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Correlation between depression, physical exercise and neurodegenerative diseases

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Abstract

Introduction:

Depression is the most common mental disorder, affecting a significant percentage of the adult population. The disease is associated with many negative health consequences and is one of the leading causes of disability and inability to work worldwide. This neurological condition is commonly associated with neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD) and Huntington's disease (HD). In recent decades, advancements have uncovered certain pathophysiological and molecular mechanisms underlying these disorders. These revelations suggest that, although they exhibit unique characteristics, there are notable parallels in the neurobiological changes associated with major depressive disorder (MDD) and the neurodegenerative processes in Alzheimer's disease, Parkinson's disease, and Huntington's disease. In this article the relevance of non-pharmacological therapies in the management of neurodegenerative diseases have been rising. Almost absent from side effects, non-pharmacological alternatives, including physical exercise have shown promising benefits.

Aim of the study:

The study aims to evaluate the association between depression symptoms and neurodegenerative diseases. Moreover, we indicate sport as a way to preserve and improve cognitive function, and to maintain a proper quality of life.

Material and methods:

We conducted a review of scientific publications published in the years 1998-2024 in English and Polish in the PubMed and Google Scholar databases. We used keywords such as "depression", "neurodegeneration" and "physical exercise".

Conclusions:

Depression has been demonstrated to be a risk factor for neurodegenerative diseases and suggested to be a possible prodrome for them. However, sport can alleviate behavioral symptoms in neurodevelopmental disorders, like anxiety, depression, indifference and sleep disruptions.

Key words: Depression; neurodegeneration; Huntington's disease; Parkinson's disease; Alzheimer's disease; physical exercise.

Introduction

Depression, a prevalent mental health condition, poses a substantial burden on global healthcare systems due to its widespread occurrence [1]. In addition to mood changes, depression results in cognitive impairment. Although depression studies have been going on for decades, the underlying mechanism still remains unclear [2]. Multiple theories exist concerning the molecular mechanisms implicated in depression, encompassing the monoamine hypothesis, hypothalamic-pituitary-adrenal (HPA) axis functioning, neuroplasticity and neurogenesis, epigenetic influences, and inflammatory processes. The monoamine hypothesis suggests that the underlying pathology of depression primarily stems from a reduction in monoamine neurotransmitters, such as serotonin [3]. Excessive activity of the HPA axis can trigger the release of glucocorticoids and cortisol, potentially playing a role in the onset of depression [4]. Significantly, changes in the functioning of the HPA axis have also been linked to declines in cognitive abilities [5]. The generation of new neurons is governed by regulatory molecules like brain-derived neurotrophic factor (BDNF), and

peripheral BDNF has been found to be downregulated in patients with MDD [6]. Several studies suggest that the microRNAs are crucial epigenetic regulators of multiple functions in the brain and play a key role in MDD pathogenesis [3]. For centuries, the belief that "physical exercise leads to a healthy body and mind" has persisted. However, it's only in recent decades that researchers have delved into the impact of physical exercise on brain structure and function. Exercise is now linked with processes such as angiogenesis, neurogenesis, and synaptogenesis, thus seen as a potential enhancer of learning abilities and memory. While the precise mechanisms underlying exercise-induced brain plasticity are not yet fully understood, evidence consistently supports the positive effects of exercise on individuals with neurodevelopmental disorders [7].

Alzheimer's disease

Alzheimer's disease (AD) stands as the predominant neurodegenerative type of dementia. Advancing age constitutes the primary risk factor for AD. Dementia has adverse effects on quality of life, overall functioning, physical well-being, and contributes significantly to increased rates of illness and death [6]. It affects approximately 5% of the elderly population over the age of 65 years [8]. The progressive cognitive decline with memory loss is a relatively early sign of the disease. People struggled with Alzheimer's disease also have problems in language, recognition and executive functioning. The brain affected by AD displays significant shrinkage in the hippocampal, frontal, parietal, and temporal regions. These alterations result from extensive neuronal loss and deterioration of synaptic connections [9]. Among the numerous factors contributing to AD is the impaired degradation of misfolded proteins. Malfunctions in this mechanism result in the accumulation of β-amyloid and the formation of toxic deposits, which are also markers of the disease [10]. The harmful effects of abnormal β-amyloid forms are associated with disruptions in Ca2+ ion regulation, interactions with cell membrane lipids, and the activation of particular receptors. Consequently, it inflicts notable harm on glutamatergic neurons situated in the hippocampus and cortex regions of the brain [11]. Dysfunctional neurons are thought to excessively release glutamic acid, whose metabolites are harmful and result in cell demise. In normal circumstances, glutamate aids in regulating neurogenesis by activating cells near the brain's precursor cells [11]. Research conducted on animal models indicates that inhibiting glutamatergic signaling leads to a substantial decrease in cell proliferation [12]. Apart from

the involvement of the glutamatergic system in neurogenesis and Alzheimer's disease pathogenesis, the cholinergic system also holds significance. Studies unequivocally establish acetylcholine's crucial role in the generation of new neurons within the dentate gyrus of the hippocampus. Gaining insight into the mechanism of blocking the enzyme responsible for the hydrolysis of acetylcholine at the synapse has resulted in new therapy in AD [13]. Observations indicate that proteins implicated in the progression of neurodegenerative diseases also contribute, under physiological circumstances, to the modulation of brain plasticity throughout its developmental stages [14].

