The role of white matter lesions in the pathogenesis of late-life depression and functional decline

Milija D. Mijajlovic, MD, PhD

Neurology Clinic, Clinical Center of Serbia; School of Medicine University of Belgrade, Belgrade, Serbia

Late-life depression (LLD) is a broad term that encompasses older adults (over the age of 65) with unipolar major depressive disorder; it includes individuals whose first episode is later in life, late-onset LLD (often identified as later than 50 years), as well as individuals whose depression started earlier (early-onset LLD) but shows recurring episodes later on. With the population aging, the prevalence of LLD and the consequent individual and public health burden has increased. The utility of LLD as a distinct disorder, separate from depression in other age groups, stems from the unique psychosocial and biological factors associated with aging, including the presence of significant comorbid diseases and conditions, cognitive impairment, and functional disability. The definition of LLD has varied over the years and between studies and has generated some heterogeneity complicating comparison and pooling of data. Most researchers currently endorse the DSM-IV criteria for major or minor depression, which when combined defines PSD. Alternatively some researchers accept a cut point on a validated depression severity scale.

LLD is a multifactorial mood disorder as it has been related to vascular disease, neurodegeneration, inflammatory processes, and other age-related changes that can lead to cognitive impairment and affective changes.

Several hypotheses have been proposed to explain etiology of LLD. First and the most probable, vascular depression hypothesis proposed by Alexopoulos et al. has linked LLD to cerebrovascular changes. According to the glucocorticoid hypothesis, LLD itself may act as a toxic stressor toward the brain that leads to cognitive impairment. Through overactive hypothalamic–pituitary–adrenal activity, chronic glucocorticoid exposure can be toxic to the brain and increase the risk of dementia. Finally, the depressive symptoms that manifest may be an indicator of prodromal dementia.

The presence of white matter lesions (WMLs) identified on T2-weighted MRI as hyperintense lesion is robustly associated with depression. A longitudinal study of white matter changes found that these lesions when taken into account with measures of quality of life and mood predicted depression in the geriatric population. Furthermore, it has been shown that depression is correlated with greater WML severity.

Risk factors such as hypertension and diabetes contribute to the development of small-vessel disease that can also contribute to the development of WMLs through ischemia as well as microscopic bleedings, which then leads to the clinical symptoms seen in LLD.
An increasing body of evidence has not only associated LLD with WML severity, but also localized these WMLs to areas of the brain associated with cognitive dysfunction and depression. A few studies have localized these WMLs to specific fiber tracts in the brain that correlated with depression severity, including the inferior and superior longitudinal fasciculus, temporal lobes, cingulum and uncinate fasciculus. Functional neuroimaging studies have given further insight into the pathogenic mechanisms underlying LLD. In a functional MRI study it was found that LLD patients demonstrated greater blood-oxygen-level dependent activity in the limbic system and that this was associated with greater WML burden. LLD is also shown to be associated with atrophy of hippocampus, independent of other neurodegenerative states. It is confirmed that LLD is associated with brain changes in both gray matter and white matter, including loss of myelin integrity. These brain changes are associated with age of onset of depression, as well as cumulative life-time depression burden, and can explain the increased dementia risk associated with LLD. LLD has been linked to cognitive impairment, poor concentration and attention span, impaired new learning, and poor motor and executive functioning, which is collectively termed the depressive-executive dysfunction syndrome. Executive dysfunction and impaired processing speeds represent the core of the cognitive deficits in LLD and are shown to be associated with the development of WMLs in specific fiber tracts in the brain. The association between disability and depression is complex, with disability well established as a correlate and consequence of LLD. It has been also linked to increased risk of suicide as well as mortality. It is obvious that LLD results from a complex interplay between biological factors: lesion size, lesion site, lesion number, and laterality and experiential factors: personal history, social circumstances, and psychological state.