



MRI-defined versus clinically-defined vascular depression; comparison of prediction of functional disability in the elderly



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ABSTRACT

Background: We compared the validity of models of subcortical ischemic depression (SID) and depression-executive dysfunction syndrome (DED) in predicting functional disability in the elderly.

Methods: We obtained data from elderly Korean subjects ($n = 1356$) aged 60 years or older at baseline from the CREDOS study from November 2005 to July 2014. A generalized estimating equation (GEE) model was constructed to measure functional disability using instrumental activity of daily living as a primary outcome. A risk factor of interest was SID and DED evaluated by a visual rating scale of deep white matter hyperintensity in MRI, Stroop test and Geriatric Depression Scale (GDS) score. Receiver-operating-characteristic plots and area under the curve (AUC) test were applied to examine the difference of the two definitions of vascular depression with predicted values of functional disability outcome.

Results: The mean (SD) follow-up duration of the participants was 1.7 (0.9) years. The GEE model showed that presence of SID at baseline predicted functional disability compared to non-depressed subjects (GDS score: Odds ratio [OR] 1.76; 95% CI 1.23, 2.53; $p = 0.002$). The association was also statistically significant among the DED group (OR 1.48; 95% CI 1.15, 1.92; $p = 0.003$). There were no significant differences in predicting functional disability (95% CI: -0.003 to 0.009 , $p = 0.366$) according to AUC differences between SID and DED.

Conclusions: The results will be useful in evaluating the cardinal features of the vascular depression hypothesis in predicting functional disability.

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1. Introduction

As the elderly population is rapidly increasing, disability in the elderly contributes to increased mortality, institutionalization and a greater impact of chronic disease (Alexopoulos, Buckwalter et al., 2002; Bruce, 2002; Kennedy, 2001). Among several chronic diseases of the elderly, depression is one of the leading causes

of disability and depression among the older population accounts for 1.6% of total disability among those over 60 years of age (Murray, 2012). Vascular depression, a term used to describe the presence of depression in an individual with cerebrovascular disease, has significant health and functionality impacts on the affected individual, more so than that of depression in a healthy individual (Alexopoulos, 2002; Alexopoulos, Kiessses, Choi, Murphy, & Lim, 2002; Kiessses & Alexopoulos, 2005; Krishnan et al., 2004; Steffens, Hays, & Krishnan, 1999).

Two alternative definitions of vascular depression have been proposed (Taylor, Aizenstein, & Alexopoulos, 2013). Depression

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executive dysfunction syndrome (DED) (Alexopoulos, Kiosses, Klimstra, Kalayam, & Bruce, 2002; Alexopoulos, Raue, Kanellopoulos, Mackin, & Arean, 2008) is defined based on clinical evidence of vascular risk factors including past history of hypertension, cardiovascular disease and stroke (Alexopoulos et al., 1997). Krishnan, Hays, and Blazer (1997) proposed the term subcortical ischemic depression (SID) as it uses white matter hyperintensity (WMH) especially deep white matter hyperintensity (DWMH) on magnetic resonance imaging (MRI) as a diagnostic and correlates with geriatric depressive symptoms. Controversy exists among researchers as to which definition is appropriate for vascular depression (Pimontel et al., 2013; Sneed, Rindskopf, Steffens, Krishnan, & Roose, 2008).

Detrimental effects of executive dysfunction and subcortical ischemia have been reported according to the particular definition of vascular depression on functional disability (Kiosses & Alexopoulos, 2005; Krishnan et al., 2004). However, few studies have compared the prognostic features of DED and SID with respect to functional disability in the same study population. Lack of a consensus definition for vascular depression makes it difficult to interpret various findings across studies (Sneed et al., 2008).

Presently, we examined the longitudinal association between DED and SID using an index of the instrumental activity of daily living (IADL), a daily self-care activities measurement tool, among non-demented, older adults. We compared the prognostic merits of DED and SID as predictors of functional disability.