Depression in Alzheimer's disease

Depression and Alzheimer's disease are two prevalent and debilitating conditions that often intersect, presenting significant challenges for patients, caregivers, and healthcare professionals alike. It is possible that depression may exert an influence in AD risk, by depleting the neuroprotective capacity of the brain, which would cause a faster progression of the disease [15]. Meta-analyses provide compelling evidence indicating that depression correlates with a greater than twofold elevation in the risk of developing dementia, indicating a causal factor hypothesis [16]. Findings from longitudinal investigations validate a consistent correlation between the intensity of depressive symptoms and the likelihood of developing dementia, with the risk accentuated in cases of severe depression [17]. Furthermore, research indicates a strong connection between the frequency of depressive episodes and the likelihood of dementia onset, demonstrating a 14% rise in the risk of all-cause dementia with each occurrence of depression [18]. Researches have shown that depressive symptoms before the onset of AD are significantly associated with the development of AD dementia, even if the appearance of depressive signs took place over 25 years prior to cognitive symptom. Moreover, depressive symptoms may therefore also be one of the earliest non-cognitive manifestations of this neurodegenerative disease [19]. We can indicate possible contributions of prior depression to later AD: increased rate of accumulation of b-amyloid, decreased clearance of b-amyloid, increased probability of neurotoxic ‘cascade’ (p-tau, etc.), reduced protective or compensatory mechanisms, modified activity of associated factors (e.g. reactive oxygen, altered IGF function, etc.), accelerated rate of brain ageing, precipitation of incipient AD (late life depression) [19].

One similarity shared by depression and AD is the fact that both neurological conditions are associated with a dysregulation of the HPA (hypothalamic-pituitary-adrenal) axis [20]. Chronic elevation of adrenal glucocorticoids and impairment of HPA axis negative feedback are observed. It's widely recognized that depression is linked to a disruption of the HPA axis, a decrease in glucocorticoid receptors in the hypothalamus and pituitary gland. This leads to reduced sensitivity to glucocorticoids and impaired regulation of negative feedback. The "glucocorticoid cascade hypothesis" suggests that glucocorticoids contribute to a chain reaction of effects on both the brain and body, resulting in gradual glucocorticoid-induced neurotoxicity and the gradual increase of adrenal steroids and dysregulation of the HPA axis [21]. Studies have shown that glucocorticoids can boost amyloid precursor protein (APP) expression, tau buildup, and induce changes in tau phosphorylation status [22]. Increased levels of glucocorticoids can lead to harm to brain structure and function, especially in the hippocampus. Structural changes in the hippocampus underlie the pathophysiology of dementia and major depressive disorder (MDD). There's evidence indicating that hyperactivity of the HPA axis might not only occur early in Alzheimer's disease but also play a role in advancing cognitive decline, hastening disease advancement, and worsening clinical conditions over time [23].

Another shared characteristic between Major Depressive Disorder (MDD) and Alzheimer's Disease (AD) is the presence of neuroinflammation, as indicated by numerous studies showing heightened activation of microglia and elevated levels of pro-inflammatory cytokines like IL-1β, IL-6, and TNF-α in both neurological disorders [24]. These proteins can influence the pathogenesis of both MDD and AD by interfering with neuronal growth, differentiation and survival, as well as synaptic activity [25]. In Alzheimer's Disease (AD), microglial cells are found surrounding Aβ plaques and have been observed to participate in plaque clearance. However, the inflammatory substances released by these cells may aid in Aβ buildup and the progression of plaques. Furthermore, by activating Toll-like receptors (TLRs) and triggering receptor for advanced glycation end products (RAGE)-dependent activation of p38 mitogen-activated protein kinase (MAPK), products from dying neurons can further enhance this response, contributing to Aβ-induced cortical synaptic dysfunction [26]. These molecular pathways are believed to lead to neurodegeneration by heightening glutamatergic excitotoxicity, impairing mitochondrial function and inducing oxidative stress, while also diminishing monoaminergic neurotransmission and neurotrophic support [27].

