Biological Psychiatry: Celebrating 50 Years

Vascular Depression: Is an Old Research Construct Finally Ready for Clinical Prime Time?

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More than 2 decades ago, geriatric psychiatry investigators introduced the "vascular depression hypothesis," kickstarting a generation of research on whether "cerebrovascular disease may predispose, precipitate, or perpetuate some geriatric depressive syndromes" (1). The incorporation of neuroimaging became routine in late-life depression research, with some groups advocating for an imaging-based definition of vascular depression relying on the presence of deep white matter and subcortical gray matter lesions viewed on magnetic resonance imaging brain scans (2). Clinical research studies, often at a single site, have reported negative consequences of these vascular changes, including diminished response to initial antidepressant medication, chronic medical illness, disability, and cognitive impairment.

Larger population-based studies that incorporate imaging may also inform our understanding of the relationship between cerebrovascular disease and occurrence and outcomes of depression later in life. For example, subcortical lesions were associated with a worsening of depression symptoms over time in the Cardiovascular Health Study (3), and the Leukoaraiosis and Disability Study found that progression of white matter change was associated with incident depression at 3-year follow-up (4). Also, in the National Institute of Mental Health Collaborative Psychiatric Epidemiology Surveys study, vascular depression was defined as meeting DSM-IV criteria for an episode of major depressive disorder within the preceding 12 months with cardiovascular or cerebrovascular disease or major cardiovascular risk factors (5). The prevalence of vascular depression was 3.4% compared with a prevalence of major depression without vascular disease of 12.2%. More than one fifth (22.1%) of those with a lifetime history of major depressive episodes met the study criteria for vascular depression.

In the current issue of *Biological Psychiatry*, investigators from the Paris Prospective Study III examined the new onset of significant depressive symptoms as predicted by carotid artery stiffness, an important peripheral marker that is associated with a higher risk of cerebrovascular disease (6). Using carotid distensibility as a measure of carotid artery stiffness, van Sloten *et al.* (6) found that those in the lowest tertile of distensibility (more stiffness) had a significantly higher risk of reporting incident depressive symptoms than those in the highest tertile (less stiffness). Thus, while the study did not involve direct observation of vascular brain changes, it adds critical new support for the vascular depression hypothesis.

The findings of van Sloten *et al.* (6) are important both clinically and scientifically. From a clinical standpoint, given the negative consequences of late-life depression, noninvasive procedures that are commonly used, such as carotid ultrasound, may inform efforts to provide follow-up screening for depression. While clinical diagnoses were not established in the present study, we previously reported high rates of major depression among 192 veterans who were referred for carotid ultrasound, including a rate of 16.1% among patients classified as being neurologically asymptomatic (7). These studies identified patients who were undergoing carotid evaluation as being at high risk for clinically significant depression.

Once late-life depression in the context of likely cerebrovascular disease is detected, clinicians must act to provide appropriate care. New research, highlighted in a recent review by Taylor *et al.* (8), has informed the clinical management of individuals with a vascular depression subtype. For example, it is important to note that depressed older adults with cerebrovascular disease frequently experience cognitive symptoms, such as psychomotor slowing, diminished initiation of thought and movement, reduced processing speed, and impairment in insight into mood. These cognitive issues may lead individuals to not recognize and to underreport depressive symptoms; thus, patients with vascular depression may not appear to meet the DSM criteria for major depressive disorder. Another clinical consideration in working with these patients is a higher risk of mortality that has been attributed to accelerated frailty, general morbidity, and cardiac death.

