Depression as a symptom of cerebrovascular diseases: A review.

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Short Report

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Abstract

Depression can be a prodromal symptom of brain diseases, but this association remains poorly studied with regards to cerebrovascular diseases. This review aimed to analyze the relationship between cerebrovascular diseases and depression. The objectives of the current review were: 1 – to assess the relationship between structural changes in the brain and depression; 2 – to evaluate the connection between cognitive performance and cerebrovascular impairment; 3 – to assess the relationship between biological correlates of brain diseases and depression. A search of the PubMed database was conducted focusing on papers published until 4th March 2021. The following terms were used: brain diseases and depression/pathology. A depressive disorder might have a relationship with structural or biological changes in the brain. However, this does not give the precise conclusion that depression definitely appears while a person has the cerebrovascular disease. Nevertheless, people with cerebrovascular diseases were observed to have high depression scale scores, while depression and cerebrovascular diseases had inflammation, cognitive change, or dopamine and serotonin changes in common. This is an overall limit concerning the definition of depression and cerebrovascular diseases. So, in this review, we observed all the possible connections between depression and brain diseases. Depression seems to be associated with cerebrovascular changes in people. They might have structural changes in the hippocampus, white matter, cortex, and other parts, as well as inflammatory processes, neuromediators changes, and cognitive decline. Thus, it is essential to evaluate depressive disorders in people with brain diseases as precisely as possible.

1. Introduction

Depression is a mental disease that has a deep and complicated connection with neurodegenerative diseases and cognitive impairment (Herbert et al., 2016). Whereas depression and dementia have been linked with brain disease development, the number of researches analyzing the possibility of depression to be a prodromal symptom of brain diseases is lacking. Most of the current reviews and meta-analysis particularly assess the relationship between major depressive disorder and cognitive decline (Epp et al., 2012; Monteiro et al., 2016; Weisenbach et al., 2014), or how depression is related to neurodegenerative disorders (Weisenbach et al., 2014; Nascimento et al., 2015).

Therefore, depression as a disorder partly responsible for cognitive impairment and brain diseases has been poorly investigated. Researches reveal, that the more depression is developed the worse the cognitive performance, which can be examined through neuropsychological tests assessing attention, memory, processing speed, and other cognitive functions (Roca et al., 2015). Some reviews describe an increased risk of Alzheimer's disease (AD) in patients with clinically diagnosed depression or dementia (Ownby et al., 2015).

In addition, the symptoms of depression in the early stages of dementia, which is also considered as one of the brain diseases, are linked to regional white matter atrophy and an elevated risk of cognitive impairment (Steffens, 2012). It has been stated that individuals with depressive disorders and high

amyloid-beta (Aβ) levels have an accelerated risk of AD development. Moreover, there was noted that people with late-life depression have different levels and metabolism of Aβ, which is similar to AD manifestation (Brendel et al., 2015).

The interaction between depression and cerebrovascular diseases is one of the most examined topics in geriatric psychiatry (Sneed JR et al., 2011). According to some clinical studies and observations, depression may be a preexisting symptom of neurodegenerative disorders as dementia, AD, Parkinson's disease (PD), and Huntington's disease (HD).

It is an ascent to the development of considerable hypotheses, connecting depressive disorders with the etiology and pathogenesis of neurodegenerative diseases.

Besides, depression can be recognized as an autonomous etiological factor, or a prodromal symptom, or a comorbid condition stimulating neurodegenerative processes in the brain.

Neurodegenerative diseases, behavioral and cognitive impairment might influence the development of depression in an opposite pathway.

Thus, there are a lot of studies investigated the association between depression and cerebrovascular diseases for decades. However, this review will combine the existing literature regarding depression prevailed cerebrovascular diseases, and associated neurological and cognitive decline.

2. Methods

2.1. Search strategy and Selection Criteria

We searched the internationally published articles, using PubMed, and the focus was on the papers published to the end of the 4th of March 2021. In addition, we used the bibliographical list of articles found from the PubMed database. In PubMed, we searched and screened studies published on the subject of cerebrovascular diseases and depression relationship. The search approach in the PubMed database included the following terms: “Brain diseases” AND “Depression/pathology”. The found results were limited to articles in the English language and research subjects of which were humans. All database-specific technical variations were taken into account during the search.

