Review Article

Potential Linkages between Alzheimer's Disease and Major Depression

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Abstract

Alzheimer's disease (AD) and major depression (MD) are frequent diseases with a significant impact on the quality of life, and epidemiological studies show a correlation between early depressive episodes and AD. Although apparently different, they nonetheless maintain significant similarities, such as the common genetic substrate, involvement of similar structures, and a number of common pathogenetic hypotheses. This in-depth literature review aims at highlighting possible linkages between the two diseases: A chronic inflammatory process that selectively alters the blood–brain barrier in certain regions can be hypothesized.

Keywords: Alzheimer's disease, degenerative diseases, major depression

Introduction

Depressive symptoms in Alzheimer's disease (AD) are very common and may occur in every stage of the pathology, oftentimes preceding cognitive impairment.[1] In subjects older than 65 years of age, when first-time depression precedes the first cognitive symptoms only by few years, such late-life depression often represents a prodromal feature of dementia. The poor response to antidepressants shows that such depression is different from depressive disorders arising at a younger age.[2] At the same time, several authors claim that subjects suffering from depression early in life are at greater risk of developing AD. Among the first to report this possibility, Agisayewa claimed that AD patients were more likely to have had a psychiatric illness earlier in life – most frequently, unipolar depression or paranoid disorder.[3] Other authors subsequently researched the subject only to reach mixed conclusions. The first meta-analysis in the early 2000s did not reach conclusive results.[4] A subsequent meta-analysis concluded that a history of depression might predispose to an increased risk of developing AD later in life.[5] In particular, two of the studies taken into consideration in this meta-analysis showed an increased risk of developing dementia among patients who had suffered from depression more than a decade earlier.[6,7] Kessing and Andersen[8] also found that the risk of developing dementia later in life increases 13% for every depressive episode leading to hospitalization, and Dotson *et al*.[9] confirmed these results, whereas according to Brommelhof *et al*.,[10] depression onset more than 10 years before dementia onset was not associated with an increased risk of dementia. Similarly, Robinson showed that people who had suffered from depression even 20 years earlier were more likely to develop AD later in life.[11] This work is particularly significant because the diagnoses of AD were confirmed at autopsy.

Recently, Nedelec *et al*. showed in a large series that depression can precede the diagnosis of AD by at least 9 years.[12]

Besides, it is well known that cognitive impairment that affects multiple domains may precede the onset of a major depressive episode, and remains present during acute episodes while also persisting during remission.[13,14]

Hence, despite some difficulties, there is substantial evidence backing the idea of a correlation between early depressive episodes and AD. This association would suggest that there are structures and/or pathogenetic causes that are common to the two diseases.

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The aim of this review is to examine such possible common pathways.

Methods

Medline literature until November 2022 was scanned using AD, major depression (MD), and anxiety. Other studies were identified by reviewing relevant bibliography quoted in the original papers.

Results

Epidemiology of Alzheimer's disease and major depression

AD is the most common dementia, with a variable incidence. In Europe was estimated at 5.5%,[15] in the United States of America (USA) the incidence raises from 2.8/1.000 persons-years in the age group 65–60 years to 56.1/1.000 persons-years in the older than 90-year age group[16] and in Saudi Arabia varies between 6.4%[17] and 11%–16%.[18]

In the USA, the lifetime prevalence of MD is 11.2%,[19] 12.2% in Canada,[20] and 1.8% in China,[21] whereas in Iran, the prevalence of all types of depression is 34.26%.[22]

Pathology of major depression

Anatomopathological studies in patients suffering from MD are scanty, often relying on small series and reaching incongruent results. Ongür *et al*.[23] described decreased glial numbers and density, and Cotter *et al*.[24] observed the same phenomenon in the anterior cingulate cortex. In the same region, Chana *et al*. described reduced neuronal soma size and increased neuronal density.[25] However Bouras *et al* and Cotter *et al* did not confirm this finding.[26,27]

Rajkowska *et al*.[28] and Cotter *et al*.[27] described alterations of the glial density and neuronal size in the prefrontal cortex. In the same region, Gawryluk *et al*.[29] described decreased levels of glutathione, while Oh *et al*.[30] reported a reduced density of GABAergic neurons. Yet, these results have not been confirmed by others.[31]

Similarly, while investigating AD patients with a lifetime history of depression, Bernstein *et al*.[32] found apoptotic cells in the hippocampus, Cobb *et al*.[33] a diminished number of astrocytes, and Rapp *et al*.[34] an increased number of plaques and tangles. However, these findings were not confirmed by several other authors.[35-38]

Brisch *et al*.[39] described alterations of the microglia in the same nucleus; however, also in this case, these results were not confirmed by Klimek *et al*.[40] and Underwood *et al*.,[41] whereas Hamidi *et al*.[42] referred to a reduction in glial cells in the amygdala and Williams *et al*.[43] an increase of myelin in the callosal genu.