Taylor *et al.* (8) also note that the presence of cerebrovascular disease in geriatric depression has consequences for acute treatment, including low remission rates in patients treated with selective serotonin reuptake inhibitor monotherapy. Patients with vascular depression may thus require multiple medication trials or more complex, rational polypharmacology. In addition, executive impairment is a common feature of vascular depression, and psychotherapies, such as problem-solving therapy, which is tailored for depressed individuals with executive dysfunction, have shown efficacy. Patients with prominent sleep complaints among their depressive symptoms may benefit from insomnia-focused cognitive behavioral therapy. In addition to pharmacotherapy and psychotherapy, neurostimulation methodologies may have a role in the treatment of vascular depression. Electroconvulsive therapy has been shown to be more effective than medication in patients with vascular risk factors, and repetitive transcranial magnetic stimulation achieved a modest remission rate in patients with vascular depression who were previously refractory to treatment with antidepressants.

A key question that readers of the van Sloten *et al.* (6) article might consider is whether sufficient evidence supporting the vascular depression hypothesis has emerged over the past 20 years to allow us to definitively declare that vascular depression is a distinct clinical subtype of major depression. After all,

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it is clear that vascular brain changes are more common in geriatric depression, particularly late-age onset of major depression.

In a 1998 review in *Biological Psychiatry*, we proposed formal diagnostic criteria for a vascular depression subtype specifier (9). This article cited a five-step method for achieving diagnostic validity in psychiatric illness that consisted of clinical description, laboratory study, exclusion of other disorders, follow-up study, and family study. The clinical description of vascular depression has been well described and consists of major depression occurring at 50 years of age and older in the context of cerebrovascular disease, characterized by profound apathy, difficulty initiating thought and movement, psychomotor retardation, and impairment in executive function. Differentiation of vascular depression from "depression due to a general medical condition" rests on cerebrovascular disease being an etiologic factor that is a biological process; by comparison, poststroke depression may be considered depression due to a general medical condition. Longitudinal studies demonstrate that negative outcomes of vascular depression include decreased antidepressant response and an increased risk of dementia. Family studies indicate a lower family history of depression in patients with vascular depression.

It is the laboratory study step that has been the focus of research to support the vascular depression hypothesis. These translational studies, largely focused on structural and functional neuroimaging research, have been reviewed by Taylor *et al.* (10). In their summary, Taylor *et al.* (10) suggest a disconnection hypothesis in which focal vascular damage and white matter lesion location each affect neural connectivity and are crucial to the development of depressive symptomatology. This vascular damage may be precipitated by inflammatory processes, and Taylor *et al.* (10) review the effects of proinflammatory cytokines on neurotransmitter pathways, the relationship between genetic markers of inflammation and depression, and the association of proinflammatory states with depression and cognitive decline. Another proposed mechanism linking vascular damage with depression noted in this review is hypoperfusion. Stability of brain perfusion depends on the interaction of processes related to systemic hemodynamics and cerebrovascular autoregulation, with cerebral arteries contracting or dilating as arterial pressure changes. The presence of cerebrovascular disease impairs these processes, and even mild decreases in cerebral blood flow may impair both affective and cognitive function.

Is there sufficient evidence to support a vascular depression subtype? Or is there more to learn about the underlying neurobiology of depression, inspired by the vascular depression hypothesis? It is likely that this is a false choice; the answer to both may be "yes." The present article by van Sloten *et al.* (6) provides an indication of the maturity of research supporting a connection between vascular disease and depression. A strong case can be made that in the vascular depression subtype we have a well-described, unique clinical syndrome that is supported by substantial neurobiological research and longitudinal studies documenting specific mood and cognitive outcomes. The clinical and imaging features that support a vascular depression subtype are as follows:

- Major depression occurring in the context of clinical and/or neuroimaging evidence of subcortical ischemic cerebrovascular disease
- Clinical presentation including marked apathy, difficulty initiating thought and movement, psychomotor retardation, and impairment in executive function
- Occurrence in individuals ≥50 years of age, either as an initial episode of depression or as a recurrence of depression
- Decreased response to initial antidepressant monotherapy
- Increased risk of negative longitudinal outcomes, such as cognitive decline, dementia, and occurrence of cardiovascular and cerebrovascular events (e.g., myocardial infarction and stroke)

As such, this specifier should be strongly considered for inclusion in the next revision of our diagnostic nomenclature.

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Article Information

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