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Mini Review

Correlation Between Depression and Alzheimer's Biomarkers: Depression may be Considered an Early Biomarker of Alzheimer?

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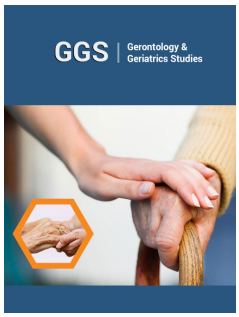

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Abstract

Depressive symptoms are associated with an increased risk of Alzheimer's Disease (AD). Some studies have highlighted depression as a possible risk factor while others suggested that depression may be an early manifestation of AD. This mini review explores the association between specific AD biomarker and depression. Plasma amyloid beta (Aβ), phosphorylated-tau, Glial Fibrillary Acidic Protein (GFAP) and neurofilament light chain (NFL) are blood biomarkers for AD. To date, the existing literature in this research field showed that there are several inconsistencies between different studies especially those regarding the association between AD specific marker and depression.

Introduction

Alzheimer Disease (AD), the predominant form of dementia, is a devastating chronic disease characterized by as the presence of amyloid plaques, neurofibrillary tangles, pro-inflammatory cytokines, inflammatory mediators, activated microglia and the induction of defined signaling pathways such as MAPK, NF-κB and PI3K/Akt. The activation of these pathways exacerbates the neurotoxicity in AD. Two types of AD can be classified: familial and sporadic forms. Autosomal dominant genetic mutations in amyloid precursor protein (APP), presenilin 1 (PS1) and presenilin 2 (PS2) genes is associated to the Familial AD (FAD) [1]. Sporadic AD (SAD), is controlled by a combination of factors such as aging, genetic factors and environment, highlighting their potential role in AD pathogenesis [2].

The hallmark of AD is a gradual cognitive decline, leading to progressive and persistent deterioration of cognitive functions, including memory, language and reasoning [3]. AD patients can also suffer from a wide range of psychiatric and behavioral problems. Depression and anxiety are frequently experienced by AD patients. Depression is considered one of the main risk factors for Alzheimer's disease. High levels of depressive symptoms were associated with a 40%-50% increased risk of AD The relationship between AD and depression is not yet fully characterized. Many studies indicated that depression is a possible risk factor for AD, while others proposed that depression is an AD early manifestation. These hypotheses are not contradictory and could coexist. Depression and AD may exhibit common underlying mechanisms and depressive symptoms may indicate a presymptomatic phase in AD progression [4]. The association between plasma AD biomarkers, such as amyloid beta peptide (Aβ), phosphorylated-tau, Glial Fibrillary Acidic Protein (GFAP), neurofilament light chain (NFL) and Sirutin1 (Sirt1) and depression is well described in literature, providing new insight into the implication of depression in the clinical diagnosis of AD.

Correlation between Aβ and tau biomarkers and depression in AD

Many studies examined the association between depressive symptoms and the two pathological characteristics of AD, Aβ and tau. It has been shown that AD patient with depressive symptoms exhibit higher levels of Aβ and tau, suggesting that depression may be considered as an early marker of AD pathology. However, other studies provided different results. Indeed, a coordinated Meta-Analysis of 8 Cohort Studies demonstrated that there are no association between Aβ42/40, p-tau181 and depressive symptoms [4]. This discrepancy may be due to differences in the AD progression stage between different cohort studies, suggesting that there is no correlation between depression and Aβ42/40 and p-tau181 levels at early clinical stages of AD. Indeed, Nascimento and colleagues revealed that depression was associated with higher plasma Aβ40/42 ratio, while depression did not correlate with higher plasma Aβ40/42 ratio in cerebrospinal fluid [5].

