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Review article

Neurochemical correlation between major depressive disorder and neurodegenerative diseases

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ABSTRACT

Major depressive disorder (MDD) is one of the most prevalent and life-threatening forms of mental illnesses affecting elderly people and has been associated with poor cognitive function. Recent evidence suggests a strong relationship between MDD and neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), Amyotrophic Lateral Sclerosis (ALS), as well as natural processes of aging. Changes in the neuroplasticity, morphology, and neurotransmission in the brain are seem to be associated to both, MDD and neurodegenerative diseases. In addition, there is evidence that psychological stress and MDD are associated with molecular and cellular signs of accelerated aging. This review will highlight the relationship between MDD, the aging process, and neurodegenerative diseases, emphasizing the neurochemical processes involved.

Contents

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1. Introduction

Living with untreated depression can complicate many chronic conditions including stroke, heart disease, and diabetes [1,2]. The estimated percentage of the United States (US) adults suffering from Major depressive disorder (MDD) is 3%, or approximately 9 million people [3]. Among those suffering from chronic neurodegenerative disorders, such as Alzheimer's (AD), Huntington disease (HD), and Parkinson's disease (PD) and Amyotrophic Lateral Sclerosis (ALS), the rates of MDD are considerable higher [4–7].

Clinically significant depressive disturbances are estimated to affect 40–50% of patients with PD [5], and 24.8% are thought to suffer from MDD [8]. MDD is considered the most common symptom among presymptomatic Huntington disease carriers [9] with an estimated prevalence of 25% [6]. However, there is still some debate as to whether the prevalence increases with progression of Huntington disease or not [6,10–11]. The estimated prevalence of MDD in patients suffering ALS is 16–25% [7].

The prevalence of depression in those suffering from dementia has been reported as 29% [12]. Specifically, the prevalence of MDD in individuals with AD has been estimated to be 5–23% [4,13]. In a retrospective cohort study conducted in the US, the prevalence of depression was found to be higher in patients with vascular dementia than AD [4].

This association between depression and neurodegenerative conditions indicates the importance of appropriate recognition and treatment of depression in these patient populations, but also begs the question of potential causation.

2. Neurodegenerative diseases

2.1. Alzheimer's disease (AD)

Alzheimer's disease (AD) was discovered by Alois Alzheimer in 1906 [14]. It is the most common form of dementia that affects 30 million individuals worldwide. The primary risk factor for this neurodegenerative disorder is age; the incidence increases dramatically after age 60 [15]. Although considered "senile dementia", it is not a part of normal aging. AD is characterized by pathologic characteristics such as, accumulation of amyloid β (Aβ42) peptide in extracellular senile plaques, intraneuronal inclusions of hyperphosphorylated tau protein in neurofibrillary tangles, and neuronal and axonal degeneration leading to cerebral atrophy [16–18]. The entorhinal cortex, neocortex and hippocampus are the brain regions most commonly affected in AD [19–21].

Several pathological alterations impair neuronal function and integrity leading to the clinical symptom of memory decline, particularly episodic memory. Symptoms progressively worsen over time, becoming severe enough to interfere with the activities of daily living [22,23].

Evidence supports an amyloid cascade hypothesis as explanation of the pathophysiology of AD. The cascade is initiated by the generation of Aβ42 and its deposition as diffuse plaques [19,24–26]. In turn, it affects the synapses leading to microglia and astrocytic activation, progressive synaptic degeneration, and neural injury [27]. An altered neuronal ionic homeostasis induces oxidative damage and tau activity dysfunction precipitating the formation of hyperphosphorylated tau and neurofibrillary tangles. The cumulative effect of these pathological mechanisms generates the dementia [19,24–26,28].

Studies point to a number of risk factors for AD development including aging, family history, genetics, metabolic dysfunction, cardiovascular disease, brain injury, depression, diabetes, hypercholesterolemia, and physical inactivity [29,30].

