Aging, depression and dementia: The inflammatory process

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Abstract

Population aging that we are currently witnessing has led to an increase in chronic age-related diseases, with dementia and depression being highlighted. Several studies establish a relationship between dementia and depression, although without defining the mechanism that links them. Some studies establish depression as a prodrome of dementia, while others consider it a risk factor for dementia. One of the events that is common between dementia and depression is the inflammatory process. In depression, an increase in inflammatory cytokines has been described, which would justify the serotonergic, noradrenergic and dopaminergic dysfunction of depression. This increase entails altering the activity of the hypothalamic–pituitary–adrenal (HPA) axis, thus linking chronic stress to depression, and the consequent weakening of the blood–brain barrier (BBB), facilitating the passage of pro-inflammatory factors. In this line, recent studies suggest that inflammation could direct the development of the pathogenesis of dementia, particularly Alzheimer's disease (AD), once the pathology has begun. In addition, sustained exposure to pro-inflammatory cytokines characteristic of aging could alter the microglial function and the expression of enzymes responsible for amyloid peptide metabolism, aggravating the pathological process. In view of the involvement of the inflammatory process in both conditions, it is necessary to investigate the events which both conditions share, such as the inflammatory process, to know the involvement of the inflammatory process in both dementia and depression, possible relationship of these 2 conditions, and consequently, to establish the clinical approach to both conditions.

Key words: dementia, Alzheimer's disease, inflammation, depression

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Introduction

Aging is an important contributing factor in the onset and development of various neurological disorders, such as cognitive impairment or dementia. However, dementia is not a natural or inevitable consequence of aging. In fact, other clinical conditions, in this case pathological processes, have been described as being associated with an increased risk of cognitive impairment/dementia, including depression, hypertension, diabetes, hypercholesterolemia, and obesity.[1]

During aging, the brain undergoes a progressive decline in energy use,[2] and according to the free radical theory of aging, free radicals and related oxidants, both environmental and derived from cellular metabolism, would be the main cause of cellular damage, also due to their accumulation over time. Thus, the changes in energy metabolism associated with aging would be responsible for the associated functional and structural cellular problems. In other words, during the last third of our lives, our brain accumulates structural and functional damage that reduces our adaptive homeostatic capacity,[3] which possibly makes it more susceptible to harmful stimuli.

In this context, one of the most affected cell types that are susceptible to such lesions are neurons, as well as different types of glial cells. Thus, in the aging brain, there is an increase in microglia, associated with a decrease in their function. Indeed, with aging, they lose their flexibility to move, which decreases their efficiency in defending the central nervous system (CNS),[4] as well as their ability to block exogenous invasion or endogenous metabolites such as β-amyloid peptides.[5,6] In this regard, one of the most relevant facts about aged microglia is the elevated expression of pro-inflammatory molecules, such as MHC-II, CD16/32 and CD86. Even the secretion of pro-inflammatory cytokines, such as tumor necrosis factor alpha (TNF-α), interferon gamma (IFN-γ), inducible nitric oxide synthase (iNOS), interleukin-6 (IL-6), and interleukin-1β (IL-1β), increases significantly in response to harmful stimuli.[7]

A possible interpretation of this shift from a microglial profile to an inflammatory or sensitization profile is based on 3 factors: 1) the increase in inflammatory markers and mediators; 2) the decrease in threshold and activation time; and 3) the increase in response and inflammation after this activation.[8,9]

In this regard, Chung et al.[10] established how age increases this sensitized state[10,11] – microglia develop an "alert, primed" phenotype, which contributes to the increased inflammatory state of the aging brain, as indicated by the increased inflammatory mediators and altered microglia phenotype (that occurs with age/aging). In this situation, results obtained in aged rodents following immune challenge, i.e., infection, show depressive-like behavioral complications and cognitive deficits.[12]

In the case of astrocytes, during aging, they also change their secretory phenotype to a pro-inflammatory phenotype under chronic stress. Even the aforementioned oxidative stress could induce astrocytes to secrete pro-inflammatory factors, such as IL-6, monocyte chemoattractant protein (MCP)-1 and metalloproteinase (MMP)-9, contributing to the inflammation in the senile brain, and altering the integrity of the blood–brain barrier (BBB).[13]

At this point, with the disruption of BBB integrity, it is important to note the enormous importance of the BBB in maintaining metabolic homeostasis in the CNS[14] and, consequently, the increased exposure of brain tissue to toxic molecules or inflammatory signals that circulate in the blood when BBB is disrupted.

Conditions associated with impaired BBB integrity include oxidative stress,[15] the presence of advanced glycation end products (AGEs) and their receptor (RAGE),[16] increased production of pro-inflammatory cytokines,[17] and vascular dysfunction, as well as chronic stress, depression or dementia.[18,19]

Having described the role of aging as a contributing factor in various neurological disorders, such as cognitive impairment or dementia, it is necessary to understand its relationship to various clinical situations or pathological processes, including depression and dementia.