Correlation between glial fibrillary acidic protein (GFAP) levels and depression in AD

Although Aβ and tau are considered the most relevant AD biomarkers, several studies investigated the relevance of other molecules as potential biomarkers of AD progression: One of them is the glial fibrillary acidic protein (GFAP), an astrocytic cytoskeletal protein that can be detected in blood samples. GFAP is a marker of reactive astrogliosis, a response of astrocytes to brain damage or injury. Many researchers reported that blood GFAP levels may correlated with early-stage of AD [6,7]. It seems that serum GFAP levels correlated with the severity of depression and it may serve as a biomarker for the differential diagnosis in major depressive disorders and also for the cognitive decline [8,9]. Indeed, a cohort study revealed that high GFAP blood levels correlated with depression and are prognostic of cognitive decline. Thus, GFAP may be an excellent biomarker for the early diagnosis and treatment of depression in old age subjects, leading to a significant decrease of the risk of progressive cognitive decline, especially among individuals with higher concentrations of GFAP [9]. Rajan and colleagues demonstrated that higher serum GFAP levels associated with cognitive decline and brain structure alterations [10]. Plasma GFAP may be a new early prognostic biomarker for AD in individuals with Mild Cognitive Impairment (MCI) [11]. On the contrary, Twait and colleagues did not find any correlation between GFAP levels and depression in a coordinated meta-analysis of 8 cohort studies [4].

Correlation between neurofilament light chain (NFL) levels and depression in AD

Neurofilament light chain (NFL) is a biomarker of neuronal degeneration that occurs several decades before the clinical diagnosis of AD. Langella and colleagues, investigated the correlation among depressive symptoms, plasma carrying the PSEN1-E280A genetic variant, which develop dementia around 50 years old age [12]. This study demonstrated that elevated NFL plasma levels associated with enhanced self-reported depressive symptoms in individuals with AD, suggesting that neurodegeneration in AD promoted the development of neuropsychiatric symptoms and that the plasma levels of NfL may represent a biomarker for the onset of depression in AD. Interestingly, higher levels of NfL associated with depressive symptoms in individuals with an APOE ε4 allele, suggesting that in those individuals with a genetic risk for AD, neurodegenerative events may promote the occurrence of depressive symptoms [12]. On the other hand, Twait et al [4] indicated that late-life depressive symptoms were not associated with plasma biomarkers in AD and did not correlate with axonal injury or astrocytic activation [4]. These controversial results may be due to differences in the cohort of patients selected for the study and may indicate that NfL may be a biomarker of depression in familiar AD patients or in subjects carrying a genetic risk factor of AD.

Correlation between Sirt1 levels and depression in AD

Sirt1 is a nicotinamide adenine dinucleotide (NAD+) dependent class III histone deacetylase (HDAC) acting on transcription factors to control gene expression and playing a role on neurogenesis by modulating the phosphoinositide 3 kinase pathway, which is involved in AD progression by regulating neuronal survival, synaptic plasticity and responses to cellular stress. Abnormal activation of this pathway induces neurodegeneration, Aβ accumulation, degradation of tau, mitochondrial dysfunction and inflammation. AD patients exhibit lower levels of Sirt1, suggesting that it could be considered a biomarker for the early diagnosis of AD [13-15]. Sirt1 expression and function are significantly altered in depression, showing both increased and decreased levels depending on the context, such as stress exposure and brain region [16]. Preclinical studies exhibit controversial results concerning the efficacy of Sirt1 blood levels as biomarker of depression. On the other hands, a study demonstrated decreased Sirt1 levels in Major Depressive Disorder [17]. However, several studies unveil that Sirt1 plays a complex role in AD and depression, suggesting that it plays a protective effect against AD pathology. In depression, Sirt1 role is complex, showing that both its decreased and increased expression potentially contribute to depressive symptoms.

Conclusion

The molecular mechanisms involved in the onset and progression of depressive symptoms are not yet elucidated, affecting the possibility to find a biomarker of depression in AD patients. Studies investigating the association between depressive symptoms and pathological hallmarks of AD produced controversial results that may be due to differences between the cohort of patients selected in different studies Further research is needed to understand the complex relationship between depression and AD and to identify potential biomarkers that can improve the diagnosis and therapy of depression in AD.

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