The Current Status of Vascular Depression

a report by
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The notion of vascular depression initially emerged from the finding that patients with late-onset depression had higher rates of hyperintensities (HIs) on structural magnetic resonance imaging (MRI) compared with patients with early-onset depression.1-4 It was further observed that patients with late-onset depression and MRI evidence of cerebrovascular disease also demonstrated greater neuropsychological impairment, including but not limited to tests of executive function.5,6 The vascular depression hypothesis refers to late-onset depression occurring secondary to structural damage to corticostriatal circuits due to atherosclerosis. Thus, those with risk factors for atherosclerosis disease—including hypertension, diabetes, and hyperlipidemia—are suspected to be at a higher risk for vascular depression in late life.

Atherosclerotic disease may cause structural damage to corticostriatal circuits important for the regulation of mood and executive functioning, which in turn creates a vulnerability to depression in late life that is characterized by deficits in planning and set shifting. According to the theory, such depression should not be precipitated by psychosocial risk factors such as neuroticism, negative life events, or lack of social support, and there is some evidence suggesting that this might be the case.4

Research Support for the Vascular Depression Hypothesis

In comparison with healthy controls, high rates of abnormality have been consistently observed in MRI evaluations of elderly patients with major depressive disorder.1,4,5,10 These differences may become greater after adjusting for cerebrovascular diseases and risk factors.11 The abnormalities appear as areas of increased signal intensity in balanced and T2-weighted images. Peri-ventricular HIs (PVH) appear as halos or rims adjacent to ventricles; deep white matter HIs (DWMH) appear as single, patchy, or confluent foci observed in the surrounding subcortical white matter; and subcortical gray matter HIs also appear as single, patchy, or confluent foci in deep gray structures such as the basal ganglia, thalamus, and pons.

There is evidence that the frequency of PVH is comparable between elderly depressed and age-matched controls, but that DWMH are over-represented in the elderly depressed.12-13 In particular, patients with late-onset depression have more DWMH compared with elderly patients with early-onset depression.14-16 For example, O’Brien et al. found that 50% of late-onset depressed patients had severe DWMH compared with 20% of early-onset depressed patients and 9.5% of normal controls. In another study of 1,077 non-demented elderly adults, de Groot et al.17 found that those with severe subcortical but not peri-ventricular HIs were significantly more likely to have late-onset depression (odds ratio 3.4). There may be an over-representation of these DWMH in anterior brain regions,11 which are thought to invade the frontal–subcortical circuits that reciprocally link pre-frontal areas such as the dorsolateral pre-frontal cortex and anterior cingulate cortex to the basal ganglia.12-15 Thus, the vascular depression hypothesis implies both the presence and specific location of HIs.

The dorsolateral pre-frontal circuit is critical to optimal executive functioning.18 Not surprisingly, patients with late-onset depression and DWMH also tend to show deficits in executive functioning. For example, Salloway et al.1 found in a small sample that patients with late-onset depression (n=15) had greater PVH and DWMH and greater impairment on neuro-psychological tasks requiring intact executive function and memory compared with an age-matched group of patients with early-onset depression. Alexopoulos et al.17 found that patients with late-onset depression and vascular disease demonstrated greater impairment on word fluency and naming of line drawings than patients with early-onset depression and no vascular disease. In another study, Lesser et al. found that 32% of late-onset depression patients had moderate to severe DWMH compared with only 9% of the early-onset depression group.
Depression

Although the late-onset and early-onset depression groups did not differ in this study in terms of cognitive functioning, when patients in the late-onset depression group were subdivided in terms of DWMH severity, those with severe HIs showed greater deficits in executive functioning. Thus, the distal effect of HIs in disrupting corticostriatal circuits provides the necessary conditions for the emergence of vascular depression characterized by executive dysfunction.

There is considerable evidence that an ischemic cerebrovascular disease process is generally responsible for excessive DWMH, with confirmation in the case of late-life depression. For example, Thomas et al. carried out in vitro MRI on brain tissue from 20 deceased elderly subjects who had a history of depression and 20 controls without a history of depression, and found that all DWMH in the depressed group were ischemic in origin compared with only one-third of those in the control group. In another study, Thomas et al. used quantitative image analysis on intercellular adhesion molecule-1 (ICAM-1)—a vascular marker of inflammation whose expression is increased by ischemia—in post mortem brain tissue of elderly depressed and normal controls. They found a significant increase in ICAM-1 in the deep white matter of the depressed group, supporting the hypothesis that DWMH are ischemia-induced. In a variety of populations, pathohistological investigation of DWMH has been compatible with an hypothesis that DWMH are ischemia-induced. In a variety of populations, pathohistological investigation of DWMH has been compatible with an hypothesis that DWMH are ischemia-induced.