2.2. Methods of the review

Four authors proceeded to choose the titles and abstracts of the publications identified in PubMed to achieve the possible eligible articles. These authors individually then collectively, selected the articles relying on abstracts of those. All abstracts were re-read and re-scanned after those full-text articles were retrieved. In the following stage, these full-text articles were obtained and evaluated for eligibility criteria: (1) the research population included patients with brain diseases; (2) studies that assessed the connection between depressive disorders and brain abnormalities (structural, mental).

2.3. Data Extraction

The data was retrieved by two authors from chosen articles to the earlier prepared tables, with the following columns: study (authors, year), country, study design, sample size and characteristics, depression inventory, and key results.

2.4. Definitions

The following are definitions for “brain diseases” and “depression”.

Brain diseases, according to National Center for Biotechnology Information, U.S. National Library of Medicine are pathologic conditions affecting the brain, which is composed of the intracranial components of the central nervous system. This includes, but is not limited to the cerebral cortex, white matte, basal ganglia, thalamus, hypothalamus, brain stem, and cerebellum.

Depression is a widespread disease that might appear across the lifespan. Depressive disorders are associated with cognitive impairment and dementia, however, the way how depression is related to memory and attention problems and how it can be considered as a prodromal symptom to a cognitive decline and brain disease development (Schweitzer et al., 2002).

3. Results

3.3.1. Structural changes in brain and depression

Douven et.al. reported a more frequent left-sided lesions in patients with depression-executive dysfunction syndrome (DES) compared to adults with executive dysfunction (ED) ($\chi2 = 6.03$; df = 1, P = 0.014) or post-stroke depression ($\chi2 = 5.77$; df = 1, P = 0.016). In addition, the DES-only group presented with higher white matter hyperintensities (WMH) compared with ED-only (F (1,158) = 5.71, P = 0.018), PSD-only (F (1,158) = 8.67, P = 0.004), and patients with none of the diseases. Patients with depression, according to Douven et.al., had more considerable brain atrophy (F (1,158) = 6.15, P = 0.014) and more frequent infarcts compared with post-stroke depressed patients ($\chi2 = 5.15$; df = 1; P = 0.023) and none-group ($\chi2 = 4.22$; df = 1; P = 0.040). Researchers mentioned the possibility of a brain-depression connection even before the stroke and completed an analysis of depression history. Moreover, they stated that individuals with depression were observed more cognitively impaired and depressive symptoms were more chronic in comparison with patients with post-stroke depression. Additionally, participants with depression did not show an improvement in cognitive performance compared with participants with executive dysfunction (2018).

Wu et.al. in their study focused on the relationship between late-onset depression and vascular changes in healthy adults. Researchers verified a higher prevalence of silent brain infarctions (SBIs), especially in basal ganglia, microbleeds (MBs), especially lobar, and lesions in the left hemisphere in patients with late-onset depression compared with healthy adults. They mentioned that lobar MBs are related to cognitive impairment, and possibly have an influence on the emotional status of an individual. Moreover, it was the first study that discussed the MBs and SBIs in non-stroke patients (2014).

A recent case-control study assessed brain structural correlates of depression in PD patients, and the results showed an association of depression scores with pre-central gyrus volume in adults with early stage of PD, correlation of depression scores with the volume of the right midbrain and right superior temporal gyrus in patients with the middle stage of PD. However, they found a negative correlation between depression scores and volume of left anterior cingulate, right superior temporal gyrus, and left superior frontal gyrus. Additionally, researchers stated that volume of the right post-central gyrus was related to the scores of HAMD-17 in patients with early-stage of PD, whereas in middle-stage PD patient's relationship between depression scores and volume of the left cerebellum and right were observed (Li et al., 2020).

