THE STATUS OF THE VASCULAR DEPRESSION HYPOTHESIS

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Late life depression and its relationship to cerebrovascular disease have been described by Gaupp as early as 1905. Developments in cognitive neuroscience and in imaging generated new interest in this area. The "vascular depression" hypothesis in its current form was advanced in 1997 and postulated that cerebrovascular disease can predispose, precipitate, or perpetuate a depressive syndrome in older adults. The hypothesis was supported by: 1. the high comorbidity of depression and vascular risk factors; 2. the high incidence of depression in stroke; 3. the high prevalence of white matter (WM) hyperintensities in late-onset depression; 4. the high frequency of cognitive impairment in depressed patients with vascular risk factors; and 5. the similarity of cognitive abnormalities of depression to those associated with WM hyperintensities. "Vascular depression" as originally proposed encompasses entities with diverse pathogenetic mechanisms.

The 1997 article argued that "direct testing of the vascular depression hypothesis is not possible since the mechanisms of depression are unknown". The hypothesis was viewed, however, as the conceptual platform for studies of the clinical presentation, outcomes, pathogenesis, and treatment of a subgroup of geriatric individuals with depression. Almost 12 years later, one can argue that the vascular depression hypothesis has served the field well in providing research direction. There is now empirical evidence that cerebrovascular disease confers vulnerability to a variety of syndromes, including depression, other mood syndromes, and psychosis, but also cognitive impairment and peripheral neurologic signs. Finally, depression of patients with vascular stigmata or cerebrovascular lesions identified through neuroimaging has poor outcomes, including persistence of depressive symptoms, unstable remission of depression, and increased risk for dementia. Investigation of the pathogenesis of "vascular depression" has proceeded along two lines. The first focuses on the neuroanatomic localization of vascular lesions leading to depression. The second line of research focuses on impairment in brain functions predisposing to depression and was first articulated on a paper on the "depression-executive dysfunction syndrome of late life".

The Duke group proposed that subcortical ischemic changes increase the risk for depression through a variety of mechanisms, including damage of mood regulation distributed networks and cognitive impairment and disability acting as chronic stressors. One of our studies used diffusion tensor imaging (DTI) and observed that mean systolic and mean diastolic blood pressure were associated with microstructural white matter abnormalities (fractional anisotropy) principally in frontal and subcortical areas. Subcortical ischemic depression constitutes a risk factor for adverse outcomes, including mortality, disability, and dementia, although the risk of similar outcomes exists even in non-depressed patients with cerebrovascular pathology. Depressed older adults with subcortical ischemic lesions often have a distinct clinical presentation with motor retardation, apathy, and disability; an increased risk for dementia; and low familial load of depression. With some exceptions, studies documented that patients with depression and subcortical vascular lesions have poor response to antidepressants.

The depression-executive dysfunction syndrome was based on the observation that impairment in frontolimbic and frontostriatal pathways, regardless of its causes, confers vulnerability to depression. In an fMRI study, we documented reduced activation of the dorsal anterior cingulate cortex (ACC) in depressed elders performing a response inhibition task compared to controls. Moreover, microstructural abnormalities in the ACC were associated with abnormal response inhibition. Based on these and other findings, the depression-executive dysfunction syndrome was conceptualized as one of the clinical expressions of frontolimbic and frontostriatal system abnormalities.

Depression-executive dysfunction syndrome is common and has a presentation consistent with its underlying abnormalities, that is, psychomotor retardation, lack of interest, limited depressive ideation and insight, and prominent disability. Furthermore, executive dysfunction is a predictor of limited response to antidepressants. In 112 elderly patients with major depression treated with citalopram, we showed that abnormal performance in a response inhibition task and cardiac disease burden each predicted low remission rates. Similar findings were reported by another citalopram study and by a sertraline study. In another sample (N=48) treated with escitalopram, depressed patients who failed to achieve remission had greater burden of microstructural abnormalities in the dorsal and rostral ACC, dorsolateral prefrontal cortex, hippocampus, and insula compared to those who remitted. Finally, we observed that depressed elderly patients with a short allele of the serotonin transporter had both lower rates of remission than long allele homozygotes and microstructural frontolimbic abnormalities. Thus, the presentation and course of depression-executive dysfunction syndrome are consistent with those of subcortical ischemic depression.

The difference between subcortical ischemic depression and depression-executive dysfunction syndrome is the assumptions on their etiology. Subcortical ischemic depression requires that subcortical impairment is due to cerebrovascular disease. In contrast, depression-executive dysfunction syndrome may be caused by vascular disease, prominent aging-related changes, degenerative brain disease, or, in most cases, an accumulation of those and other factors. Accumulation, and perhaps a synergy, of noxious factors is consistent with the clinical reality of geriatric populations in whom a variety of processes contribute to brain dysfunction, leading to depression and to cognitive impairment. For example, the originally described pure vascular dementia has ended up being a rather rare entity; however, vascular lesions facilitate the expression of dementia in patients with early-stage Alzheimer's brain pathology.

Identifying a disease or a syndrome provides a short hand that communicates information on clinical presentation but also on the presumed pathogenesis and treatment. Subcortical ischemic depression and depression-executive dysfunction syndrome are entities for which the etiologic contributors can be identified and ameliorated with existing treatments, e.g. antiplatelet agents, calcium channel blockers, antioxidants, and treatment of hypertension and hypercholesterolemia. Moreover, the choice of treatment may be influenced by the knowledge that serotonin acting agents are of limited efficacy in patients with subcortical vascular lesions and executive dysfunction. Although definitive studies are unavailable, dopamine acting agents may be effective in depressed patients with frontostriatal impairment. Finally, antidepressants and other psychotropic agents with alpha blocking action may inhibit behavioral recovery following ischemic lesions, whereas psychotropic drugs increasing cathecholaminergic activity may promote recovery. These findings may guide the selection of antidepressant approaches in subgroups of depressed patients.