Neuroimaging
Microbleeds are associated with depressive symptoms in Alzheimer’s disease

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Abstract

Introduction: Co-occurrence of cerebrovascular disease and depression led to the “vascular depression hypothesis”. White matter hyperintensities (WMHs) have been associated with depressive symptoms in population-based studies. We studied the association between small vessel disease and depressive symptoms in a memory clinic population.

Methods: We included >2000 patients with subjective cognitive decline (SCD), mild cognitive impairment, and Alzheimer’s disease (AD). Magnetic resonance imaging was rated for WMHs, lacunes, and microbleeds. Depressive symptoms were assessed using the Geriatric Depression Scale. We performed logistic regression analysis.

Results: Depressive symptoms were present in AD: 17%; mild cognitive impairment: 25%; and SCD: 23%. SCD patients with WMHs showed higher propensity of depressive symptoms than AD patients with WMHs. AD patients with microbleeds were more likely to have depressive symptoms compared with AD patients without microbleeds (odds ratio = 1.70; 95% confidence interval: 1.08–2.68).

Discussion: Microbleeds are associated with depressive symptoms in AD, supporting a potential role of cerebral amyloid angiopathy in the occurrence of depressive symptoms in AD.

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Keywords: Small vessel disease; White matter hyperintensities; Lacunes; Microbleeds; Depressive symptoms; Alzheimer’s disease

1. Introduction

Depressive symptoms are common in older people and have been associated with cognitive and functional impairment and lower quality of life [1,2]. Depressive symptoms in older people are often referred to as late-life depression and are related to an increased risk of dementia [3,4]. Approximately 30% of patients with dementia experience depressive symptoms [2]. Cerebrovascular disease often co-exists with Alzheimer’s disease (AD). Cerebral small vessel disease (CSVD) is the most common vascular cause of dementia and a major contributor to mixed dementia [5]. Magnetic resonance imaging (MRI) markers of CSVD include white matter hyperintensities (WMHs), lacunes, and microbleeds [6]. Associations between depressive symptoms and CSVD have been found cross-sectionally and longitudinally in (healthy) older people and have led to the “vascular depression hypothesis” in late-life depression [7–14]. Depressive symptoms could be an entity on their own—unrelated to cognitive decline and dementia, but depressive symptoms have also been hypothesized to be a prodromal, early manifestation of neurodegeneration or a risk factor for...
dementia [15]. Alternatively, depressive symptoms could be a psychological reaction to perceived cognitive impairment.

Studies investigating the relationship between depressive symptoms and CSVD are mostly limited to large population-based studies [3,7,10,16], in patients without cognitive impairment. This study is among the first using a large cohort of memory clinic patients. We hypothesize that the relationship between CSVD and depressive symptoms is modulated by disease severity and expect this relationship most prominently in nondemented subjects. To test this hypothesis, we investigated in a cross-sectional study whether MRI markers of CSVD were associated with depressive symptoms in patients with subjective cognitive decline (SCD), mild cognitive impairment (MCI), and AD.

2. Methods

2.1. Subjects

We included 2136 patients (810 SCD, 488 MCI, and 838 AD patients) with available MRI scans and Geriatric Depression Scale (GDS) scores from the memory clinic-based Amsterdam Dementia Cohort [17].

All patients visited the memory clinic between August 2001 and September 2016 and underwent standardized brain MRI. All patients underwent a 1-day standardized dementia screening that included medical history, physical and neurological examinations, screening laboratory tests, neuropsychological assessment, and standardized brain MRI. Clinical diagnosis was established by consensus in a multidisciplinary team. AD patients met the NINCDS-ADRDA criteria for probable AD [18] and also met the core clinical criteria for probable AD proposed by the National Institute on Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association for probable AD [18] and also met the core clinical criteria for probable AD proposed by the National Institute on Aging-Alzheimer’s Association workgroup [19]. Diagnosis of MCI was based on the Petersen and National Institute on Aging–Alzheimer’s Association criteria for MCI [20,21]. Patients were considered to have SCD when they presented with cognitive complaints, and results of clinical assessments were normal (i.e., criteria for MCI or psychiatric disorder were not fulfilled and other underlying neurologic diseases were ruled out). For all patients, history of depression, the use of antidepressants (e.g., selective serotonin reuptake inhibitors [SSRIs], tricyclic antidepressants, monoamine oxidase inhibitors), and the presence of vascular risk factors (i.e., hypertension, diabetes mellitus, and hypercholesterolemia) were determined based on self-reported medical history and medication use. Smoking status was dichotomized into never and former or current smoker. Level of education was classified into the system of Verhage ranging from 1 to 7 (low to highly educated) [22]. The study was approved by the medical ethics committee of the VU University Medical Center. All patients provided written informed consent for their data to be used for research purposes.

2.2. Evaluation of depressive symptoms

Depressive symptoms were assessed using the 15-item self-reported GDS, which has a maximum score of 15 [23]. The GDS-15 is frequently used in clinical practice and research and is a valid and reliable screening instrument for depressive symptoms in older people [23]. A systematic review found a sensitivity of 0.89 and specificity of 0.77 of the GDS-15 at a cutoff score of 5 [24]. In our study, the GDS was orally administered to patients by a neuropsychologist. We classified patients as having depressive symptoms if their score on the GDS was 5 or higher.

2.3. Evaluation of MRI markers

MRI was performed on 1.0T ($n = 548$), 1.5T ($n = 189$), or 3.0T ($n = 1391$) scanners. The MRI protocol included T1-weighted, T2-weighted, fluid-attenuated inversion recovery (FLAIR) and gradient echo T2*-weighted images. The severity of WMHs using the Fazekas scale was determined on the FLAIR sequence (possible range: 0–3) [25] and was dichotomized into absent (Fazekas 0–1) or present (Fazekas 2–3). WMH data were available for 2128 patients. Lacunes were defined as sharply demarcated deep lesions with CSF-like signal on all sequences and were dichotomized into absent or present ($\geq 1$ lacune). Lacune count was available for 2074 patients. Microbleeds are small dot-like hypointense lesions on T2*-weighted MRI [6]. Microbleed count was dichotomized into absent or present ($\geq 1$ microbleed). Microbleed count was available for 2090 patients.

We classified patients as having CSVD if their MRI showed presence of WMHs (Fazekas score $\geq 2$), presence of lacunes ($\geq 1$ lacune), and/or presence of microbleeds ($\geq 1$ microbleed). Global cortical atrophy (GCA) was defined on axial FLAIR images (range 0–3) and dichotomized into absent (0–1) or present (2–3) [26]. Medial temporal lobe atrophy (MTA) was determined on coronal T1-weighted images using the Scheltens scale (range 0–4) [27], the mean of left and right MTA scores was dichotomized into MTA absent (<1.5) or MTA present ($\geq 1.5$).

2.4. Evaluation of APOE

DNA was isolated from 10-mL blood samples in ethylenediaminetetraacetic acid. Apolipoprotein E (APOE) $\varepsilon 4$ genotype was determined with the LightCycler APOE mutation detection method (Roche Diagnostics GmbH, Mannheim, Germany). APOE was analyzed according to the presence or absence of an APOE $\varepsilon 4$ allele. APOE $\varepsilon 4$ data were available for 2020 patients (SCD: 757/810; MCI: 462/488; and AD: 801/838).

2.5. Statistics

PASW Statistics 22.0 for Mac (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. Analyses of
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