The expert study aimed to look at neurological correlates of late-life depression by post-mortem overview of brains donated by people who participated in research on cognitive functions (Medical Research Council Cognitive Function and Ageing Study (MRC CFAS)). Tsopelas et.al. stated that there is no difference between patients with depression and patients without depression in neuropathology. Interestingly, those individuals with depression were also diagnosed by moderate to severe Lewy body pathology in the substantia nigra, or moderate-to-severe Lewy body pathology in the locus coeruleus. Additionally, researchers mentioned the relationship between depression and severe loss of neurons in the hippocampus, substantia nigra, raphe nucleus, and nucleus basalis. However, AD was not found to be related to the impairment in the cerebral cortex (2011).

In the study of Levenson, the emotional and behavioral symptoms in neurodegenerative disease were studied. They referred to the literature where patients with depression were observed to have elevated intrinsic connectivity visceral motor emotion development along with subgenual anterior cingulated cortex and thalamus. Also, the decreased activity in the functional structure of the prefrontal cortex (dorsolateral) while inactive or in response to emotional stimuli was described. Authors described another literature where involvement of depression in emotional signals due to incapability to regulate amygdala reactivity. According, to Levenson, some authors have concluded that individuals with depression have reduced volumes of pregenual anterior cingulated cortex, dorsolateral prefrontal cortex, dorsomedial prefrontal cortex, inferior frontal gyrus, thalamus, and hippocampus (2014).

Starkstein et.al. in their study on neuroimaging correlates of apathy and depression in AD revealed significant depression and region interaction: depressed patients were observed to have increased WMH volume in the right parietal lobe compared with non-depressed patients (2009).

Tully et.al. in their longitudinal study assessed associations between white matter lesions and depressive symptoms among incident depression and dementia individuals. According to the results, WMH volume was related with low positive affect in a group of depressed people *(β = 0.15;95% confidence interval [CI]:0.02–0.29; p = 0.026*), whereas deep WMH volume was connected with depressed influence in the group of incident dementia patients *(β = 0.36; 95% CI: 0.05–0.68; p = 0.025).* In general, WMH volume was observed to be associated with social problems in people with depression and dementia. Investigators

concluded that findings supported the hypothesis that periventricular and total WMHs were connected with somatic-vegetative depressive symptoms (2015).

Perez et.al. studied the vice-versa relationship: whether silent brain infarcts (SBIs) and white matter lesions (WMLs) increase the risk of depression development. The results showed that SBIs patients had a much higher risk of depression recurrence; however, the incidence of depression was not associated with SBIs. Additionally, the authors mentioned that small vessel damage may disrupt neurotransmitters and affect mood regulation; this implies that depression can be an outcome of cerebral disease (ischemic brain damage). They also mentioned that increased infarct accumulation makes individuals more sensitive to depression development. However, they mentioned that depressive disorder might lead to vascular risk factor development, which enhances the risk of cardiovascular diseases (CVDs), and depression burden accelerates the next depressive episode separate from vascular concern. Perez et.al. during this follow-up excluded patients who developed dementia and stated that associations between SBIs, WML, and depression have no significant relationships with dementia. Furthermore, the associations were free from depressive disorder history, and it suggests that vascular brain disruption appears before depression (2012).

Wolf et.al. in their systematic review showed that individuals with cerebrovascular damage, particularly in the cerebellum, had greater scores of depression and anxiety. However, another study they mentioned revealed no significant difference between individuals with lesions of cerebellum and healthy individuals on depression or anxiety results while assessing with HAM-D and the Hamilton Anxiety Scale. Thus, hospitalized adults with cerebral disorders were observed to have higher depression rates than healthy ones according to the study used the Profile of Mood States questionnaire. Additionally, rates of depressive disorder differed in patients with brainstem or cerebellum disruption compared with patients with middle cerebral artery strokes. Thus, the last ones also varied with the healthy individuals in the emotional response (2009).

Wilson et.al. in their clinical-pathologic cohort study assessed more than 1764 older adults with no cognitive decline during 7.8 years. Participants underwent depressive disorders assessment using scales and other 17 performance tests. As well as neurologic and neuropathologic examination on b-amyloid plaques and tau tangle density measurement in the brain to identify diseases, such as hippocampal sclerosis, Lewy body, or cerebral infarcts. The results reveal the growth of depressive symptoms among participants during the follow-up, and an association between mild cognitive decline (52.2%) and a high level of depression before the dementia diagnosis. Also, before dementia onset, their association between incident dementia and high depressive symptom levels was found, as well the relationship between incident dementia and very quick symptomatology decrease after dementia onset. However, there was no relationship between the level of depression and neuropathological markers, but an increased level of depressive symptoms was connected with fast cognitive impairment, making up 4.4% of the decreased variability not referable to the neuropathology. Thus, depression, according to Wilson, had not influenced the association between cognitive impairment and neuropathological markers (2014).