In the case of depression and dementia, we must bear in mind that there is no single mechanism that explains both pathologies, although similar neurobiological changes or even a similar pattern of neuronal damage have been described for both conditions, thus deepening our understanding of a complex relationship between both pathologies. Cognitive changes are common in the context of depression, and mood-altering symptoms of this condition often accompany cognitive disorders of dementia.[20–23] Our research group has found that the presence of depression increases the risk of dementia by 16%. However, we have also noted factors that condition this relationship, such as age or the presence of other diseases, for example, type II diabetes.[24]

Both dementia and depression present biological mechanisms that link them, such as vascular disease, atrophy of the hippocampus, a larger deposit of β-amyloid plaques, and inflammatory alterations.[25,26] In this sense, according to the latest studies, and as we have explained throughout this section, the inflammatory process is an important key effector in both processes.[27,28]

This common point between depression and dementia is a promising research focus with clear clinical applicability for addressing both conditions.

Depression and inflammation

Although the main approach to depression is based on the historically accepted "monoamine depletion hypothesis,"[29,30] this hypothesis is not sufficient to explain the depressive disorder; especially in the last 20 years,

several studies are pointing to the involvement of the inflammatory process in the disorder. This fact would justify the serotonergic, noradrenergic and dopaminergic dysfunction[31,32] inherent to depression; thus, we can speak of an "inflammatory hypothesis". Authors such as Liu et al.[28] link depression to the inflammatory process through increased levels of pro-inflammatory cytokines such as TNF-α and IL-6, decreased circulating levels of IL-1β and IL-8 in blood and cerebrospinal fluid,[33] and increased corticotropin-releasing hormone levels; the latter results in an increase in the activity of the hypothalamic–pituitary–adrenal (HPA) axis, which in turn introduces stress into the process.

Chronic stress induces the weakening of BBB (described in animal experiments) and the consequent passage of circulating pro-inflammatory mediators.[34] Therefore, authors such as Dudek et al.[34] describe how stress-induced alteration of BBB permeability is linked to the inflammation of endothelium and involvement of tight junctions.

Furthermore, as noted above, increased IL-6 and C-reactive protein (CRP) levels could predict the development of depressive symptoms.[35,36] Both molecules are predictive, indicating that inflammation precedes depression, but are also associated with cognitive symptoms of depression.[37]

Therefore, the passage of peripheral myeloid cells into the brain in depressive processes would constitute an important clue supporting the existence of a central inflammatory response in depression that would be mainly driven by peripheral inflammatory events.[38]

The verification of this inflammatory response in depression suggests the possible existence of other causal biological pathways/processes in depressive processes[39] and opens the door to the improvement of the response of current antidepressant therapies since, as reported by authors such as Miller and Raison,[31] 30–50% of depressed people do not respond to commonly prescribed antidepressant treatments and only 30% of patients remit.

Dementia and inflammation

In recent years, the inflammatory process has become important in the neurodegenerative pathology of Alzheimer's disease (AD). Inflammation can "conduct" the pathogenesis of AD once the pathological process has begun.[40,41] Even the studies conducted by Lee et al.[42] highlight the ability of pro-inflammatory microglia activation to aggravate and initiate the pathological process. At present, AD is considered to be a tauopathy initiated by β-amyloid peptide accompanied by neuroinflammation, thus connecting the 3 pathophysiological and anatomopathological events typical of AD.[42–45]

In elderly population, age affects the microglial function and is associated with an alteration in amyloid metabolism, aggravated by sustained exposure to pro-inflammatory cytokines, such as TNF-α, and the whole process can inhibit microglial function.[46]

In this regard, the disruption of BBB by inflammatory mediators during the progression of AD has been described. In the BBB, the neurovascular unit (NVU) is responsible for neurovascular coupling, i.e., the interaction of neuronal (neurons and glia) and vascular tissues (endothelial cells, pericytes and adventitial cells).[14] Several authors show how this coupling is impaired in AD,[47] suggesting the important role of NVU in the progression of cognitive impairment. Other situations in which this coupling is also altered, and which are also related to AD, are hypertension[48] and ischemic stroke[49] (postmortem studies emphasize the important role of vascular pathology in a significant percentage of AD patients).[50]

In this way, aging appears to be an aggravating factor in the development of neurodegenerative diseases such as AD. In addition, and based on the studies reviewed, aging also contributes to an increase in vulnerability to certain conditions such as depression,[51,52] through sustained activation of pro-inflammatory signals (Fig. 1).

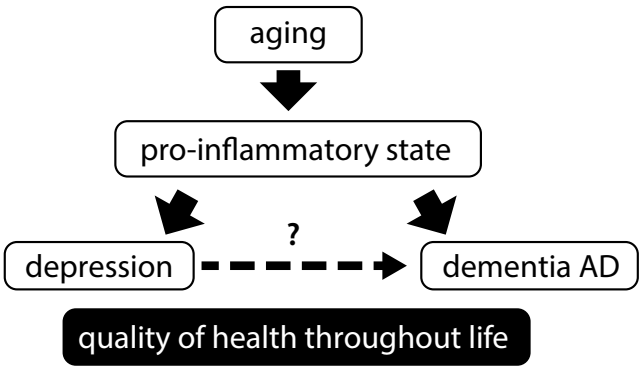

Fig. 1. Scheme linking aging, depression and dementia

AD – Alzheimer's disease.

Given this knowledge, it is necessary to develop new research lines in order to establish the link between depression and dementia; and, based on what is known, to establish strategies of modulation of pro-inflammatory states that could modify the prevalence of neurodegenerative diseases such as dementia.

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