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Research paper

Trajectories of depressive symptoms and their relationship to the progression of dementia☆

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ABSTRACT

Background: The relationship between progression of Alzheimer's disease and depression and its underlying mechanisms has scarcely been studied.
Methods: A sample of 282 outpatients with Alzheimer's disease (AD; 105 with amnestic AD and 177 with Alzheimer's dementia) from Norway were followed up for an average of two years. Assessment included Cornell Scale for Depression in Dementia and Clinical Dementia Rating Scale (CDR) at baseline and follow-up to examine the relationship between AD and depression. Additionally, MRI of the brain, CSF dementia biomarkers and APOE status were assessed at baseline. Progression of dementia was defined as the difference between CDR sum of boxes at follow-up and baseline (CDR-SB change). Trajectories of depressive symptoms on the Cornell Scale were identified using growth mixture modeling. Differences between the trajectories in regard to patients' characteristics were investigated.
Results: Three distinct trajectories of depressive symptoms were identified: 231 (82.8%) of the patients had stable low-average scores on the Cornell Scale (Class 1); 11 (3.9%) had high and decreasing scores (Class 2); and 37 (13.3%) had moderate and increasing scores (Class 3). All classes had average probabilities over 80%, and confidence intervals were non-overlapping. The only significant characteristic associated with membership in class 3 was CDR-SB change.
Limitations: Not all patients screened for participation were included in the study, but the included and non-included patients did not differ significantly. Some patients with amnestic MCI might have been misdiagnosed.
Conclusion: A more rapid progression of dementia was found in a group of patients with increasing depressive symptoms.

1. Introduction

The number of individuals with Alzheimer's disease (AD) is increasing worldwide. In 2015, 46.8 million people were identified as having AD, and it is estimated that 131.5 million will have the disease by 2050 (Alzheimer's Disease International, 2015). A curative treatment for AD is still lacking. Therefore, efforts are being made to develop strategies to prevent the disease or to delay its progression. Several modifiable risk factors such as depression, diabetes and hypertension have been reported for AD dementia (Deckers et al., 2015; Kivipelto et al., 2006; Norton et al., 2014; Ngandu et al., 2015).

The literature regarding factors influencing the progression of AD is scarce. The identification of such factors, especially potentially modifiable factors, would be of crucial importance. The treatment of such

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conditions may be seen as a form of secondary prevention by slowing the progression of the disease and diminishing the negative consequences of AD. In this paper, we will focus on depression and its relationship to the progression of AD.

The relationship between depression and dementia in AD is complex. Depression has been reported as a risk factor for all types of dementia, including AD (Saczynski et al., 2010; Byers and Yaffe, 2011; Ownby et al., 2006; Diniz et al., 2013; Deckers et al., 2015). In addition, several authors have pointed to the potential of preventing dementia by treating depression (Lyketsos et al., 2011; Kessing, 2012). Depression can be a prodromal symptom of dementia, especially when depression has its onset late in life and appears close to the onset of dementia (Li et al., 2011; Bennett and Thomas, 2014; Masters et al., 2015). It is also well known that depression can be a consequence of dementia (Lyketsos and Olin, 2002; Olin et al., 2002; Barca et al., 2010).

The findings in regard to whether depression accelerates the progression of AD are controversial. One population study found that depression did not accelerate the progression of dementia among patients with AD (Leoutsakos et al., 2015), whereas other studies reported the opposite (Rapp et al., 2011; Wilson et al., 2002). However, pathophysiological mechanisms underlying depressive symptoms in AD and their roles in the progression of the disease have not yet been investigated.

Depression and AD may have common etiological mechanisms. Depression may cause increased circulation of glucocorticoids, which, in turn, could lead to hippocampal atrophy (Byers and Yaffe, 2011). One study reported that patients with depression in AD had more medial temporal lobe atrophy (MTA) than patients with AD without depression (Dhikav et al., 2014), and a post-mortem study revealed that AD patients with a history of depression had more neuritic plaques and neurofibrillary tangles in the hippocampus than those without a history of depression (Rapp et al., 2006). Another similarity is that cardiovascular diseases are risk factors for both depression and AD (Almeida et al., 2007; Kivipelto et al., 2006). Moreover, neuroinflammation has been reported in both depression and dementia, with increased levels of similar pro-inflammatory cytokines (Hong and Kim, 2016). Therefore, depression could pose an additive effect in AD. Indeed, it has been shown that depression (Modrego and Ferrandez, 2004) and, especially, increasing depressive symptoms over time (Kaup et al., 2016) are risk factors for all-cause dementia. However, whether increasing depressive symptoms over time in AD accelerate cognitive decline or the progression of dementia has not yet been investigated.