According to Lavretsky et.al., depression along with other neuropsychiatric symptoms was common among patients with dementia. Also, the association between depression and lacunes total volume, lacunes volume in WM and putamen was observed. As well as increased lacunar volume in the thalamus was found to be related to depressive disorder. However, researchers were not able to find any significant correlations between cognitive functions and MRI results. Generally, Lavretsky et.al. supposed that cerebrovascular diseases might have an impact on late-life depression development, as well as other mood disorders. Also, white matter volumes are considered to be important in the pathophysiology of mood disturbances and connect the brain and psychiatric disorders. Overall, researchers stated that subcortical dementia, along with the vascular type of it might be more influential in depressive disorder development than cortical dementia (2008).

Auning et.al. in their study researched the neurobiological correlates of depressive symptoms in people with either subjective (SCI) or mild cognitive impairment (MCI) and disclosed that depressed patients had larger hippocampus volume (P = 0.06), increased orbital glucose metabolism (P = 0.02), and lower orbital radial diffusivity (DR) (less WM damage) (P = 0.10) relatively to those without depression. However, the results have changed after the Bonferroni correction, and there was no significant difference between cognitively impaired people with depression and people without depression. Moreover, diffusion tensor imaging showed no significant association between whole brain and symptoms of depression, but SCI or MCI patients with depression were noticed to have less WM disruption in comparison with those without depression (P = 0.05). Also, Auning et.al. could not find a statistical difference between patients with depression and people without depression on AD markers, such as АЯ42 and P-tau (2015).

Ferraro et.al. published a case of a woman who complained about low mood, depressed symptoms, and memory difficulties. Twice MRI scanning was performed, with the 5 years difference, where the first one revealed multiple lesions in the periventricular WM and diffuse cortical atrophy, whereas the second one showed an increase of the T2-hyperintense lesions in the cerebral WM, also small brainstem lesions, and corpus callosum atrophy. At the same time, neuropsychological assessments were carried out, including Babcock Story Recall Test, Rey's Auditory–Verbal Learning Test, phonemic and semantic word fluency, Stroop Word–Color Interference test, Frontal Assessment Battery, and revealed verbal memory deficits and word fluency in 2003, while in 2008 general continuous decline in memory, language, attention and executive functions were observed. Additionally, analysis of cerebrospinal fluid disclosed normal microbiological parameters, the intrathecal IgG synthesis indexes were slightly high. However, results of MR-angiography declared no cerebral autosomal dominant arteriopathy with subcortical infarcts, as well as leukoencephalopathy. They concluded, that follow-up MRI showed lesion load as stable, but inflammatory activity was gradually declining (2011).

3.3.2. Cognitive performance and cerebrovascular impairment

Amieva et.al. assessed the psychomotor slowing as a predictor of dementing illnesses. Results of the longitudinal study showed low digit symbol substitution test (DSST) performance in all-type dementia

older adults (HR 3.41, $p < 0.0001$). Additionally, low DSST performance was connected with risk AD (HR 3.18, $p < 0.0001$), or PD (HR 2.98, $p = 0.04$). There was a correlation between low DSST performance and instrumental activities of daily living (IADL) (HR 1.82, $p < 0.0001$), activities of daily living (ADL) (HR 1.95, $p = 0.001$) disability, and depression (HR 1.53, $p = 0.03$). There was also a correlation between incident stroke and low DSST performance (HR 1.88, $p = 0.09$) (2019).

