

Editorial

Risk Factors of Alzheimer's Disease: Depression in the Cross Fire

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Treatable risk factors of Alzheimer's disease

Alzheimer's disease (AD) is the most frequent cause of cognitive decline by the elderly, leading to immense medical and economic burden on our aging society. The 2015 World Alzheimer Report estimated 48.8 million people worldwide living with dementia. Likely, their numbers will double every 20 years [1]. In the last decades, fascinating studies revealed many molecular pathways in the background of AD. However, most of the clinical trials aiming to treat the disease have failed. Recently, growing body of evidence suggests that we have to pay more attention to primer prevention and to active aging. Ongoing studies emphasize that creative leisure activities, physical activity and appropriately selected diet could prevent the development of dementia or slow the progression of the disease [2]. The mechanism is not entirely clarified; it seems to be related to the improved lipid metabolism, to optimal level of antioxidant and anti-inflammatory factors and to activated brain plasticity and vascularization.

It is well known that traditional cardiovascular risk factors including hypertension, diabetes, obesity, smoking, hyperlipidemia and homocysteinemia also have a major role in the development of AD [3]. Psychosocial considerations such as late-life depression and anxiety disorders are also important but frequently underestimated risk factors of AD.

Late-life depression as risk factor of dementia

Affective disorders, especially depression have a high prevalence in the elderly; 1-4% of the aged population present with major depression and 4-13% show the symptoms of minor depression [4]. Depression is generally associated to poor cognitive function leading to a condition traditionally termed depressive pseudodementia. It is still not entirely clarified, that whether depression is a prodrome of AD, or is an independent risk factor. The MIRAGE study revealed high, 2.13 odds-ratios (OR) between prior depressive symptoms and AD [5]. Interestingly, the association was robust (OR: 1.71) with even those families where depression occurred more than 25 years before the onset of cognitive decline. Studies on mild cognitive impairment (MCI) also showed similar results; depressed patients have more than twice the risk for conversion of MCI to AD than non-depressed MCI patients [6]. Based on large metaanalysis studies, twin studies, current reviews, and on our clinical experience we believe that

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late-life depression, even years before the beginning of cognitive deterioration, is an important and independent risk factor of AD, while depressive symptoms within 1 year prior to the onset of dementia might be considered a prodrome of the disease [7, 8].

Common pathophysiology of depression and dementia

The pathophysiological relationship between depression and AD is not perfectly explained. Damage of neurotransmitter systems are discovered in both entities. The primarily affected system is the cholinergic pathway in AD, however, decreased level of serotonin and noradrenaline have been demonstrated both in depression and AD. Another important shared pathology could be the microvascular damage of the frequently invisible but strategically important white matter tracts. Hippocampal atrophy has been pointed out both in demented individuals and in depressed patients as well. An article from Korczyn and his co-workers perfectly summarizes the possible mechanisms, and introduces the hypothesis that chronic stress-related hypercortisolism could lead to apoptotic death of the highly sensitive hippocampal neurons in depression [9].

Antidepressant therapy in dementia

Despite numerous studies, results on the prospective benefit of the application of antidepressant drugs (ADDs) in the prevention of AD are inconsistent [10]. However, elderly people should be strictly screened for depression because it [4] could be one of the most common reversible reasons in the background of cognitive decline [11], and an important, independent risk factor for dementia [9]. Noticeably, current studies demonstrated the positive preventive effect of AADs on the development of dementia [12]. However, it should be noted that elderly patients with treated depressive symptoms often present dementia later in their life [13]. Thus, strict follow-up is required for patients developing late-life depression.

Treatment of depressive symptoms in evolved dementia has also many benefits. Studies pointed out that ADDs are well-tolerated, have valuable therapeutic effects and their application leads to improved life quality of patients living with AD [14]. Unfortunately, their effect on cognitive functions is questionable in AD. However, many studies propose that the anti-inflammatory action of ADDs might mitigate the microglial activation associated chronic neuroinflammation [15].

CONCLUSION

Depression is a remarkable risk factor and a frequent comorbidity of AD. In the daily practice, we commonly underestimate its importance in the prevention of cognitive decline. It has been proposed that the reduction of the established risk factors could potentially prevent as many as 3 million AD cases worldwide [2]. Antidepressant therapy might have a positive impact on the progression of Alzheimer-disease and on the life quality of patients living with dementia. Further studies are required to clarify the yet ambiguous findings.

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