2. Materials and methods

2.1. Participants

The Clinical Research Center for Dementia of South Korea (CREDOS) dataset was used for our analyses. The CREDOS study (NCT 01198093) was a nationwide multicenter study designed to assess the occurrence of and risk factors for cognitive deterioration in the elderly. The study recruited subjects from 31 university-affiliated hospitals from November 2005 to July 2014. All participants and their caregivers underwent comprehensive medical, neurological and psychiatric interviews at outpatient clinics. Baseline evaluations (physical, psychological and neurological exams) were conducted at baseline and at each visit during the follow-up period. The subjects were all elderly and Korean of Asians. A detailed description of the CREDOS study is available elsewhere (Son et al., 2012). Of 2268 participants with data available for WMH, Stroop Test, geriatric depression scale score and IADL scores at baseline and during the follow-up period, 1356 subjects who completed at least one follow-up visit were finally included in this study. Subjects met the following inclusion criteria: (i) age ≥ 60 years, (ii) at least one visit during the follow-up period after baseline examination and (iii) cognitively non-impaired with Mini-Mental State Examination (MMSE) scores ≥ 24 . Exclusion criteria were: (i) history of hearing or visual impairment (that could potentially hinder the interview process); (ii) history of large-vessel cerebrovascular disease, such as territorial infarction; (iii) high signal abnormalities on MRI due to vasculitis, multiple sclerosis or leukodystrophy (this was in order to limit the recruitment of participants to only those with small-vessel cerebrovascular disease); (iv) history of intracranial hemorrhage, brain tumor, Parkinson's disease, hydrocephalus, severe head trauma and dementia; (v) history of depression before the 60 years of age; (vi) history of psychiatric disorders (e.g., schizophrenia, mental retardation or mania); (vii) history of psychoactive drug use and (viii) presence of comorbid medical conditions including respiratory disease, malignancy and hepatic or renal disease. The Institutional Review Boards of the participating centers approved this study. After a complete description of the study to the subjects, written informed consent was obtained.

2.2. Measurements

2.2.1. DWMH

Degree of WMH with MRI was evaluated on MRI T2-axial or fluid-attenuated inversion recovery images according to the modified criteria proposed by Fazekas, Chawluk, Alavi, Hurtig, and Zimmerman (1987) and Scheltens et al. (1993). WMH was rated visually and DWMH lesions were identified. The severity of DWMH lesions was classified according to the longest diameter of a given lesion. The scales used were mild (deep white matter < 10 mm in diameter), moderate (10 to < 25 mm) or severe (≥ 25 mm). Intra-class correlation coefficients were conducted on the Fazekas/Scheltens classification by the CREDOS study central committee. The Kappa coefficients for DWMH visual rating scale was good ($\kappa = 0.726\text{--}0.905$) (Noh et al., 2014).

2.2.2. Executive dysfunction measure

Executive dysfunction was quantified using the Stroop Test-Color Reading cognitive test using the Seoul Neuropsychological Screening Battery (SNSB) standards (Kang & Na, 2003). The Stroop test is a response inhibition component of frontal/executive function. Age, sex and education-specific norms were used for the test. Stroop test scores below the 1.5 standard deviation of the norm were classified as executive dysfunction, consistent with previous definitions of impairment of neuropsychological test and mild cognitive impairment (Kang & Na, 2003).

2.2.3. Definition of depression, subcortical ischemic depression and depression executive dysfunction syndrome

Depression was assessed using the Korean version of the Geriatric Depression Scale (GDS)-Short Form self-report assessment validated for use in elderly Korean subjects (Bae & Cho, 2004). The questionnaire consists of 15 Yes/No questions related to depression. A cut-off point of 8 exhibits a sensitivity of 85% and a specificity of 69% for diagnosing a major depressive episode as compared to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition-Text Revision (DSM-IV-TR). GDS scores of elderly subjects were categorized into two groups: 0–7 (normal) and 8 (depressed). This evaluation for self-rated depression using GDS was confirmed by psychiatrist and neurologist's interview conducted in the outpatient clinic. Given the lack of consensus of vascular depression criteria, we used core features of vascular depression hypothesis by selecting concurrent underlying vascular pathologies in radiological or neuropsychological evaluation as our definition. According to the notions of SID on the basis of core features in Krishnan's criteria, we defined SID as a patients with both depression and moderate/severe degree of DWMH using the visual rating scale described in the Fazekas/Scheltens classification (Krishnan et al., 1997). We also categorized DED syndrome in patients with depression and executive dysfunction in response inhibition domain measured by Stroop test based on previously published criteria (Alexopoulos, Kiosses, Klimstra et al., 2002; Sneed et al., 2007).

2.2.4. Other predictor variables

Questionnaires were conducted at baseline to evaluate (i) demographic characteristics (including age, sex and years of education); (ii) vascular burden (including current smoking, hypertension (HTN), diabetes mellitus (DM), dyslipidemia, cardiovascular disease (CVD) and stroke); (iii) cognitive burden (including score for the Korean version of the Mini-Mental State Examination-MMSE) (Kim, Shin, Yoon, & Lee, 2002) and (iv) functional disability (accessed by IADL with 15 questionnaires validated for use in elderly Korean subjects) (Ku, Kim, & Kwon, 2004). IADL risk was counted as positive for patients with a score ≥ 8 points (Ku et al., 2004). Age and years of education were

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