Late Life Depression and Dementia

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The number of people living with dementia and Alzheimer's disease is growing rapidly, making dementia one of the biggest challenges for this century. Many studies have indicated that depression plays an important role in development of dementia, including Alzheimer's disease; depression, especially, during the late life may either increase the risk of dementia or even being its prodromal stage. Despite a notably large number of carried observational studies and/or clinical trials, the association between the late life depression and dementia remains, due to the complexity of their relationship, still unclear. Moreover, during past two decades multiple other (non-)modifiable risk and possibly protective factors such as the hypertension, social engagement, obesity, level of education or physical (in)activity have been identified and their relationship with the risk for development of dementia and Alzheimer's disease has been extensively studied. It has been proposed
that to understand mechanisms of dementia and Alzheimer's disease pathogeneses require their multifactorial nature represented by these multiple factors to be considered. In this work, we summarize the recent literature findings on roles of the late life depression and the other known (non-)modifiable risk and possibly protective factors in development of dementia and Alzheimer's disease. Then, we provide evidences supporting hypotheses that (i) depressive syndromes in late
life may indicate the prodromal stage of dementia (Alzheimer's disease) and, (ii) the interplay among the multiple (non-)modifiable risk and protective factors should be considered to gain a better understanding of dementia and Alzheimer's disease pathogeneses. We also discuss the evidences of recently established interventions considered to prevent or delay the prodromes of dementia and provide the prospective future directions in prevention and treatment of dementia and Alzheimer's disease using both the single-domain and multidomain interventions.

Keywords: dementia ; Alzheimer's disease ; late life depression ; apolipoprotein E ; testosterone ; obesity ; social engagement ; substance abuse

1. Introduction

Depression, particularly in late life, is highly prevalent and is commonly believed being a risk factor for development of dementia . Psychiatrists expect the number of people with dementia to almost triple over the next 30 years. During the past few decades researchers have identified multiple other (non-)modifiable risk and protective factors. Since the early stage diagnoses with the relevant interventions may help to significantly delay the prodromes of dementia, therefore the association of the other (non-) modifiable risk and protective factors with dementia has been also extensively studied.

2. Relationship between the Late Life Depression and Dementia

Depression and dementia, which are the most common mental health problems in the elderly, have a complicated relationship that is not yet fully understood. We remind the reader that depression causes cognitive changes, while dementia is frequently accompanied by various mood symptoms [1][2]. Whether late life depression does or does not increase the risk of dementia, has become a fundamental question that is still undergoing extensive investigation. Most studies performed during past 30 years on depression and dementia are based on scores from existing self-report questionnaires used as depression screening tests [3][4][5][6]. The main limitation of these epidemiological studies is usually the relatively short follow-up period between the assessment of depression and the prodromes of dementia [6][7][8][9][10][11]. Some of these earlier investigations have suggested that the late life depression increases the risk of dementia and AD [12][13][14][15]. This conclusion was also supported by the well-known study of Ownby et al. [16], where, based on systematic meta-analysis and metaregression analysis, the authors found that individuals with a history of depression would be more likely to be diagnosed with dementia in later life. Evidences from other studies have, however, indicated that depression either has only a mild effect on dementia [17], does not increase the risk for development of dementia [18] or can be even the prodromal stage of dementia [19][20]. It is worth noting that severity and frequency of depression, differences in the

sample sizes and types (e.g., women and men, education level), the culture and ethnical differences (e.g., Sweden, Finland, UK, USA, Australia, Japan, Taiwan), variation in used measures (e.g., operationalization and definition of depression) and different study lengths could be the main reasons for all these inconsistencies.

A majority of psychologists and psychiatrists agree that longer follow-up studies back at least into the midlife period are needed to clarify the relationship between a history of depression and the prodromes of dementia. In response, several long-term prospective cohort studies on depression and dementia have been recently performed [20][21][22][23]. Among them only a 17-years follow-up cohort study has indicated that depressive symptoms in older individuals can nearly double the risk for development of dementia and/or AD [24]. Findings of other long-term cohort studies support the hypothesis that late life depression can be indeed the long and progressive prodromal symptom of dementia [25][26][27]. Especially, Singh-Manoux et al. [49] in their 28-year long follow-up study have proposed that depression and dementia share the same common risk factors. Since depressive symptoms such as a lack of motivation or depressed mood occur first, therefore they have suggested that these symptoms should be considered just the prodromal states of dementia and not its early triggers.

Although the additional long-term systematic investigations are still needed to support their conclusions, preliminary findings of these long-term cohort studies may already open a pathway for an early stage diagnosis of dementia, that is, an early stage diagnosis of dementia may require tracing the depressive symptoms back to the at least midlife.

3. Future Possible Research Directions and Trends in the Treatment of Dementia

The vulnerability of individuals to cognitive decline and an increased risk of dementia or AD is complex. It depends, in addition to age and genetic predisposition (non-modifiable risk factors), on several protective and potentially modifiable risk factors. Hence, it is generally accepted by psychologists and psychiatrists that the cognitive functions can be maintained and the risk for cognitive decline and, correspondingly, the development of later life dementia and AD can be notably reduced by interventions targeting individuals' risk factors [28]. These interventions may target one given dementia risk factor, often referred as the "single-domain" interventions, or multiple risk factors of dementia, also known as "multidomain" interventions. We also emphasize here that the results of recent long-term follow-up studies support the hypothesis that the prodromes of dementia may possibly start more than decade before any clinical symptoms can be observed [21][22][23]. The short duration of treatment (trials) and small sample size are among the main limitations of the most published randomized control trials [29]. Other limitations can even include a not well-defined cognitive outcome. We only note that many researchers are using different measures, sample sizes and terminologies, complicating the interpretation and generalization of their findings. As a result, existing trial studies usually do not provide sufficient information on what intensity of intervention targeting a given risk factor is needed to preserve cognitive function. We can, therefore, conclude that a possible future research direction could be targeting the relationship between the intensity of a given intervention and cognitive functioning.

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