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Alzheimer's disease (AD) and Aging-related tau astrogliopathy (ARTAG)

Abstract

The core pathology of Alzheimer's disease (AD), amyloid plaques and neurofibrillary tangles, has been the target of attention for over 100 years. But how they came into being has always been anonymous. Recently, early diagnosis of AD, especially mild cognitive impairment (MCI), and even subjective cognitive decline (SCD) has become increasingly emphasized to slow down the progression of the disease. Recently, another fresh disease or pathological phenomenon has attracted attention, aging-related tau astrogliopathy (ARTAG), which has been found to be not only related to tauopathy, such as progressive supranuclear palsy (PSP), corticobasal degeneration (CBD) or frontotemporal lobar degeneration (FTLD), but about 50% of AD and geriatric brains have such pathologies. Because astrocytes play an important role as a bridge in the brain, they are not only an important component of the blood- brain barrier (BBB), but also form links with neurons and other glial cells. It is likely to play an important role in the early formation of AD. This review studied the connection between ARTAG and AD, providing a striking sign for earlier prevention of AD.

Keywords: alzheimer's disease (AD), aging-related tau astrogliopathy (ARTAG), astrocyte, tau

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Introduction

Aging is the most common risk factor for Alzheimer's disease (AD), a progressive neurodegenerative disorder. It has been over one hundred years that the main pathological features of the disease were recognized. The documented core pathology of AD is amyloid (Aβ) plaques and neurofibrillary tangles (NFTs). Patients may display pathological features of Aβ plaques for up to or more than a decade prior to any obvious clinical AD diagnosis. In AD, tau proteins are phosphorylated at multiple sites, resulting in the detachment of tau proteins from microtubules and causing the collapse of microtubule structures and the destruction of some cells.[1]

It is well known that on neuropathological examination, pathological changes of AD can be seen in the brains of about 40% of patients with normal cognitive function over the age of 60, and this preclinical stage can also be observed in patients with mild cognitive impairment (MCI).[2,3] It is uncertain whether clinically normal individuals with AD pathology would develop clinical manifestations if they lived longer.[4,5] Recommendations defining the preclinical phase of AD are aimed at early detection for potential therapeutic interventions, so these efforts need to recognize amyloid and tau pathology as well as synaptic deficits as substrates of the clinical presentation of AD.[6] Patients with MCI who have memory deficits do not always meet the pathologic diagnosis of AD at autopsy, even though they are at up to a 10%-15% risk of developing dementia, and sometimes they do not have any recognizable pathologic changes at autopsy.[7,8] Indeed, the clinical diagnostic criteria for AD take care to document dementia and progression of the disease while excluding other possible diseases, with special emphasis on patients with positive amyloid and tau biomarkers.[9] Much of this work is still in the research phase. Most clinicians do not have access to amyloid and tau biomarkers.

a) Aging-related tau astrogliopathy (ARTAG) is highly prevalent in the brains of aging and clinical AD

With the development of neuropathology, the brain pathology of AD has been accepted as a complex pathology. Recently a new announcement, ARTAG has been recognized. It is a common independent tau protein pathology change in patients over 80 years of age and is frequently seen in the brains of elderly AD.[10–12] It is like AD and consists of 3R and 4R isoforms. ARTAG represents astroglial tau pathology, which is distinct from that observed in primary tauopathies, including PSP, CBD, and GGT.

Now that it has become clear that ARTAG is highly prevalent in the brains of the aging and the cases of clinical AD, we cannot help but ask what role do astrocytes assume in the development of AD?

b) The role of astrocytes in the brain

Astrocytes are critical for neuronal function and central nervous system (CNS) health, and astrocyte dysfunction as a primary or secondary event may lead to neurodegeneration. ARTAG is a frontotemporal lobe degeneration with tau (FTLD-tau) type of disease is widely recognized; however, ARTAG is just being discovered. This disorder is a self-described neuropathology seen primarily in individuals over the age of 60. Astrocyte tau aggregates in a spiny or granular/fuzzy pattern and is commonly seen in normal aging as well as in coexistence with a variety of neurodegenerative diseases. However, there are still many unknown factors associated with ARTAG, including etiology, progression, and the nature of any clinical association. Different ARTAG morphologic subtypes may have different etiologies. This is an emerging and exciting area of research that encompasses complex neurobiological and clinic pathologic investigations.

