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REVIEW ARTICLE

Neurovascular dysfunction and vascular amyloid accumulation as early events in Alzheimer's disease

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Abstract

Alzheimer's disease (AD) is clinically characterized by a progressive loss of cognitive functions and short-term memory. AD patients present two distinctive neuropathological lesions: neuritic plaques and neurofibrillary tangles (NFTs), constituted of beta-amyloid peptide (Aβ) and phosphorylated and truncated tau proteins. Aβ deposits around cerebral blood vessels (cerebral amyloid angiopathy, CAA) is a major contributor to vascular dysfunction in AD. Vascular amyloid deposits could be early events in AD due to dysfunction in the neurovascular unit (NVU) and the blood–brain barrier (BBB), deterioration of the gliovascular unit, and/or decrease of cerebral blood flow (CBF). These pathological events can lead to decreased Aβ clearance, facilitate a neuroinflammatory environment as well as synaptic dysfunction and, finally, lead to neurodegeneration. Here, we review the histopathological AD hallmarks and discuss the two-hit vascular hypothesis of AD, emphasizing the role of neurovascular dysfunction as an early factor that favors vascular Aβ aggregation and neurodegeneration. Addtionally, we emphasize that pericyte degeneration is a key and early element in AD that can trigger amyloid vascular accumulation and NVU/BBB dysfunction. Further research is required to better understand the early pathophysiological mechanisms associated with NVU alteration and CAA to generate early biomarkers and timely treatments for AD.

Keywords Alzheimer´s disease · Cerebral amyloid angiopathy · Neuroinflammation · Neurovascular dysfunction · Pericyte degeneration

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Introduction

Diseases associated with aging, such as Alzheimer's disease (AD), are expected to be more prevalent due to increasinging life expectancy worldwide. There are over 50 million people across the globe living with dementia in 2021. With nearly 10 million new cases every year, by 2030, 82 million people are predicted to be affected by AD (WHO 2020). This number will rise to 152 million by 2050 (WHO 2020), up from 900 million in 2015 (Christensen et al. 2009; WHO 2018).. ThisIt is.

Aging includes numerous molecular and cellular changes that result in decreased physical and mental capacities and a higher risk of developing several diseases. Common medical conditions affecting elderly people include hearing and vision loss, cardiovascular and pulmonary problems, osteoarthritis, chronic metabolic disorders, depression, and dementia (Christensen et al. 2009; Wortley et al. 2017). Dementia comprises a heterogeneous group of neurological disorders caused by abnormal changes in the brain that lead to memory loss and impaired cognitive abilities, including perception, language, and behavior (Arvanitakis et al. 2019). AD is the most common cause of dementia (60–80% of all cases) in the elderly population (Bogdanovic et al. 2020; WHO 2020). Vascular dementia (VaD) is the second most common cause of dementia, contributing to approximately 15% of cases (Uwagbai and Kalish 2021). VaD is characterized by blood vessel blockage and microbleeds in the brain. Cognitive impairments are common after an ischemic or hemorrhagic stroke, with the clinical manifestations difficult to determine by neuropsychological tests.

Cerebral amyloid angiopathy (CAA) is a cerebrovascular disorder characterized by beta-amyloid (Aβ) deposition in the walls of cerebral blood vessels and meninges. CAA can cause cerebral microbleeds, intracerebral hemorrhages, cognitive decline, and dementia (Kuhn and Sharman 2020). CAA is strongly age-dependent, commonly affecting people over 60 years of age. Individuals with CAA are initially asymptomatic. When symptomatic, the most common clinical symptom includes lobar hemorrhage (Yamada 2015). One of the most commonly and severely affected brain regions is the occipital lobe, followed by the parietal, frontal, and temporal lobes (Kalaria and Attems 2014; Kalaria 2018). CAA is one of the most prevalent pathologies associated with AD brains and also frequently occurs in VaD and other dementias (Haglund et al. 2004; Kim et al. 2020). CAA's true incidence and prevalence are hard to determine as pathological diagnosis can only be achieved after postmortem tissue examination. In the elderly, CAA incidence has been reported to range from 31 to 79% (Boyle et al. 2015; Xu et al. 2003). More specifically, it has been estimated that CAA is present in around 36%, 46%, and 58%—99% of individuals over 60, 70, and 90 years old, respectively (Attems 2005; Holton et al. 2002; Vinters and Gilbert 1983). The incidence of CAA in AD brains is around 70%–97% (Attems 2005). In other dementias, such as Lewy body disease and progressive supranuclear palsy, CAA is present in 50% and 25% of cases, respectively (Dugger et al. 2014).