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Diagnostic Criteria for Vascular Major Depressive Disorder

Much about the vascular depression hypothesis is compelling, which has led researchers to propose a number of diagnostic criteria sets for the illness. Alexopoulos et al. regarded clinical and/or laboratory evidence of vascular disease and depression onset after the age of 65 years as cardinal features, and neuropsychological impairment as a secondary feature. Steffens and Krishnan regarded clinical and/or neuroimaging evidence of cerebrovascular disease or neuropsychological impairment as the cardinal features, and age of onset greater than 50 years as an additional supporting feature. Krishnan and his colleagues have further refined the notion of vascular depression, requiring only MRI evidence of cerebrovascular pathology to define it; they have referred to this syndrome as subcortical ischemic depression (SID). Alexopoulos has also refined the notion of vascular depression, proposing a depression executive dysfunction (DED) disorder of late life that, while recognizing the potential role of cerebrovascular pathology in the etiology of the illness, requires only executive dysfunction to meet diagnostic criteria. Currently, there is no consensus as to how best to define vascular depression and which diagnostic criteria set most accurately defines the illness.

Despite the lack of consensus regarding how the illness is defined, researchers have suggested that vascular depression meets criteria for a valid diagnostic subtype on the basis of external validity studies (e.g. clinical profile, family history of affective disorder, and treatment outcome). This literature is briefly reviewed below.

Clinical Profile

Based on the notion that vascular depression results from ischemic damage to corticostriatral circuits, Alexopoulos et al. found support for the hypothesis that the clinical profile of vascular depression would be similar to the clinical profile of frontal lobe syndrome; that is, it would be characterized by psychomotor retardation and lack of insight. Krishnan et al. found that lassitude—i.e. difficulty getting started—predicted membership in a vascular depressed group defined by MRI lesion severity. Hickie et al. also found that the clinical profile of patients with late-onset depression and DWMH was characterized by impaired psychomotor speed. Thus, the clinical profile of vascular depression may be characterized by psychomotor retardation.

Family History of Affective Disorder and Vascular Disease

Researchers have also shown that patients with vascular depression may be unlikely to have a family history of affective disorder. Hickie et al. found a negative association between patients with late-onset depression and DWMH and family history of affective disorder. Krishnan et al. found that there was an inverse relationship between vascular depression and family history of affective illness. Although patients with vascular depression appear to have a low rate of affective disorder in their families, it would be reasonable to hypothesize that these patients would at the same time have a high rate of family history of vascular risk factors such as hyperlipidemia, hypertension, and diabetes; however, a clear pattern has not emerged in the literature.

Acute Treatment Outcome

Research suggests that vascular depressed patients may respond poorly to acute antidepressant treatment. Hickie et al. found that treatment outcome was negatively associated with DWMH in patients treated with antidepressants. In another study, having five or more basal ganglia HIs and any HIs in the pontine reticular formation significantly predicted patient resistance to 12 weeks of antidepressant treatment. Taylor et al. found that the odds of non-response increased significantly for those who showed a progression of DWMH. Baldwin et al. found that late-onset depressed non-responders were more impaired on executive function tasks than responders to antidepressant medication.

Interestingly, we found that only response inhibition, a fundamental component of the executive functions, predicted poor treatment response in an eight-week study of citalopram in the elderly and the elderly depressed. Neither late-onset depression nor HI burden predicted non-response in this study. Presumably, patients with vascular depression respond poorly to antidepressant medication because they have sustained structural damage (lesions) to mood-regulating neurocircuitry such as the dorsolateral pre-frontal cortical circuit.

Problems with External Validation Studies

We have argued that it is insufficient to attempt to establish the diagnostic validity of a proposed illness on the basis of external validity...
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Establishing vascular depression as a distinct subtype has important implications for the future of psychiatric nosology. Unlike diagnostic criteria for other DSM disorders, which have been based only on phenomenology, the defining features of vascular depression are likely to include laboratory values (e.g., MRI and neuropsychological tests). Statistically evaluating different proposed diagnostic criteria is also a more empirically grounded approach to defining diagnosis than previous DSM classification efforts, which have relied primarily on expert consensus. Thus, vascular depression may serve as a prototype for future psychiatric diagnostic systems that will rely on a combination of phenomenological and laboratory tests in addition to requiring evidence of both internal and external validity. Such an approach may aid in the development of rational, etiologically based specific treatments.

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