Tao et.al. in their study assessed brainstem raphe (BR), hypogenecity of which was found in neurological disorders such as PD, HD, idiopathic Rapid Eye Movement (REM) sleep behavior disorder, and other cerebrovascular diseases. Authors revealed the difference in HAM-D score between patients with migraine (mean 9.1, SD 7.0, range 0–24) and controls (mean 4.9, SD 3.4, range 0–11) ($p = 0.001$), and HADS-D scores (mean 6.5, SD 4.5, range 0–18 in patients with migraine; mean 3.2, SD 2.2, range 0–7 in controls; $p = 0.000$). Additionally, the results showed the higher depression scales scores in patients with hypoechogenic BR (HAM-D, mean score 18.6 ± 4.6; HADS-D, mean score 12.6 ± 3.8) compared to those with normal BR (mean score 6.1 ± 4.6; HADS-D, mean score 4.6 ± 2.7) ($p = 0.000$) (2019).

The longitudinal study of Hollocks assessed differential relationships between depression and apathy with white matter changes and functional consequences and revealed that the individuals with small vessel disease (SVD) had higher depression and apathy scores compared with those without SVD. Researchers assessed executive function, long-term memory, processing speed which showed an association between reduced median fractional anisotropy and decreased cognitive performance with apathy rather than depression. They found no significant relationship between white matter parameters and depression symptoms. Moreover, Hollocks et.al. performed an analysis once again using the Geriatric Depression Scale and were not able to find a connection between depression and changes in the brain structure (2015).

3.3.3. Biological correlates of brain diseases and depression

Dalle et.al. revealed that in the early onset of Parkinson's disease (PD) stress may provoke or intensify neurodegeneration through increasing of extracellular availability of serotonin (5-HT) and DA (dopamine). Non-motor symptoms, such as depression, anxiety, sleep disturbance, mood and behavioral changes, and 5-HT loss are usually connected with PD. Researchers mentioned the advantage of depression treatment in the early identification and management of PD (2018).

Waisman et.al. suggested that due to the high expression of Interleukin-17 (IL-17) in patients with psoriasis and depression and anxiety symptoms, depression can be detected by IL-17 analysis. Additionally, they mentioned the possibility of IL-17-producing cells damaging the blood-brain barrier (BBB) and potentiating ischemic insult. In this review authors describe the interaction of IL-17 on endothelial cells, which leads to disruption of tight junctions and BBB breakdown, basically influencing unrestrained lymphocyte infiltration into the central nervous system (CNS) (2015).

In a study that focused on molecular aging of the brain and neuroplasticity, Sibille et.al. found declined brain–derived neurotropic factor (BDNF) levels, signaling in the amygdala, and anterior cingulated cortex in subjects with depression compared to subjects without depression. BDNF is a significant signaling neuropeptide during growth and adult life, particularly in managing neuroplasticity and correct work of neurons. There is a suggestion that the pathogenic mechanism in depression is explained by a combination of decreased BDNF as a response element for neuro-dendritic inhibition and reduced markers of GABA interneurons (2013).

Vu et.al. mentioned the glucocorticoid hypothesis in their review. Authors suppose that exposure to glucocorticoid on a chronic basis may be toxic to the brain, lead to cognitive impairment and be the risk factor for dementia. Finally, they link the manifestation of depression as a prodromal symptom of dementia. However, the focus of the review was on the vascular changes in late-life depression (LLD). The authors reviewed the literature on the pathogenesis of LLD, the relationship between LLD and dementia, vascular changes contributing to depression, and they revealed that reduced gray matter volume is associated with depression in older adults (2013). Moreover, they reviewed one of the earliest studies where reductions have been found in the prefrontal cortex, hippocampus, amygdala, and basal ganglia. It was confirmed by the study of Lupien et. al. - high glucocorticoid levels express in advance hippocampal atrophy in later life. Few studies, added in the review mentioned correlation of greater WMH severity with depression, and to an outcome of cerebrovascular diseases (Kumar et al., 2000; Thomas et.al., 2002).

Chagas et.al. in their study reviewed comorbidity of depression and PD through different types of neuroimaging. Studies they mentioned in the review described dopaminergic and serotoninergic systems as an important part of the origin of depression in PD. Other studies supported this evidence of this hypothesis by observing lower levels of 5-hydroxyindoleacetic acid in cerebrospinal fluid of depressed patients with PD, which is responsible for serotonin metabolism compared with those without depression (1991). Also, they mentioned the possible involvement of the noradrenergic system based on the findings of lower uptake in the locus coeruleus in depressive patients compared with non-depressive patients (2013).