On the other hand, accumulating evidence suggests that the vascular damage resulting from amyloid accumulation in the blood vessels precede AD and VaD. Because CAA patients are typically asymptomatic an onset andAD develops many decades before the first symptoms become apparent, the intricacies of disease progression are unclear (Carrillo et al. 2013; Dubois et al. 2014; Vinters and Gilbert 1983). As AD progresses, the patients may experience short-term memory loss, disorientation, impaired judgment, apraxia, aphasia, amnesia, and agnosia (DeTure and Dickson 2019; Perl 2010). In the subsequent sections, we will describe the characteristic histopathological AD hallmarks such as neurofibrillary tangles (NFTs), amyloid plaques, and CAA. Subsequently, we will analyze the vascular amyloid accumulation as well as dysfunction in both the neurovascular unit (NVU) and the blood–brain barrier (BBB) as early pathological events in AD that can result in neurodegeneration.

Neurofibrillary tangles

NFTs constitute of paired helical filaments, which are structurally composed by assembled hyperphosphorylated and truncated tau (Fig. 1A) (Wong et al. 2012). Tau is a microtubule-associated protein, abundant in the central nervous system and primarily associated with axonal microtubules, somatodendritic compartments, and oligodendrocytes (Mietelska-Porowska et al. 2014). It is also expressed in peripheral tissues such as the kidney, lung, testis, heart, intestine, and pancreas (Dugger et al. 2016; Gu et al. 1996). Alternative splicing of the *tau* gene generates six isoforms that range from 352 – 441 aminoacids. These isoforms differ by the presence/absence of one or two inserts in the amino-terminal region and three or four domains in the carboxy-terminal domain (Buée et al. 2000). All isoforms have particular physiological roles, as they express differentially during human development (Buée et al. 2000; Sergeant et al. 2008).

Amyloid plaques

Amyloid plaques are extracellular Aβ deposits in a beta-sheet structure (Figs. 1B and 3) (LaFerla et al. 2007). Aβ is produced through the proteolytic processing of amyloid

