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Markers of cerebral small vessel disease and severity of depression in the general population

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ABSTRACT

The vascular depression hypothesis postulates that cerebral small vessel disease can cause or exacerbate depression in elderly persons. Numerous studies explored the association of imaging markers of cerebral small vessel disease including white matter lesions (WMLs) and lacunar infarcts with depressive symptoms or disorders. However, cerebral microbleeds have not been tested in depression. In the current study, we aimed to explore the association of WMLs, lacunar infarcts and cerebral microbleeds with depression continuum in a large population-based sample, the Rotterdam Study. Study population consisted of 3799 participants (aged 45 or over) free of dementia. WML volumes, lacunar infarcts and cerebral microbleeds were measured with brain magnetic resonance imaging. Depressive symptoms, depressive disorders and co-morbid anxiety disorders were assessed with validated questionnaires and clinical interview. WML volumes and lacunar infarcts were associated with depressive symptoms and disorders. Cerebral microbleeds, especially in deep or infratentorial brain regions, were related to depressive disorders only. Our results indicate that WMLs and lacunar infarcts might be non-specific vascular lesions seen in depressive symptoms and disorders. Association of cerebral microbleeds with more severe forms of depression may indicate impaired brain iron homeostasis or minor episodes of cerebrovascular extraversion, which may play a role in depression etiology.

1. Introduction

The co-occurrence of cerebrovascular diseases and depression led researchers to propose the vascular depression hypothesis in late-onset depression. Since the hypothesis was first described by Alexopoulos et al. (1997) and Krishnan et al. (1997), research on the etiology of vascular depression has been advanced along two conceptually different lines. Some researchers have focused on the localization of the vascular lesions to explain the etiology of the vascular depression (Sneed and Culang-Reinlieb, 2011). Others have explored the cognitive deficits due to the vascular cerebral lesions predisposing to depression. In the last decade, this approach has led researchers to define "the depression-executive dysfunction syndrome" in which symptoms of executive dysfunctions such as difficulty with planning, organizing, abstracting are seen as part of clinical depression (Sneed and Culang-Reinlieb, 2011; Taylor et al., 2013b). Despite the supporting evidence, it is still debatable whether the vascular depression exists as a clinical entity. Extracerebral vascular diseases seem to be less consistently associated with depression in elderly than to cerebral vascular diseases (Almeida, 2008; Almeida et al., 2007). While vascular risk factors, lesions and diseases are very common in elderly, the prevalence of depression does not increase in parallel. If the vascular depression hypothesis was of public health importance (i. e. vascular factors strongly predispose, precipitate, and perpetuate depression), the prevalence of depression in elderly would be expected to rise more strongly with age (Almeida, 2008).

Early studies have tested the link between depression and clinically overt vascular events. In these patients, the effects of the

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functional deficits on depression as a result of the vascular event are difficult to control for. In a recent report of the Rotterdam Study, myocardial infarction was related to depression in men, only when recognized that supporting the importance of psychosocial effects of an overt disease (Jovanova et al., 2016).

Nowadays, a narrower definition of vascular depression hypothesis is used in which the vascular component is considered as clinical or non-clinical cerebrovascular events. Non-clinical vascular events are consisted of imaging findings of cerebral small vessel disease. Such findings occur as a result of hypertension, arteriolosclerosis, inflammation or amyloid deposition in small arteries, arterioles or venules of the brain (Pantoni, 2010). These imaging findings are common in the elderly people. The most commonly explored imaging findings of cerebral small vessel disease are white matter lesions (WMLs) and lacunar infarcts. For decades, WMLs have been explored in different severity degrees of depression. Cross-sectional and longitudinal association of WMLs with depressive symptoms, major depressive disorder (MDD), poor treatment response, and occurrence and recurrence of MDD (Arnone et al., 2012; Baldwin, 2005; de Groot et al., 2000; Godin et al., 2008; O'Brien et al., 1998; Olesen et al., 2010; Saavedra Perez et al., 2013; Taylor et al., 2013a) and comorbid anxiety disorders have been demonstrated (Fiedorowicz et al., 2011). Similarly, lacunar infarcts has been related to depressive symptoms (Grool et al., 2013; Wu et al., 2014), MDD, and recurrence of MDD (Saavedra Perez et al., 2013).

Cerebral microbleeds are now recognized as an imaging phenotype of the cerebral small vessel disease. (de Jong et al., 2002; Pantoni, 2010; Poels et al., 2012; Vernooij et al., 2008c). Cerebral microbleeds are perivascular collections of hemosiderin induced by prior tiny hemorrhage. Similar to the WMLs and lacunar infarcts, cerebral microbleeds are detected commonly in elderly (Poels et al., 2010). In general, there are two types of cerebral microbleeds on the basis of location: deep or infratentorial microbleeds and lobar microbleeds. Deep or infratentorial microbleeds were generally related to vascular risk factors whereas lobar microbleeds were associated with cerebral amyloid angiopathy (Vernooij et al., 2008b). Cerebral microbleeds and their locations have not yet been extensively tested in depressive disorders. Studies assessing the relation between cerebral microbleeds and depressive disorders are mostly limited to the stroke cases in clinical settings (Tang et al., 2014a, 2011a, 2011b, 2014b). In a recent longitudinal study, it was shown that cerebral microbleeds were not related to incident depressive symptoms (van Sloten et al., 2015). However, the relation of cerebral microbleeds with different severity degrees of depression including depressive symptoms, depressive disorders and comorbid conditions of depressive disorders have not been tested in general population.