Leonard et.al. in their study assessed the connection between inflammation and depression with dementia. Results of the review showed that major depression and dementia have neuronal damage in common. Chronic inflammatory changes serve as a path from depression to dementia through microglia activation. Moreover, due to the activation of the kynurenine pathway by pro-inflammatory cytokines, as a result of microglia activation, there is a high possibility of neurotoxins quinolinic acid and 3 hydroxyanthranillic acid increase. Additionally, depression and dementia have a common feature which is characterized by a decrease of the synthesis of neurotrophic factors, leading to neuronal repair reduction. Authors said that it can be boosted later by phospholipase D pathway disruption, undoubtedly bringing neuronal damage and pattern of the neuronal process. They stated that this hypothesis might help to explain the neurodegenerative processes in the hippocampus and the brain totally as characteristics of

major depressive disorder (chronic). Additionally, it may be helpful to understand how depression might be a prodromal symptom of dementia (2006).

Wuwongse et.al. conducted a review where high rates of depression were observed in AD patients and it showed that depression was one of the earliest signs of neuropsychiatric disorder (2005). Wuwongse et.al. mentioned growth in pro-inflammatory cytokines in both depression and neurodegenerative disease – AD. It is explained by the impact of pro-inflammatory cytokines on neuronal functioning, particularly on the prefrontal cortex and hippocampus. Also, researchers mentioned that central neurotransmitters are adjusted by pro-inflammatory cytokines, and involved in depression. Moreover, there is a thought that depressive disorder might presage other neurodegenerative disorders, such as PD or IS (2006).

Aznar et.al. in their review described the results of various epidemiological studies lead to the hypothesis that depression might be an underlying symptom of dementia. They proposed different ideas of how depression is associated with AD. First, they mentioned the distribution of 5-HT1A and 5-HT2A receptors in the brain and their connection to the limbic system or cortical areas. Additionally, studies showed that there is a relationship between depression and levels of 5-HT1A and 5-HT2A. Also, lowered levels of serotonin and 5-HT1A and 5-HT2A receptor density are observed in AD patients. However, some of these conclusions were based on animal studies. Nevertheless, Aznar et.al. mentioned another correlation that might be observed in both depressed and AD patients. It is considered, that depressed patients tend to have impairment of the HPA axis in stress regulation, which leads to brain pathologies and depressive episodes. They also connect reduction in hippocampal volume through exposure to glucocorticoids and depression development. Moreover, depressive individuals are observed to have lower BDNF levels, while AD patients have lower BDNF mRNA expression in the hippocampal area and temporal lobe (2011).

4. Discussion

The main finding of our review is that depressive disorders can be a prodromal symptom that identifies brain abnormalities. It seems that proper depression diagnosis might be a preventive measure for cerebrovascular diseases. Overall, left-sided lesions and brain atrophy were noticed in patients with depression-executive dysfunction, while others, in addition to this, mention silent brain infarcts in basal ganglia and microbleeds in lobes of the brain as accountable for cognitive decline and depression (Douven et al., 2018; Wu et al., 2014). These results have in common with those revealed by Perez et.al. They stated the ability of WM lesions and SBIs to have a significant role in depression development. Moreover, they mentioned that brain damage appears before depressive disorder (2012). Volumes of the pre-central gyrus were mentioned as accountable for depression scale scores and PD, however, the association between depression and left anterior cingulate, right superior temporal gyrus, and left superior frontal gyrus was negative (Li et al., 2020). Some studies mentioned no relationship between depression and neuropathology. Thus, patients with depression were observed to have Lewy body pathology in substantia nigra or a locus coeruleus, changes in the hippocampus, raphe nucleus, and nucleus basalis, but not in the cerebral cortex (Tsopelas et al., 2011; Wilson et al., 2014).