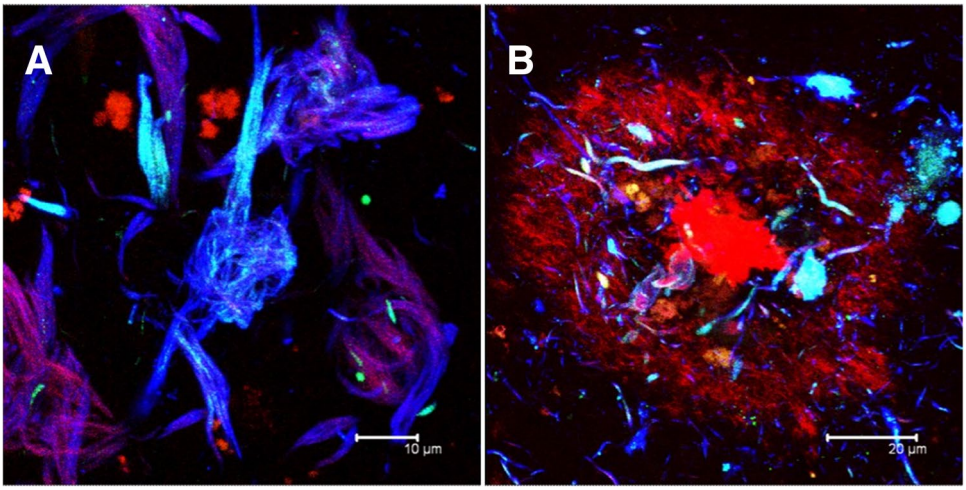

Fig. 1 Histopathological lesions in Alzheimer's disease, evidenced by the antibodies AD2 (phosphorylated tau at 396 and 404, green channel) and p396 (phosphorylated tau at 396, blue channel) and counterstained with thiazine red (TR) (assembly marker with the beta folded conformation, red channel). A) Neurofibrillary tangles of layer II of the entorhinal cortex. B) Neuritic plaque. Fibrillar beta-amyloid deposit is recognized by TR, where the dense core and a more tenuous crown are shown. Dystrophic neurites are evidenced by the AD2 and p396 antibodies. Immunofluorescence and analysis by confocal microscopy. SP8 LEICA confocal Microscopy

precursor protein (APP) by β- and γ- secretases (Haass and Selkoe 1993) via the amyloidogenic pathway (LaFerla et al. 2007). APP is a single-pass transmembranal protein mainly expressed in neurons. The *APP* gene consisting of 18 exons is located on chromosome 21. *APP* gene processing generates eight isoforms, of which three are the most common: the 695, 751, and 770 amino acid forms (O'Brien and Wong 2011). Although the exact physiological role of APP is not fully understood, its expression has been associated with neuronal development, signaling, and survival (Zheng and Koo 2006), as well as regulation of anterograde transport and synaptic formation/transmission (Priller et al. 2006). APP can be processed in two ways: one physiological or non-amyloidogenic and the other pathological or amyloidogenic. In the amyloidogenic pathway (Fig. 2), β-secretase initiates APP proteolysis, releasing a soluble APP portion (APPsβ) and a 99 amino acid fragment (C99). Subsequently, C99 is cleaved by γ-secretase, generating the APP intracellular domain (AICD) and Aβ (40–42 amino acids). Aβ can aggregate to form fibrils that deposit as extracellular plaques (Martins et al. 1991; Sagare et al. 2013b; Wilquet and De Strooper 2004). Aβ is present in other neurological disorders like CAA (Fig. 4 and supplementary material).

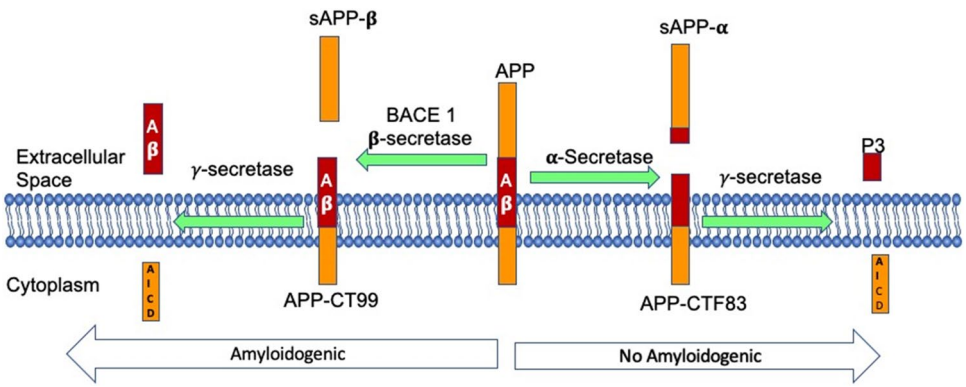

Fig. 2 Amyloid precursor protein (APP) processing. APP is processed by two routes: 1) The amyloidogenic and 2) Non-amyloidogenic pathway. The amyloidogenic pathway is characterized by the proteolytic action of the β-secretase to generate a soluble fragment of sAPP-β. Subsequently, APP-CTF99 (βCTF) is cleaved by γ-secretase, leaving the beta-amyloid peptides Aβ1-40, 1–42. In the non-amyloidogenic pathway, the α-secretase proteolyzes APP to the middle of Aβ to release the fragment sAPP-α. The fragment APP-CTF83 is cleaved by γ-secretase to release the intracellular domain of APP (AICD) and the P3 fragment