Astrocytes have several important functions in the brain. There are approximately five times as many astrocytes as neurons,[13] and astrocytes are highly organized in regions so that each astrocyte is responsible for a specific area. Within these regions, astrocytes have access to a wide variety of structures, including neurons, myelin sheaths, other glial cells, and blood vessels, and it has been estimated that a single astrocyte can contact hundreds of dendrites and hundreds of thousands of synapses in the human brain.[14,15] Although astrocytes are considered non- excitable because they cannot generate action potentials, they express sodium and potassium channels to provide inward currents[16] and can regulate intracellular calcium, thus it acts as a bridge to convey excitation from neurons in contact with it to the blood vessels, which are vasodilatable or constrictive thus enabling direct electrical and biochemical communication. Astrocytes can also communicate information from the blood to neurons and influence neuronal excitation or inhibition, such as in liver failure, hyperammonemia in the blood, which affects brain function. Through these mechanisms, astrocytes can influence the excitation or inhibition of peripheral neuronal networks and influence neuronal activity.[17] Indeed, astrocyte function is critical for normal synaptic transmission through trafficking and redistribution of neuroactive substances such as glutamate.[18]

c) ARTAG can promote AD formation, which in turn accelerates ARTAG

The multicellular network formed by astrocytes is necessary for the maintenance of normal CNS functions that include, but are not limited to, the regulation of blood flow through the release of molar ions. Senescence is defined as age-related loss of function, and astrocytes are known to express typical markers of senescence with age, including p16 and p21.[19] When senescent astrocytes are co-cultured with neurons, neuronal survival is reduced, and synaptic function is altered.[20] Stress has also been shown to induce premature senescence,[21] suggesting that this phenotype can be reached through various pathways. Increased astrocyte senescence markers have been found in both normal aging and neurodegenerative diseases, such as AD.[22] In vitro studies have shown that tau and amyloid-beta proteins transform healthy astrocytes into astrocytes with a senescent phenotype,[23] and that patients with AD senescence to a greater extent than age-matched patients, suggesting that Astrocytes senesce normally with aging, but their senescence is further increased with AD.[22]

Neuroinflammatory processes may occur in a sustained manner through astrocyte activation, leading to disease progression. Recent findings suggest a close interaction between Tau phosphorylation mechanisms, microtubule disruption, synaptic deficits and AD pathology. Aging and metabolism-related diseases are risk factors for AD. Since sirtuins prolong lifespan by regulating cellular metabolism, studies have reported a significant reduction of SIRT1 in the parietal cortex of AD patients. The findings suggest that the absence of SIRT1 is closely related to the accumulation of Aβ and tau in the cerebral cortex of AD patients.[24–28]

ARTAG is associated with aging, particularly in those over 60 years of age,[29] and is more common in men.[30] Studies have consistently demonstrated the presence of ARTAG in more than one-third of elderly cases, including a large autopsy study of community-dwelling older adults,[31] as well as a few smaller studies reporting the presence of ARTAG in 25-50% of cases with normal neurologic status,[31] and 100% of ARTAG in a small sample of centenarians over the age of 110 years.[32] The prevalence increases with age and comorbidities, including cerebrovascular disease.[30,33]

d) Sites in the brain where ARTAG is most commonly found?

The amygdala has been identified as a preferred site for ARTAG during aging, and in up to 64% of AD cases, AD pathology is associated with subcortical, white matter, and perivascular ARTAG in the limbic region.[30]

The significance of the morphology and location of ARTAG astrocytes is not fully understood, but there are several proposed mechanisms to be further investigated. Cerebral sub-leptomeningeal and perivascular ARTAGs are associated with severe BBB dysfunction due to their proximity to the glia[30] and that blood-brain barrier (BBB) disruption is more common with age.[34] Indeed, connexin-43, which is expressed by astrocytes on the BBB and plays an important role in gap junctions and immune function, was increased 6-fold in ARTAG,[35] and AQP4 was also significantly increased, suggesting BBB dysfunction and local hypo perfusion.[36] Since permeability of the BBB has been suggested as an early mechanism of disease, it has been suggested that ARTAG may be an indicator of early neurodegenerative processes,[36] such as in AD. The relationship between astrocyte senescence and AD has been further studied.

e) ARTAG may be the next target for prevention and treatment of AD

In vitro cell culture studies have shown that astrocyte senescence leads to neurodegeneration. Such senescence due to the accumulation of tau in astrocytes may be the next target for treatment of AD.[23] So far, whether ARTAG correlates with the clinical phenotype is unclear, as the lack of available ante-mortem clinical data makes it difficult to draw meaningful clinicopathologic conclusions.

ARTAG frequently coexists with AD pathology,[30] and to date, most studies assessing the clinical relevance of ARTAG have been conducted in populations with significant AD pathology. Some studies have shown no association between ARTAG and cognitive status,[33,37] whereas others have shown an association between ARTAG and the aphasia syndrome of AD,[38] deterioration in language and visuospatial functioning,[39] and cognitive decline with or without Parkinson's disease.[40] It is also important to consider the regional distribution and contribution of multiple lesions, as a large longitudinal survey of people aged over 90 years showed that cortical ARTAG, hippocampal sclerosis, and cerebrovascular disease were associated with dementia, but limbic and brainstem ARTAG were not.[41] These studies emphasize the importance of considering ARTAG type and location when validating findings and interpreting data.

Conclusion

There is growing evidence that ARTAG coexists with AD pathology. This review examines the link between ARTAG and AD, providing possible directions for early prevention of AD. The article emphasizes the need to unravel the mechanisms associated with aging to facilitate optimal measures to delay the onset of aging-related diseases to prolong lifespan and improve health.

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None

Conflicts of interest

The authors declare no conflict of interest.

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