005). This was also reported in the Framingham Heart study (Saczynski *et al.*, 2010).

In The Women's Health Initiative Memory Study (WHIMS) (Goveas *et al.*, 2011), a cohort of postmenopausal women aged 65–79 years at study baseline who met the screening cutoff for depressive disorder, a greater risk of subsequent MCI and incident dementia was found after a mean follow-up of 5.4 years than in those who were not depressed. These findings remained significant after adjusting for multiple potential confounding variables, including demographic characteristics, lifestyle variables, cardiovascular risk factors, presence of cerebrovascular disease, antidepressant use, baseline cognitive function [as measured using the modified mini-mental state examination (3Ms)], and prior use and current prescription of hormone therapy. The participants who were depressed had approximately twice the hazard of developing MCI and probable dementia.

Benson *et al.* (2005) compared the performance of the mini-mental state examination (MMSE) total score and item scores in separating four groups of elderly (55–85 years of age) individuals: normal controls, patients with MCI, patients with mild AD, and patients with depression. They concluded that the MMSE effectively separates those with mild AD from the other three groups and MCI from normal aging, but it is relatively ineffective in separating normal elderly individuals from those with depression and individuals with MCI from those with depression. Measures other than the MMSE may need to be implemented to evaluate the mental status to more effectively separate MCI from depression and depression from normal aging. Was the use of 3Ms an effective choice for adjusting the confounding factor of baseline cognitive function in WHIMS? It is a question that needs further research.

Accordingly, the findings of the current study were consistent with that of the Italian Longitudinal study on Aging and the study by Becker and colleagues. In contrast, these findings were inconsistent with that of the Baltimore Longitudinal Study of Aging, the Personnes Agée QUID study, and WHIMS.

This is not a prospective study. Therefore, we cannot ignore the recall bias factor with regard to the history of depression. In contrast, answering 'yes' to the question of 'did you (your parent) have a past history of depression?' usually denotes the presence of previous depressed mood rather than a full-blown picture of depressive disorder.

Accordingly, we can observe that studies that comment on depressed mood [Italian Longitudinal study on Aging, Becker *et al.* (2009), and the current study] did not find any relation with future development of dementia. In contrast, studies that commented on depressive symptoms (Baltimore Longitudinal Study of Aging, the Personnes Agée QUID study, and WHIMS) found a positive relation with future development of dementia. It seems that the presence of memory symptoms of depressive disorder is a risk for development of future dementia rather than just the presence of depressed mood. In contrast, because the neurodegenerative changes seen in AD precede the clinical diagnosis by several years, these memory symptoms of depressive disorder may be the earliest manifestation of this neurodegenerative disease, suggesting that depressive disorder with memory symptoms was actually a prodrome of AD. This hypothesis needs to be further studied.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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