Aggregation pattern of Aβ in the brain parenchyma

The aggregation of Aβ fibrils results from a complex self-assembly process that involves different stages of aggregation. Protofibrils and oligomers are deposited within this self-aggregation process, forming mature neuritic plaques (NPs) in AD. These NPs activate an uncontrolled inflammatory process in AD patients' brains (Thal et al. 2015). The presence of Aβ deposits in the brain parenchyma is characterized by diffuse aggregation, evidenced only by the BAM10 antibody that recognizes the Aβ peptide (Fig. 3A). This aggregation increases, being more related to the BAM10 antibody (Fig. 3B). It is important to note that this initial Aβ aggregation is soluble since these first deposits are not evidenced by the thiazine red dye (TR) (Mena et al. 1995). In the first Aβ aggregation (Fig. 3A), dystrophic neurites (DNs) are practically absent. As more Aβ is added, the DNs associated with plaques increase. Within the NP maturation process, the soluble Aβ aggregates (Fig. 3A,B) undergo a conformational change with the β-folded structure, thus generating an affinity for TR. In the evolution and maturation of NPs, the affinity of TR is in practically the entire plaque (Fig. 3C). Subsequently, this fibrillar aggregate presents a higher concentration of the Aβ peptide (Fig. 3D). In the final stage, the plaque core has a greater affinity for TR and is bordered by a diffuse TR stained periphery. It is at this stange that the BAM10 antibody identfies these lesions. However, it is worth mentioning that the observations of our laboratory focused on demonstrating the fibrillar state in the maturation process of NPs in AD cases (Fig. 3C-D).

Vascular Aβ deposition

Aβ deposition in the cerebral blood vessels has been described as mainly associated with the vessel walls, as indicated in the supplementary material included in the supplementary materials is a video of a blood vessel stained by by TR;and a bordering plaqueis evident. In patients with AD, the Aβ deposit in the blood vessel wall effects the internal diameter and thickness of the vessel, which are reduced (Ojo et al. 2021). In one of our confocal microscopy analyses, we were able to observe through optical sections of vessels stained with TR; the presence of fibrillar aggregates in the cytoplasm of endothelial cells was detected (Fig. 4). In Fig. 4, panel A, a small-caliber vessel with a high affinity for TR is observed. Associated with this vessel, a large number of DNs (immunoreactive to phosphorylated tau protein) were observed in the brain parenchyma. Panel B shows the projection of a blood vessel of greater caliber stained by TR. DNs that express to different degrees phosphorylated tau