The link between cerebral small vessel disease and depressive symptoms has been tested in large population-based studies. However, the association between cerebral small vessel disease and depressive disorders was assessed mostly in small clinical studies.

In the current study, we aimed to test the associations of several imaging phenotypes of cerebral small vessel disease with different severity degrees of depression including depressive symptoms, depressive disorders and depressive disorders with comorbid anxiety disorders in general population. We hypothesized that WMLs, lacunar infarcts, and cerebral microbleeds are all related to the depression continuum.

2. Methods

2.1. Study sample

This study was embedded in the Rotterdam Study, a prospective population-based cohort of middle-aged and elderly persons (Hofman et al., 2015). From 2005 to 2008, a random sample within the Rotterdam Study was formed for the regular research center visits. They were invited for brain magnetic resonance imaging (MRI). In total 3855 participants were involved. Of these, 44 (1.1%) had no depression assessment and 10 (0.3%) persons with dementia were excluded. This left 3799 people in the study sample.

Of the 3799 persons in one or more analysis, 3741 had a valid WML measurement, 3742 had data on microbleeds and 3701 participants had data on lacunar infarcts.

The Rotterdam Study has been approved by the institutional review board of the Erasmus University Medical Center and by the review board of The Netherlands Ministry of Health, Welfare and Sports. All participants provided written informed consent after complete description of the Rotterdam Study.

2.2. Assessment of depressive symptoms and anxiety disorders

We diagnosed depressive disorders with a two-step procedure. First, we tested all participants for depressive symptoms using the Center for Epidemiological Studies-Depression (CES-D) scale during the home interview at study entry. A cut-off of 16 was used to define "clinically significant depressive symptoms". This cut-off score has a very high sensitivity for major depression in older adults in the Netherlands (Beekman et al., 1997; Radloff, 1977).

In the second step, we invited the participants with a CES-D score of 16 or greater to a semi-structured interview, the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (Wing et al., 1990). Clinicians were conducted the interviews in close proximity in time to screening. Clinical depressive disorders included DSM-IV-TR–defined major depressive disorder and dysthymia. Thus, both clinically significant depressive symptoms and DSM-IV depressive disorders were assessed in this study.

To determine participants with depressive disorders and comorbid anxiety disorders, we used a slightly adapted version of the Munich version of the Composite International Diagnostic Interview (M-CIDI). The interview was performed by trained interviewers (Wittchen et al., 1998). All DSM-IV anxiety disorders including generalized anxiety disorders, panic disorder with or without agoraphobia, social phobia and specific phobia were assessed except obsessive-compulsive disorder and post-traumatic stress disorder (rare and difficult to diagnose reliably in the general population). We grouped anxiety disorders into a category of "any anxiety disorder".

2.3. Brain MRI

Brain MRI was performed on a 1.5-T scanner (GE Healthcare, Milwaukee, WI) with an 8-channel head coil including T1-weighted, proton-density weighted, fluid-attenuated inversion recovery, and T2*-weighted gradient echo sequences (Ikram et al., 2011).

Post-processing steps have been described elsewhere and include a conventional k-nearest-neighbor brain tissue classifier extended with WML segmentation (Ikram et al., 2011). Using this classifier, we obtained quantitative measures of WML volume and intracranial volume (in mL). (Vernooij et al., 2007).

We defined lacunar infarcts as focal hyperintensities that are ≥ 3 mm on FLAIR and T2-weighted images. An experienced physician scored all infarcts.

All scans were reviewed by 1 of 5 well-trained raters who were blinded to the clinical data. Intra-observer (n=500, 1 rater) and inter-observer (n=300) reliabilities were κ=0.87 and κ=0.85, which indicates very good agreement. In line with previous studies, we defined categories of microbleeds restricted to a lobar location (strictly lobar microbleeds) and microbleeds in a deep or infratentorial location (Poels et al., 2011; Vernooij et al., 2008a).

2.4. Covariate assessment

Age, sex, education, smoking status, hypertension, diabetes mellitus, body mass index, total and HDL cholesterol concentrations and cognitive function were used as potential covariates on the basis of prior literature (Luijendijk et al., 2008). Education was grouped into eight categories in an ordinary scale from primary education (1) to university level (8) on the basis of the Standard Classification of Education. For the analyses, we further categorized it into three categories; low, intermediate, and high. Smoking status was coded in categories as never, former and current smokers. Systolic and diastolic blood pressures were calculated as the average of two consecutive measurements. Hypertension was defined as a systolic blood pressure $\geq$ 140 mm Hg or a diastolic blood pressure $\geq$ 90 mm Hg or the use of antihypertensive medication according to pharmacy records. Data on diabetes mellitus was collected on the basis of the general practitioners' reports and the