Pathology of Alzheimer's disease

The pathology in AD pathology is well known and is mostly due to amyloid deposits and neurofibrillary tangles. According to Braak and Braak,[44] the spread of the neurofibrillary tangles follows a well-defined order, as they start in the transentorhinal cortex (Stage I), subsequently reaching outer layers of the entorhinal region (Stage II), the occipitotemporal gyrus (Stage III), the middle temporal gyrus (Stage IV), the peristriate area (Stage V), and finally, the striate cortex (Stage VI).

Some structures are very vulnerable, including the hippocampus, layer II of the entorhinal cortex, layer III of the cerebral cortex and the subcortical nuclei projecting directly to the cortex, as well as the nucleus basalis of Meynert, the raphe nuclei, and the locus coeruleus.

Hence, while there are still many uncertainties around the MD pathology, it would appear that certain structures – including the hippocampus, the nucleus of Meynert, and the raphe nuclei – are compromised both in the MD and during the early stages of AD.

Radiological studies of major depression

Radiological studies of patients with MD are more numerous than anatomopathological studies.

According to a meta-analysis of magnetic resonance imaging (MRI) investigating structural brain alterations in MD patients,[45] the most repeatable features include:

1. Lower hippocampal volume in subjects with recurrent MD, although the volume may normalize after remission of the pathology
2. Smaller and thinner amygdala in patients who first experienced MD during adolescence
3. Subtle alterations of the cortical thickness in several regions and most frequently in the orbitofrontal cortex
4. Greater alterations among patients taking antidepressants.

Another meta-analysis focused on studies using diffusion tensor imaging[46] found that several authors reported a reduction of the fractional anisotropy in the genu of the corpus callosum, in the right superior longitudinal fasciculus, and in the right anterior thalamic projection among medication-free patients with a first episode of MD. On the other side, patients during drug-washout periods displayed a reduced fractional anisotropy in the right cerebellum lobule, in the body of the corpus callosum, and bilaterally in the superior longitudinal fasciculus. The authors conclude that reduced fractional anisotropy – both in the genu of the corpus callosum and in the right anterior thalamic projection – is likely associated with the disease.

Other studies have shown alterations in the default mode network and in the salience network. The former consists of several subsystems and includes regions distributed throughout the association cortex, whereas the salience network is a cortico-striatal-thalamic-cortical loop.[47]

The default mode system appears to be implicated in the spontaneous cognition,[48] whereas the salience network integrates sensory inputs to guide attention and modulate behavior.[49] Several alterations of the functional networks have

been described in such a way that MD could be categorized as a network-based disorder.[50] However, similar alterations were also found in psychiatric disorders, i.e. Shao *et al*.[51] found functional hyperconnectivity between the default mode and the salience network in schizophrenia and MD, albeit with some differences, which are possibly reflective of distinct underlying pathophysiological mechanisms.

Radiological studies of Alzheimer's disease

While MRI studies in AD patients are numerous, results have tended to be conflicting, particularly in the early stages of the illness, to the point that a recent review concluded that the structural MRI does not necessarily provide definitive indications for an early AD diagnosis among patients with mild cognitive impairment (MCI).[52]

Some authors obtained better results by using the fluorodeoxyglucose positron emission tomography to measure the cerebral metabolic rates of glucose during the resting state: the prediction of conversion from MCI to AD was improved and patients complaining of subjective cognitive impairments showed decreased metabolism in AD-related regions;[53-56] however, these results need to be confirmed by studies with larger samples.