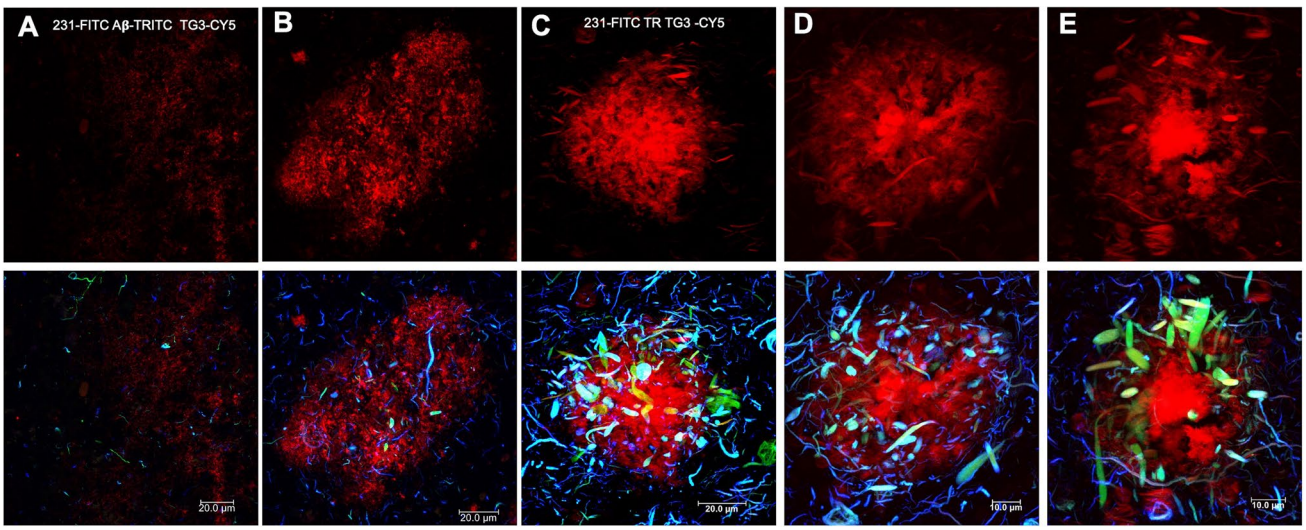

Fig. 3 Aggregation pattern of beta-amyloid (Aβ): soluble fraction (BAM10 antibody red channel) A, B) and fibrillar (TR dye. Red channel) C-E). Image A) corresponds to the initial extracellular Aβ deposits, where a diffuse granule staining is observed, and the presence of dystrophic neurites is poor. B) Neuritic plaque immunoreactive to BAM10. C) Fibrillar neuritic plaque. A core in the center of the plaque begins to be weakly defined. A greater abundance of dystrophic neurites (DN) associated with these dense fibrillar deposits and recognized by TR is observed. D) Neuritic plaque with a more defined core and abundant DNs associated with the plaque was evidenced. E) Mature neuritic plaque, evidenced by TR and with a well -defined dense center is shown. DNs are abundant and with a voluminous morphology. A-E) The antibodies used to evidence tau were 231-FITC and TG3-CY5. A-B) The antibody BAM10-TRITC was used to recognize Aβ1-40 and Aβ1-42. C-E) counterstained with TR. Immunofluorescence and analysis by confocal microscopy. SP8 LEICA confocal Microscopy