This is an exploratory study that aims to investigate the different trajectories of depressive symptoms among patients with AD and the relationship between the progression of AD and different trajectories.

2. Methods

2.1. Participants

The Prognosis of Alzheimer's disease and Resource use (PADR) study is a longitudinal, observational study among Norwegian patients from two memory clinics and one geriatric outpatient unit, with one assessment at the time of the patients' first visit to the clinics and one follow-up assessment after 16–37 months. Inclusion criteria were: having a diagnosis of MCI or dementia, having the capacity to provide consent at baseline, having an available proxy, being fluent in the Norwegian language, living in proximity to the center (close enough to be reassessed) and having no serious comorbid diseases at baseline.

Of 555 patients screened, 198 were not included at follow-up due to various reasons, resulting in 357 patients being assessed after an average of two years. Patients with diagnoses other than AD, such as non-amnestic mild cognitive impairment and other types of dementia (N = 75) were excluded from the present study, resulting in 282 patients with Alzheimer's disease: 177 with dementia due to AD and 105 with prodromal AD defined as amnestic MCI, (see "Diagnoses" for details). Fig. 1 Patients who completed follow-up had completed more years of education compared to those who did not complete follow-up. Otherwise, there were no differences regarding age, gender, Cornell score, CDR sum of boxes, and MMSE score.

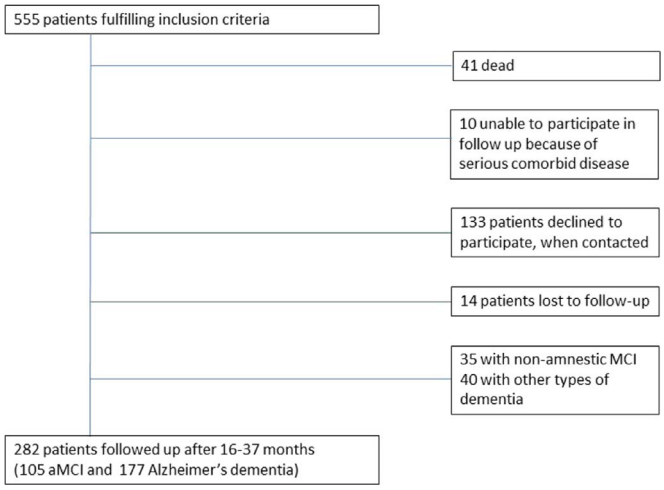

Fig. 1. Flow-chart.

2.2. Assessments

The baseline assessments of the patients were performed by physicians at the outpatient clinics and included a clinical history from patients and their caregivers, neuropsychological tests, physical and cognitive examinations, blood analyses (including analysis of APO E status among 252 patients) and, usually, structural brain imaging with MRI or CT. In some cases, SPECT and PET were also performed. Cerebrospinal fluid (CSF) was drawn from 110 of the 282 patients for the analyses of amyloid-β (Aβ), total tau (T-tau) and phospho tau (P-tau). Nurses interviewed the caregivers with structured instruments to evaluate activities of daily living and neuropsychiatric symptoms including depression. The follow-up assessment was conducted by research physicians using a protocol similar to that at baseline. Additionally, saliva was collected, three times during the same day.

The demographic characteristics included were age, gender and level of education. Cardiovascular diseases were dichotomized based on the history of cardiovascular disease at baseline. Anatomical Therapeutic Chemical (ATC) codes were registered for all drugs. Antidepressants were identified by the pharmacological subgroup N06A and dichotomized for any antidepressant used at baseline.

The Cornell Scale for Depression in Dementia (CSDD) was used to rate the severity of depressive symptoms (Alexopoulos et al., 1988). The scale has been validated in Norwegian memory clinics, and a cut-off ≥6 was found for depression (Knapskog et al., 2011). Each of the 19 items is rated from 0 (no symptom) to 2 (severe symptom), giving a sum score of 0–38, with higher scores indicating more severe depression. Several items in the Cornell Scale were scored as "not possible to evaluate". Such items would affect the sum score, making it artificially low. Therefore, the average score was used as a continuous variable at baseline and at follow-up.

The Physical Self-Maintenance Scale was used to assess the patients' abilities to perform personal activities of daily living (PADL). This scale has six items, and each item can be scored between 1 and 5. The Instrumental Activities of Daily Living Scale (IADL) was used to evaluate instrumental activities of daily living. This scale has eight items, and each item can be scored between 0 and 3–5; a higher score denotes greater impairment (Lawton and Brody, 1969). Both scales were summarized to evaluate activities of daily living (ADL) as one continuous variable.

The Mini-Mental State Examination (MMSE) was applied to rate global cognitive functioning. The score on the MMSE varies between 0