Parkinson's disease

Parkinson's disease (PD) is a progressive neurological condition characterized by motor impairment, impacting approximately 10 million individuals worldwide, with projections indicating a potential doubling of this figure by 2030 [28]. Several non-motor symptoms such as olfactory dysfunction, sleep disturbances, mood alterations, and gastrointestinal issues may manifest years before the onset of motor deficits. While dopamine replacement therapies effectively alleviate primary motor symptoms like slowness of movement, muscle stiffness, and tremors, they often fail to address non-motor symptoms [29]. Neglecting these non-motor manifestations can lead to a poorer prognosis and diminish the overall quality of life for PD patients [30]. Although dopaminergic dysfunction is the hallmark feature of PD pathology, other neurotransmitter systems such as cholinergic, glutamatergic, noradrenergic, and serotonergic pathways may also contribute to non-motor symptoms [31].

Depression in Parkinson's disease

Depression is the most prevalent non-motor psychiatric symptom in people with PD. More than 40% of individuals with PD have symptoms of depression [31]. In particular, PD patients carrying parkin, PINK1 and GBA mutations have more severe depression compared with idiopathic PD [32]. Although there are limited longitudinal investigations into the progression of depression among individuals with Parkinson's disease (PD), numerous studies indicate that depression frequently precedes the onset of PD and is commonly present at the time of diagnosis. In fact, it has been suggested that approximately 10–15% of patients exhibit Major Depressive Disorder (MDD) at the time of PD diagnosis, with individuals diagnosed with PD being twice as likely to develop MDD [33]. While it is widely accepted that MDD and PD are comorbid conditions, few studies have addressed whether MDD increases the risk of developing PD or if it is an early manifestation of PD itself [34]. Two theories have been posited regarding the connection between Parkinson's disease (PD) and Major Depressive Disorder (MDD). The prodromal hypothesis proposes that MDD represents an early symptom and component of the typical progression of PD. This idea is backed by the shared feature of both conditions involving the reduction of monoaminergic neurotransmitters, as well as the observation that PD and depression can manifest concurrently [27]. Research has demonstrated that in individuals with Parkinson's disease (PD), the serotonergic neurons located in the raphe nuclei, which are closely linked with depressive symptoms, are typically

impacted before the dopaminergic neurons in the substantia nigra [35]. On the contrary, the risk factor hypothesis suggests that premorbid depression could predispose individuals to a susceptibility for Parkinson's disease (PD) [35]. According to this theory, there might be a delay between the two diagnoses, as the connection between the two disorders isn't straightforward [33]. Supporting this theory, recent research suggests that the severity of Major Depressive Disorder (MDD), such as whether it requires hospitalization or outpatient treatment, correlates with the likelihood of developing PD later on. Additionally, studies indicate that the highest probability of receiving a PD diagnosis occurs within three months following an MDD diagnosis, with this risk diminishing thereafter [33]. One interpretation of these findings is that the pathophysiological process of MDD (such as: neuroinflammation, stress, HPA axis dysregulation) can increase the susceptibility to the pathophysiological process of PD, thus supporting the risk factor hypothesis. Alternatively, it's plausible that the identification of MDD could influence the clinical parameters utilized in diagnosing PD later on, thus aligning with the prodromal theory. Regrettably, challenges arise due to various factors such as determining the precise timeframe between the diagnosis of these two conditions, delays in diagnosis, insufficient recognition of Major Depressive Disorder (MDD) in older individuals, and the gradual onset of Parkinson's disease (PD). These complexities make it difficult to comprehensively grasp the precise connection between MDD and PD. Consequently, there is a necessity for prospective studies to thoroughly clarify this relationship [33].

Huntington's disease

Huntington’s disease (HD) is an inherited autosomal dominant neurodegenerative disease. Aside from cognitive manifestations, the main symptom of the disease is chorea – initially focal, with a tendency to generalize in the advanced phases of the illness. Gait disturbances are characteristic marked by considerable unsteadiness and a heightened risk of falls. Approximately 60% of patients experience falls, which align with the seriousness of both motor and neuropsychiatric impairments [36]. The etiology is relatively well understood and is linked with an elevated presence of CAG (cytosine, adenine, guanine). There is an excess of CAG triplets within the huntingtin (HTT) gene, which transform into polyglutamine (poly Q) segments at the end of the huntingtin (HTT) protein, changing the protein’s properties. Under physiological conditions, the number of CAG repeats in the HTT gene from 6 to 35. If

the number of CAG repeats exceeds 40, the huntingtin starts forming harmful protein aggregates in the nuclei of neurons, resulting in neuronal demise [37]. The greatest changes occur in the medium spiny neurons (MSN) of the striatum, which are responsible for motor functions [38]. Studies in HD transgenic mice demonstrated a significant decline in both cell growth and specialization, leading to a decrease in the overall quantity of neurons within the hippocampus. Animal experiments also suggest that a lowered level of dopamine in the striatum contributes to diminished neurogenesis [37]. Intriguing insights stem from investigations on cell cultures, particularly regarding the examination of genes linked to calcium regulation. Enhancing the activity of the IP3R receptor via elevated expression of the Huntingtin Associated Protein 1 (HAP1) protein disrupts calcium ion transportation, leading to the death of neurons [39].