Promising results were also obtained by using radiotracers of tau, both in the early stage of AD and while monitoring later stages, but larger studies are needed also in this case.[57]

The functional MRI showed a correlation between global reduction of connectivity and age progression, especially in the default mode network. In AD patients, the decline is more rapid,[56] with the default mode network appearing to be compromised in all clinical variants of the disease.[58]

Neuropsychology of major depression and Alzheimer's disease

Several cognitive disorders have been associated with episodes of depression. Here, too, the results are often conflictual: While some authors described problems affecting a wide range of cognitive domains – including attention, memory, and executive functions, others described impairment in different and specific functions, such as the executive function or deficit in attention.[59]

The MCI is considered an intermediate stage between normal cognitive aging and dementia, often of the AD type. According to the revised Mayo Clinic criteria,[60] the MCI may be classified as "amnestic" if it presents a deficit in the episodic memory, or "nonamnestic" if it presents a deficit in nonmemory cognitive domains. According to NINCDS-ADRDA criteria,[61] the AD of the amnestic type usually begins with an impairment in learning capacities, and in the recalling of recently learned information. Yet, other symptoms are equally possible: (1) language symptoms with a deficit in word-finding capacity; (2) visuospatial symptoms with a deficit in spatial cognition; and (3) executive dysfunctions with deficits in reasoning, judgment, and problem-solving capacity.

Pathogenetic hypothesis

The pathogenesis of both diseases is unknown and several different hypotheses have been proposed. For MD, the oldest hypothesis is the monoaminergic one founded on the mechanism of action of drugs acting on monoamines and considers the depression to be caused by reduced levels of neurotransmitters, mainly serotonin and adrenalin.[62]

The stress hypothesis emphasizes the importance of the hypothalamic–pituitary–adrenal (HPA) axis, which mediates the release of glucocorticoids produced in response to stressful events. In MD, Stetler and Miller[63] reported an elevation of both the adrenocorticotropic hormone and cortisol, and a reduction of the corticotropin-releasing hormone, while Lebedeva *et al*.[64] reported that high levels of cortisol are associated with an atrophy of the cerebral cortex. Besides, radiological studies showed smaller surface areas of the amygdala – a region rich in glucocorticoid receptors – among patients suffering MD from adolescence.[46]

Excess glucocorticoids decrease the hippocampal volume acting on neurogenesis or neural morphology.[65-67]

The neuroinflammatory theory originates from the observation that there is a correlation between cytokines and depression.[68] This hypothesis describes an overactivation in some brain regions such as the hippocampus, the amygdala, or the prefrontal cortex controlling mood and cognition. In turn, the cytokines can activate the HPA axis.[68] Besides, the inflammatory process can provoke alterations in the blood–brain barrier and alterations in this barrier have been described in some psychiatric pathologies. Pearlman *et al*.[69] found a correlation between severity of depression and increased protein S100, a marker of glial alterations and Greene *et al*.[70] reduction of the protein claudin-5, responsible for the permeability of the tight region in the hippocampus of patients with depression and schizophrenia.

Other authors have emphasized the role of Vitamin D, namely low levels of Vitamin D are associated with depression and cognitive deficits.[71] Others have drawn attention to the possible role of some neurotransmitters such as histamine involved in regulating both the mood and cognitive processes.[72]

There are also several hypotheses about the origin of AD.[73] The cholinergic hypothesis assumes an acetylcholine deficiency; drugs acting as acetylcholinesterase inhibitors relieve for short-time symptoms of AD.

For many years, the amyloid cascade hypothesis had prevailed. This assumes that the accumulation of amyloid-β, which is toxic to neurons, is due to imbalances between production and removal of the amyloid. According to some authors, the abnormal tau protein alters the signal's transmission, whereas according to other authors, both hereditary and environmental factors are responsible in altering the mitochondria's functions.

Others have also drawn attention to the action of some elements such as calcium because high intracellular levels damage

the neurons. Memantine, which works by blocking receptor N-methyl-D-aspartate and reducing the flow of calcium ions, causes a modest improvement of cognitive disorders.

The inflammatory hypothesis emphasizes the responses of microglia and astrocytes to inflammation.[74] Reactive astrogliosis is characteristic of AD and correlates with cognitive deficit. Astrocytes control several brain functions: deliver nutrients to neurons and regulate ion and metabolic balance and the blood–brain barrier. Nation *et al*.[75] showed that the blood–brain barrier in the hippocampus is damaged early regardless of amyloid or tau deposition.