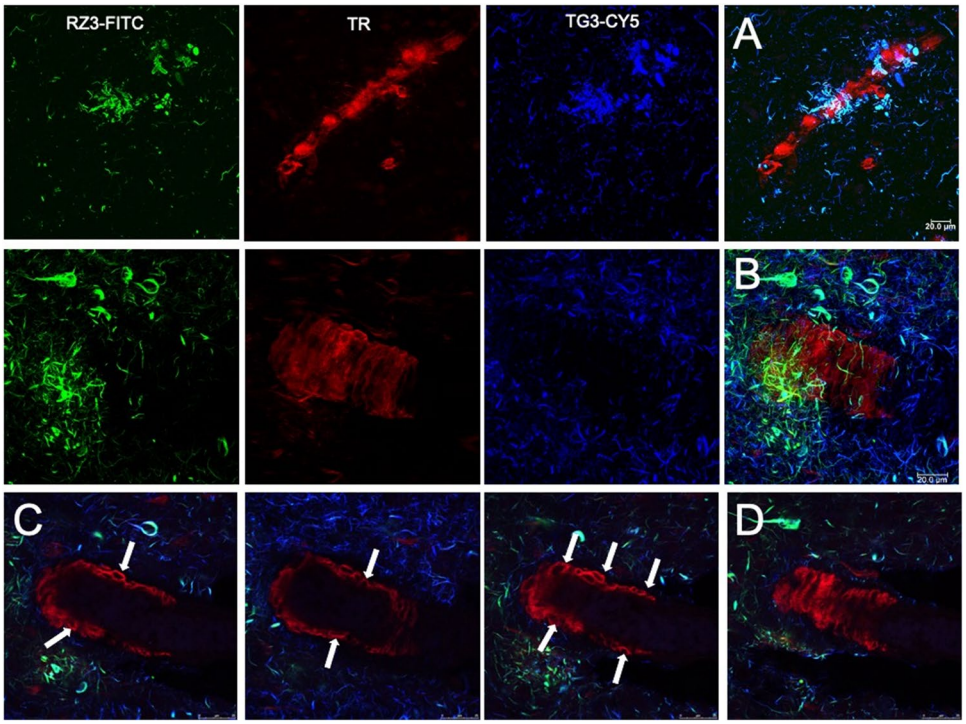

Fig. 4 Beta-amyloid (Aβ) deposits in blood vessels of a case with Alzheimer's disease. A) Aβ deposits are seen diffusely in the periphery of the blood vessels. The presence of phospho tau Thr231 (RZ3) and conformationally modified tau (TG3) is abundantly observed in the vicinity's dystrophic neurites. B) Fibrillar Aβ is observed in the vessel. TR staining within the endothelial cells is observed (arrows). C -D) Optical sections of the vessel shown in panel B). C-D) Aβ in the cytoplasm of the endothelium of the lateral vessel wall is noticed. In the complementary video, Aβ deposits associated with the blood vessel can be observed. These Aβ deposits are also observed in endothelial cells and positive for the BAM10 antibody. Immunofluorescence and analysis by confocal microscopy. SP8 LEICA confocal Microscopy

protein (RZ3) in the green and blue channels (TG3) were observed in the periphery. NFTs with the same immunoreactive characteristics as the tau protein markers were also observed. Panel C shows several optical sections where the endothelial cells that make up the blood vessel wall and the dark spaces corresponding to the nucleus of the endothelial cells are perfectly evident (arrows). This aggregation of intracellular fibrillar Aβ can effect endothelial cell functions. More in-depth studies are essential to elucidate the impact on endothelial cell function, alteration of the BBB, and modifications of tight junction proteins.

According to the two-hit vascular hypothesis of AD, there is a vascular dysfunction (*hit one*) followed by the Aβ accumulation (*hit two*) that promote and precede neurodegeneration (Zlokovic 2011). Corresponding to *hit one*, it is suggested that vascular risk factors, such as hypertension, dyslipidemia, and diabetes, could lead to several pathological events such as i) dysregulation of the NVU / BBB; ii) decreased cerebral blood flow, also known as oligemia); iii) tau hyperphosphorylation; and iv) neuronal dysfunction and subsequent neuronal death (Soto-Rojas et al. 2021b; Zlokovic 2011):. *Hit two* suggests that these pathological events can promote defective Aβ clearance, thereby promoting increased production and aggregation of cerebrovascular Aβ (Mawuenyega et al. 2010; Zlokovic 2011). In this context, it has been shown that among Aβ peptides, the Aβ1-40 peptide is mainly associated with the pathophysiology of CAA, while Aβ1-42 with the AD development (Miyakawa et al. 2000; Morelli et al. 1999; Stakos et al. 2020). It has been recently reported that pyroglutamylated Aβ (pE-Aβ), especially AβN3(pE), could be more neurotoxic and present an enhanced oligomerization compared to full-length Aβ vascular deposits (Aβ1-40 and 1–42) (Nussbaum et al. 2012; Russo et al. 2002; Schilling et al. 2006). Interestingly, a previous study by our group showed that in the brains of AD patients, in addition to Aβ1-40 and 1–42, there were also vascular deposits of N-terminal truncated species, including AβN3(pE) and AβN11(pE) (Soto-Rojas et al. 2021a). This study demonstrated for the first time that insoluble vascular deposits of both full-length and truncated Aβ species were associated with dysfunction of the cellular components that constitute the NVU, as well as with BBB disruption (Soto-Rojas et al. 2021a). Therefore, abnormal vascular Aβ accumulation may trigger the inflammatory response, reactive oxygen species production, increased BBB permeability and lead to loss of integrity of the blood vessels, resulting in brain hemorrhages and cognitive impairment (Askarova et al. 2012; Greenberg et al. 2020; Iadecola and Gottesman 2018; Smith and Greenberg 2009).

