Late-life Depression Modifies the Association Between Cerebral White Matter Hyperintensities and Functional Decline among Older Adults

Celia F. Hybels, Ph.D., Carl F. Pieper, Dr.P.H., Martha E. Payne, Ph.D., R.D., M.P.H., David C. Steffens, M.D., M.H.S.

Objective: *Vascular lesions seen through brain imaging as hyperintensities are associated with both depression and functional impairment in older adults. Our objective was to determine if the relationship between the volume of cerebral white matter hyperintensities (WMHs) and functional decline differed in the presence of late life depression.* **Design:** *Secondary analysis of data collected through the Neurocognitive Outcomes of Depression Study. Analysis techniques included general linear mixed models examining trajectories of functional change predicted by lesion volume at baseline.* **Participants:** *381 participants (244 patients diagnosed with major depression and 137 never depressed comparison participants) ages 60 years and older followed for up to 16 years.* **Measurements:** *WMH volume was measured through analysis of brain magnetic resonance imaging data. Functional limitations included difficulties with basic activities of daily living tasks, instrumental activities of daily living tasks, and mobility.* **Results:** *Those participants who were both depressed and had a higher volume of WMHs at baseline were most at risk for functional decline across all measures of function. Among the never depressed, those with a higher WMH volume at baseline had a more accelerated rate of functional decline than those with lower WMH volume, and those who were depressed with lower volume of WMH started with more limitations than the never depressed but appeared to progress at a rate similar to those who were never depressed with lower WMH.* **Conclusion:** *Older patients with both cerebrovascular risk factors and depression are at an increased risk for functional decline, and may benefit from the treatment of both conditions.* (Am J Geriatr Psychiatry 2015; ■:■−■)

Key Words: Depression, functional impairment, lesions, white matter hyperintensities, longitudinal

Received September 9, 2014; revised February 21, 2015; accepted March 9, 2015. From the Department of Psychiatry and Behavioral Sciences (CFH, MEP), the Department of Biostatistics and Bioinformatics (CFP), the Duke Neuropsychiatric Imaging and Research Laboratory (MEP), and the Center for the Study of Aging and Human Development (CFH, CFP, MEP), Duke University Medical Center, Durham, NC; and the Department of Psychiatry (DCS), University of Connecticut Health Center, Farmington, CT. Send correspondence and reprint requests to Celia F. Hybels, Ph.D., Department of Psychiatry and Behavioral Sciences, Center for the Study of Aging and Human Development, Duke University Medical Center, Box 3003, Durham, NC 27710. e-mail: celia.hybels@duke.edu

http://dx.doi.org/10.1016/j.jagp.2015.03.001

Late life depression is associated with a number of negative medical and psychological outcomes, due, in part, to a course that is often chronic and recurring.[1] One such negative consequence of depression is a decline in functional status. Although the associations between depression and functional impairment have been well documented, the pathways are complex, as both conditions can be a cause, consequence, or comorbidity of the other.[1–3] Depression is one of the leading causes of disability, yet the components and correlates of the depression experience that impact functional decline are still under study.

Increased volume of cerebral white matter hyperintensites (WMHs), as observed through brain imaging, has been linked to both late life depression and functional impairment. Specifically, "vascular depression" has been proposed as a subtype of late life depression, particularly among those with a late onset, which exhibits increased severity of hyperintensities in both subcortical gray and white matter.[4–6] In additional to a later onset, increased WMH volume has been linked to poorer outcomes in geriatric depression.[7] Much research has focused on cognitive decline associated with increased WMH volume, particularly among older depressives.[8–11] WMH volume has also been associated with functional limitations,[12,13] impaired mobility,[14] gait and motor disturbances, falls, and poor balance[15–17] in community studies of older adults. In longitudinal studies, increased WMH volume predicted incident falls and increased functional impairment, decreased mobility, and becoming frail.[13,18–22] Increased WMH volume has also been shown to predict becoming dependent because of motor and cognitive deterioration.[23]

That vascular changes in the brain are associated with both functional decline and late life depression raises the possibility that depression and disability may share a common risk factor in vascular lesions. A second hypothesis is that depression modifies the relationship between WMH and functional status.[1] It is not fully established whether increased WMH volume predicts functional decline within the context of late life depression or whether depression modifies the relationship between WMH volume and functional decline.

The purpose of the analyses presented here was to determine if the longitudinal association between WMH and functional decline differed in the presence of late life depression. We hypothesized that greater WMH volume at baseline would predict an increase in functional limitations over time, and that the effect of WMH volume would be greater among patients with late life depression compared with those never depressed.

METHODS

Study Sample

The study sample comprised 381 participants ages 60 years and older, including 244 patients who met DSM-IV criteria for major depression and 137 never depressed comparison participants who were enrolled in the Neurocognitive Outcomes of Depression in the Elderly (NCODE) study at Duke University. The study has been described elsewhere.[8] In summary, NCODE is a guideline-based prospective naturalistic treatment study of older patients with major depression currently in its 19th year. The sample includes both incident and recurrent cases of depression recruited from psychiatry and primary care clinics. Patients and comparison participants had to be free of dementia or suspected cognitive impairment at the time of enrollment. Other exclusion criteria included a diagnosis of another major psychiatric condition, any primary neurological illness, active alcohol abuse or dependence, or metal in the body which could interfere with brain magnetic resonance imaging. Comparison participants were recruited from the Duke Center for Aging subject registry. Participants in this analysis have been followed for up to 16 years. All participants provided written consent at the time of enrollment. The research protocol was reviewed and approved annually by the Duke University institutional review board.

Study Measures

Participants were administered the Duke Depression Evaluation Schedule (DDES)[24] at enrollment and annually thereafter. This composite questionnaire includes the Center for Epidemiologic Studies–Depression scale[25] to screen for depression in addition to questions about health and functioning. All potential cases of