Some hereditary factors are implicated in the genesis of both diseases. Apolipoprotein ε4 (APO ε4) is a well-known risk factor for AD. Mice carrying APO ε4 are more susceptible to chronic unpredictable mild stress.[76] In depressed humans, the results are controversial: a meta-analysis found associations in the Han ethnicity,[77] whereas Burns *et al*.[78] did not find such an association in the Australian population, while Steffens *et al*.[79] failed to find similar correlations among twins.

Among first-degree offspring of patients with depression, the risk of depression increases two- to three-fold. Several responsible genes have been identified – however, each gene alone contributes little to the development of the disease.[80] While late AD onset is sporadic, several genes may predispose to the disease.[81] Mendes-Silva *et al*.[82] demonstrated that seven microRNA found in both diseases are involved in proteostasis control, maintenance of the genomic integrity, regulation of transcriptional activity, immune inflammatory control, and neurotrophic support.According to Chen *et al*.[83] 79 genes are shared between AD and MD and Guo *et al*.[84] found 77 genes related to metabolism and immune response in common between these two diseases.

Discussion

Despite several points remain to be clarified, we can still make some preliminary assumptions to explain the association between AD and MD. Arguably, there is a common genetic substrate: in some populations, there seems to be an association between MD and APO ε4 – a well-known risk factor for AD – as well as some genes involved in numerous functions concerning genome integrity, inflammatory response, and neurotrophic support.

Epidemiological studies have shown that depression can precede AD by many years, and that in the course of depression, some cognitive disorders can persist even after the resolution of depressive symptoms.

Hence, it is reasonable to suppose that a pathogenetic Noxa acts over many years affecting similar structures. In considering pathogenetic hypotheses, some similarities among the two pathologies should be considered. One is that chronic stress acts on the HPA axis, which in turn controls the release of glucocorticoids.

Hypercortisolemia and dysfunctions of the hypothalamic–pituitary–gonadal (HPG) axis were also reported in AD.[85] Some reported a dysregulation of the HPG also in depressed patients.[86] HPA alterations have also been reported in diabetes and in metabolic syndrome, which are both considered risk factors for AD.[87,88]

Another hypothesis revolves around the role of inflammation, which has also been considered in other psychiatric and neurodegenerative diseases. In subjects who used chronic anti-inflammatory drugs, a lower incidence of both AD and MD was observed. For this reason, trials with anti-inflammatory drugs were performed in both diseases, obtaining however no or poorly correlated results.[89,90]

The immune system consists of microglia and astrocytes; it has the task of maintaining or restoring homeostasis through the secretion of substances, such as cytokines, that bind to specific receptors. An increase in microglial numbers in the direct vicinity of amyloid plaques, an upregulation of pro-inflammatory microglial activity, and an impairment of microglial activity have all been associated with AD.[91] In addition, inflammation acts on adult neurogenesis with both facilitating and inhibiting actions.[92] Furthermore, in the MD, authors have often observed increased levels of pro-inflammatory cytokines in the blood, in the cerebrospinal fluid, and in the brain, especially in specific regions, including the amygdala, the hippocampus, and the prefrontal cortex, which are all responsible for controlling both mood and cognition.[93] Such inflammatory phenomena are so important that some authors have proposed to distinguish a subtype of "inflammatory depression."[94] According to Liao *et al*.[95] in the MD, the astrocytes modulate extracellular adenosine-5-triphosphate, energy metabolism, and neuroinflammation. In turn, astrocytes facilitate amyloid aggregation, thus constituting a risk factor for AD. Some structures are selectively involved in both pathologies: the entorhinal region, the hippocampus, and the amygdala, all closely connected with the olfactory bulb. According, olfactory dysfunctions are also present in animal models of AD,[96] and in humans are considered preclinical signs in both AD and Parkinson's disease.[97] At the same time, the bilateral olfactory bulbectomy is also a well-known model of depression.[98]

AD and MD are two very common and apparently distinct pathologies. However, examining the literature, several points of contact emerge, especially inflammatory phenomena and alteration of the blood–brain barrier. Although these alterations have also been described in other neuropsychiatric pathologies, hypothetically it can be thought that a chronic inflammatory process selectively alters the blood–brain barrier in certain regions (hippocampus, amygdala, and entorhinal region). Obviously, there are many aspects that still need being clarified, and considering the frequency and severity of these two disorders, further research is warranted.

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There are no conflicts of interest.

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