The development and evaluation of efficient therapeutic approaches to AD need to be evaluated in animal models and ultimately in humans for prevention or treatment of the disease, since medications used can temporarily slow the progression of symptoms and improve quality of life for the patients [31,32].

2.2. Alzheimer's disease (AD) and major depressive disorder (MDD)

Some neurodegenerative processes, such as impaired neuronal plasticity and neurogenesis or cell death may contribute to the development of MDD. Although, MDD is not considered a typical neurodegenerative disease some theories support the idea that there is an increase in the probability of AD patients develop MDD, as well as chronic MDD patients' increase the susceptibility to develop AD. Patients with late life depressive symptoms had cognitive impairments [33]. In the same study, individuals with better education backgrounds performed better in memory tests, and lower education was associated with depressive symptoms [33]. Behavioral symptoms and frontal lobe alterations were more prevalent in patients with mild cognitive impairment, AD, and depressive symptoms when compared to patients without depressive symptoms [34]. Patients with comorbid MDD and AD demonstrated worse cognitive performance when compared to controls and patients with only AD or MDD [35]. A higher stroke risk was revealed in AD patients with MDD when compared to controls [36]. In addition, stroke risk was linked to impaired memory performance and speed measures processing; however, there were no significant difference in stroke risk or cognitive performance between AD participants with depression and those without depression [36].

The hippocampus plays a principal role in memory processing and AD pathophysiology, but it is also involved in MDD. In fact, hippocampal atrophy was linked with greater depression severity in older adults and proposed as a biomarker for cognitive decline in MDD patients [37]. Impairment of hippocampal neurogenesis was accompanied by cognitive deficits in an animal model of AD; however, this impairment was not linked to depressive behavior in mice [38]. Indeed, alterations in limbic structures, including temporal and cortical regions, are common in patients with depression and AD [39]. A cohort study comparing neuroanatomical changes in patients with and without depressive symptoms in addition to AD revealed increased cortical thinning in AD patients with depressive symptoms compared with those without [39]. In addition, it was suggested that β amyloid pathology in the limbic structures contributed to the development of depressive symptoms in AD.

Neuroinflammation has been implicated in the development and progression of AD. Elevated levels of inflammatory cytokines in cerebrospinal fluid (CSF) have been associated with neuropsychiatric symptoms in patients with dementia, including agitation and depression. High levels of interleukin-10 (IL-10), an anti-inflammatory cytokine, were associated with lower depression scores and agitation in AD patients, suggesting a protective effect to compensate for heightened neuroinflammation in the brain of AD patients [40]. Though many studies have revealed an association between inflammation and MDD or AD [41,42], the precise pathway that bridges the pathophysiological mechanisms of MDD and AD has yet to be identified [43]. Therefore, it is understood that other pathways must be involved to account for the association between MDD and AD.

Some researches have identified amyloid β (Aβ) as a link between MDD and AD. Indeed, the serum Aβ40/Aβ42 ratio was higher in MDD patients than healthy controls, suggesting that Aβ metabolism may be affected in MDD and these alterations could be a risk factor for developing AD in patients with MDD [44]. Ledo et al. [45] demonstrated that intracerebroventricular infusion of Aβ oligomers (AβO) in mice lead to depressive-like effects and cognitive deficits. The brains of AβO-injected mice had an increase in pro-inflammatory cytokines and reactivity of microglia and astrocytes. Interestingly, the antidepressant fluoxetine reversed the depressive-like behavior, cognitive impairment and inflammation [45]. In MDD patients, Aβ 42 was reduced in the CSF, which may be a response to increased Aβ plaque formation in the brain [46].

Brain-derived neurotrophic factor (BDNF), cAMP-response element-binding protein (CREB) and glycogen synthase kinase-3β (GSK3β) are all signaling proteins involved in synaptic plasticity, memory, and neuronal survival; these proteins may also be involved in the pathophysiology and treatment response of both AD and MDD. Pláteník et al. [47]