In addition, Levenson et.al. connected prefrontal cortex structure, thalamus changes, volume reduction in the dorsolateral prefrontal cortex, pregenual anterior cingulated cortex, inferior frontal gyrus, hippocampus, and thalamus in people with depression. This was also supported by Auning et.al. mentioning the large hippocampal volume, along with increased metabolism of orbital glucose and white matter changes in general among those with depressive disorder (Auning et al., 2015).

The range of associated comorbidities is not limited to conditions, Starkstein et.al. revealed that depressed patients had increased volumes in WMH in the right parietal lobe compared with non-depressed patients (2009), while Tully et.al suggested that WMH volumes are related to depressive symptoms in patients (2015). Another relevant issue still in need of further investigation is the importance of WM volumes in the pathology of late-life depression (Lavretsky et.al.,2018)

Moreover, the report of the case of Ferraro et.al. identified patient with diffuse cortical atrophy and periventricular, having verbal memory deficits and word fluency, and later whereas the second one showed an increase of the T2-hyperintense lesions in the cerebral WM and general continuous decline in memory, language, attention. Along with the data mentioned above, brain disorders were also studied by the cognitive examination implementation. Overall, results of DSST performed by Amieva et.al. among the participants showed the connection between poor performance and all-dementia type older adults. Brainstem raphe condition is another critical domain that will be needed to be assessed in order or identify depression in patients/ Tao et.al. in their study mentioned that hypoechogenic BR was found in AD, PD patients as well as the identification of which was followed by high depression scales scores such as HAM-D and HADS-D.

However, the relationship between depression and WM was not found in the study of Hollocks, but they mentioned that patients with SVD were noted to have high depression and apathy scores (2015).

In addition, depression can be related to brain diseases, such as Parkinson's disease by increased levels of serotonin or dopamine. Additionally, another study also mentioned that dopaminergic and serotoninergic systems play a significant role in depressive disorders in PD (Chagas et al., 2013). This data that we accentuate in our review also overlap with the information provided by Aznar et.al. concerning the association between 5-HT1A and 5-HT2A serotonin receptors and depression, as well as with AD (2011).

Furthermore, the existence of depressive disorder can be detected through the results of IL-17 analysis, which is also linked to the blood-brain barrier, ischemic stroke, and central nervous system diseases. Moreover, it was observed that depression and neurodegenerative disorders have inflammatory processes in common. This was supported by Wuwongsee, who stated that there is an increase in pro-inflammatory cytokines in both depression and neurodegenerative diseases (2010). These results agree with those of Leonard et.al. concerning the possibility of inflammatory changes to serve as a pathway from depression and dementia. In the reported review researchers mentioned kynurenine pathway activation as a booster of neurotoxins’ increase (2006).

Decreased BDNF-levels suggest the presence of depression and change in the inhibition of neurons. These findings concerned Sibille et.al. due to the responsibility of BDNF in neuroplasticity (2013). In addition, the relationship of depression with glucocorticoid levels, which later can lead to dementia development, was noted.

It was the first review where depression was assessed as a symptom of brain diseases, not a consequence. The study results were classified by type of investigation: structural changes in brain and depression; and cognitive impairment and cerebrovascular diseases.

Some limitations among the included studies were: the difference in depression assessment which could affect the results; the difference in the analyzed brain disease (part) may affect the generalizability of the results.

5. Conclusion

This review has explored the research publications that assessed the depression manifestation in patients with brain diseases. Our review does not allow making a precise and full conclusion on the relationship between depressive symptoms and brain abnormalities. However, we highlighted the numerous studies which observed the relationship between structural changes in the brain and depressive symptoms. Indeed, depression can be a prodromal symptom of cerebrovascular diseases if diagnosed correctly. It is important that depressive symptoms might appear when disruptions in the brain already exist. They can be manifested by cognitive function decline, which can be observed during memory, attention, or processing speed evaluation. However, while depression can be observed by neuropsychological tests, MRI examination might not show the change in the brain structure. Thus, it seems that it is essential to evaluate depressive symptoms as precisely as possible to diagnose or notice the first signs of cerebrovascular changes, or to limit the risk of its development.

Declarations

Ethics approval and consent to participate: not required for this study.

Consent for publication: not required for this study.

Availability of data and materials: The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

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