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Editorial

The Enigma of Vascular Depression

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Editorial

Vascular Depression (VaDep) is regarded as a subtype of Late-Life Depression (LLD) characterized by a distinct clinical presentation associated with cerebrovascular damage. Although depressive symptoms in the elderly (around/after 60 years) are common (estimated at 12-50% of Major Depressive Disorder/MDD), the concept of VaDep is still not widely accepted, validated diagnostic criteria are lacking, and it is not included in current psychiatric manuals as DSM-V, a fact that limits its use in clinical settings. After the International Congress on Vascular Dementia 2015 in Ljubljana, an international group of experts has prepared a Consensus Report on the clinical features, brain lesions detected by MRI and neuropathology (microvascular burden, gray and white matter lesions, and other structural brain changes), clinico-pathological correlations, and the current evidence for the neuropathobiology of VaDep [1].

The "VaDep hypothesis", introduced by Alexopoulos et al. in 1997 [2], suggested that cerebrovascular disease, in particular subcortical microvascular and white matter lesions, may predispose, precipitate or perpetuate depressive symptoms in aged people as a consequence of structural damage to fronto-subcortical circuits. Later, the term "MRI-defined VaDep" was introduced [3], supporting the hypothesis that loss of brain volume and white matter integrity are associated with depressive symptoms in the aged [4], although this has not been confirmed by others [5,6].

The clinical manifestations of VaDep, characterized by psychomotor slowing, lack of initiative, apathy, executive dysfunction, impaired processing speed, more motivational problems, risk of cognitive impairment, and poorer outcome, summarized as "depressive-executive syndrome" [7], are distinct from non-vascular depression in the elderly without risk of suicidal activity, agitation and a family history of depression [8,9].

Individuals with LLD in general are at greater risk to develop cognitive impairment, more likely related to Vascular Dementia (VaD) than to Alzheimer Disease (AD) [10]. However, recent data showed that LLD and VaDep are not a risk factor for AD [6,11], although older cognitively unimpaired patients with depressive episodes may have more underlying AD pathology, in particular β-amyloid deposition [12], leading to the amyloid hypothesis of LLD [13]. In general, depression in VaD is clinically different from that in AD [10].

MRI-defined VaDep requires neuroimaging evidence of cerebrovascular changes, in particular White Matter Hypointensities (WMH) and subcortical microinfarcts (lacunes), which may predate the development of depressive symptoms, WMH volume showing a strong relationship with depression [14]. While others could not demonstrate such an association [15], large confluent WMHs are associated with persistent depressive symptoms, poorer executive function and cognitive impairment [16,17]. Additional gray matter changes in orbitofrontal cortex, hippocampus, amygdala and other subcortical areas, causing disruption of fronto-limbic and cortico-striatal networks, are associated with both depressive symptoms and cognitive decline [18]. WMHs especially within cortico-subcortical neuronal circuits may be interpreted as sequelae of underlying microstructural dysfunctions affecting major brain connectivities, suggesting an association between cerebrovascular disease and depression [19, 20]. However, not all studies supported the relevance of WMHs for VaDep [21,22]. Post-mortem studies in clinically well-documented cases of LLD did not confirm the notion that diffuse WMHs, subcortical microvascular lesions, cortical microinfarcts or AD pathology including Cerebral Amyloid Angiopathy (CAA) may be essential for the development of LLD [6,23-28], challenging the "VaDep hypothesis" and revealing a significant gap in our understanding of the pathobiology of LLD. It should be admitted that other, nonvascular factors, like aging, neuroinflammation, glial and amyloid pathology or affection of the mesolimbic dopamine system may also contribute to VaDep [29-31].

Although there is considerable empiric support for the validity of a VaDep subtype of LLD, fundamental questions remain open, including how the illness is defined, how vascular disease and depression influence each other, why VaDep is not a progressive disorder although the possibly related brain lesions tend to accumulate, and whether WMHs and global vascular risk factors are responsible for poor outcome and poor response to antidepressive treatment [13,32,33]. Genetic, neuroinflammatory, cardio- and cerebrovascular, neurodegenerative and other hitherto unknown factors may all be involved in the complex pathogenetic cascade that precedes depressive, behavioral and cognitive symptoms in advanced age. A growing body of evidence from neuroimaging and peripheral biomarker studies suggests that depressive symptoms in old age may be associated with vascular-related and other pathobiological processes, but the theory of VaDep as a distinct subtype of LLD is still not fully established. There are several possible interrelations between cerebrovascular disease and depressive symptoms: (1) Depression as the consequence of vascular disease; (2) development of depression independent of vascular disease, which, however, may stimulate the onset and course of depression; (3) cerebrovascular disease and depression are two manifestations of similar pathogenetic mechanisms. Since the temporal relationship between brain pathology and depressive and related symptoms as well as the etiology of VaDep cannot be established on the basis of post-mortem findings alone, long-term clinico-pathologic studies including premortem

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and postmortem neuroimaging are needed in order to further elucidate the relations between structural/functional brain lesions, related molecular-biology and depression in advanced age in order to definitely establish the existence of VaDep as a subtype of LLD as a basis for the prevention and successful treatment of this disorder.

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