Depression in Huntington's disease

The majority of research indicates that depression occurs in 15% to 69% of individuals with Huntington's disease (HD), with some studies indicating that depression rates in HD are twice those observed in Alzheimer's disease (AD) and Parkinson's disease (PD). Moreover, several investigations suggest that depressive symptoms may precede motor and cognitive impairments by many years, if not decades, making it the most frequent psychiatric complaint among preclinical HD patients [40]. Consequently, despite the considerable variability in reported prevalence, the significance of Major Depressive Disorder (MDD) in HD cannot be overlooked. In fact, it has been suggested that the psychiatric manifestations of HD might impact quality of life more profoundly than the classic motor symptoms [41]. In the prodromal stage of HD, a correlation was found between depressive symptoms, evaluated on the Center for Epidemiologic Studies-Depression (CES-D) scale, and functional connectivity in the ventromedial prefrontal cortex, which is a node of the defaultmode network (DMN). Additionally, the research demonstrated that this association was more pronounced in individuals with longer CAG repeat lengths. Similarly, in the pre-symptomatic period of Huntington's disease (HD), a specific connection was shown between the DMN and basal ganglia network (BGN) associated with depression symptoms, indicating that the DMN is a key promising target for different stages of the disease [42]. Interestingly, pre-symptomatic and early-stage HD patients with the highest cumulative probability to onset showed a different structural integrity in the white matter associated with depression. Likewise, in

another investigation, pre-symptomatic individuals with Huntington's disease (HD) were divided into ‘far from’ and ‘close to’ clinical onset (i.e. motor symptoms) and observed that presymptomatic HD patients close to onset have increased symptoms of depression associated with activity in the right dorsolateral prefrontal cortex and anterior cingulate cortex during a working memory performance, corroborating the relation between depression and cognitive impairment in HD [43].

Similar to Alzheimer's disease (AD) and Parkinson's disease (PD), disturbances in monoaminergic metabolism and neurotransmission are extensively documented in Huntington's disease (HD). For instance, studies conducted post-mortem have revealed diminished serotonin receptor binding and changes in monoamine oxidase (MAO) enzymatic activity in the brains of individuals with HD [44]. Additionally, a reduction in the levels of serotonin metabolites has been observed in HD patients, further supporting the notion of serotonergic deficits in HD [27].

Physical exercise in neurodegenerative diseases

Increasing evidence suggests that physical exercise has positive impacts on brain well-being and plays a crucial role in decreasing modifiable risk factors for Alzheimer's disease and Parkinson's disease, thereby lowering the likelihood of developing dementia [45]. Tolppanen and colleagues conducted a study spanning 28 years, involving participants diagnosed with dementia/Alzheimer's disease. They discovered that individuals who participated in low to moderate levels of leisure-time physical activity during midlife had a greater likelihood of developing dementia compared to those classified as highly active [46]. Indeed, physical exercise appears to be linked to enhancements in various cardiovascular risk factors, including diabetes, high blood pressure, and obesity, all of which are acknowledged as reversible factors for dementia. Moreover, evidence indicates that PE can counteract AD-related pathogenic changes, lower AD biomarkers, preserve neurogenesis and favor neuroplasticity[47].

Conclusions

Depression represents a prevalent yet frequently overlooked diagnosis among patients with neurodegenerative diseases. It has a significant impact on the prognosis and clinical outcomes

as well as the quality of life. Nevertheless, the existing literature in neuropsychiatry is still not sufficient in addressing this issue comprehensively and we have problems with understanding of the intricate neuropathology underlying these conditions. Noteworthy advancements in comprehending these diseases have been made through concepts such as neuroinflammation, neuroplasticity, dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis, and more recently, the monoamine oxidase pathways. However, more research needs to be done to establish the reason for a very high rate of co-existence of these two conditions, and whether depression is a risk factor or a consequence of neurodegenerative disorders. The boosting effect of physical activity, observed both at preventing and in treating neuropathological conditions, is particularly evident when preferentially aerobic-based metabolic stimulus is provided, such as those characterizing endurance training or voluntary physical activity. The development of enhanced treatment strategies, particularly exploring the potential of neuroprotectants and anti-inflammatory regimens, represents a promising avenue for intensive future research.

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