On the other side, among the three human APOE gene alleles, APOE4 has been linked as a risk factor for age-related cognitive impairment and vascular cognitive impairment during physiological aging (Liu et al. 2013) and as the strongest genetic risk factor for AD (Harold et al. 2009; Lambert et al. 2009), according genome-wide association study (GWAS). Likewise, a meta-analysis revealed a close association between APOE4 with severe CAA (Rannikmae et al. 2014). Furthermore, the *APOE4* gene has

been correlated with neurovascular dysfunction before cognitive impairment and Aβ accumulation (Zlokovic 2005, 2013) and is closely related to BBB dysfunction in the AD brains (Hultman et al. 2013; Zipser et al. 2007). It may have been suggested that APOE4 may cause microbleeds due to increasing CAA (Liao et al. 2017). Also, APOE4 can inhibit the Aβ clearance and promote dysfunction in the synapse and cerebrovascular functions (Liao et al. 2017).

In both CAA and AD, Aβ deposition results from an imbalance in its generation and clearance via interstitial fluid and perivascular drainage (Brenowitz et al. 2015). However, the brain mechanisms that lead to AD and CAA do not seem to overlap. In AD, deposited Aβ results in loss of neurons and synapses, cortical tissue, and.

hyperphosphorylation of tau. In CAA, these lesions lead to loss of blood vessel integrity, decreased CBF, hemorrhages, ischemia (Greenberg et al. 2020), and subsequently contribute to synaptic dysfunction (Cisternas et al. 2020). However, due to the characteristics of CAA, this is a potential risk factor for the appearance of AD or some type of dementia. CAA diagnosis encompasses clinical, imaging and pathological criteria, also known as "The Boston criteria" (Table 1), which evaluate the probability of developing CAA. However, a definite diagnosis can only be made by postmortem examination of the brain (Kuhn and Sharman 2020; Yamada 2015).

Blood-based biomarkers focused on Aβ are being used to support the diagnosis of AD and CAA. Growing evidence has shown that plasma Aβ concentrations can accurately predict cerebral amyloidosis in AD and mild cognitive impairment (MCI) patients (Vergallo et al. 2019). It has been proposed that a low Aβ42/Aβ40 plasma ratio in brain tissue is associated with higher amyloid cortical burden, steeper accumulation trajectories, greater cognitive decline, or increased risk of developing AD dementia (Doecke et al. 2020).

Recent studies demonstrate that a low Aβ42/Aβ40 plasma ratio is given by early effects of APOE4 on Aβ. Furthermore, it has been suggested that once Aβ fibrillogenesis occurs, APOE4 favors the formation of CAA, reduction in tau clearance, thereby promoting amyloid accumulation, NFTs, and neuroinflammatory processes (Chalmers et al. 2003; Fryer et al. 2005; Iadecola 2017). CAA increases the risk of hypertension, intracerebral hemorrhage, and stroke in patients with a clinical diagnosis of AD, suggesting a mechanistic link between vascular factors and AD (Iadecola and Gottesman 2018). Even though CAA frequency is increasing, the difficulty of achieving an early and more accurate diagnosis in living patients still persists. This, decreases the probability of starting a correct treatment or undergoing a brain biopsy (Kinnecom et al. 2007). Consequently, more in-depth research on this matter is necessary to improve the CAA diagnosis and avoid future complications.

Synaptic dysfunction and neuroinflammation in Alzheimer´s disease

Two critical factors may affect AD pathophysiology: a neuroinflammatory environment and synaptic dysfunction.

In the context of CNS insult, microglia convert to an active phenotype, migrate toward the lesion, and start an innate immune response. This is mediated by receptors including class A scavenger receptor A1, CD36, CD14, α6β1 integrin, CD47, and toll-like receptors (TLR2, TLR4, TLR6, and TLR9) (Heneka et al. 2015). An excessive inflammatory response is produced in response to these changes, contributing to tissue damage and AD pathology (Lyman et al. 2014). Inefficient clearance of Aβ fibrils by microglia (due to its resistance to enzymatic degradation) becomes a major pathogenic pathway in sporadic AD cases (Lee and Landreth 2010). Likewise, astrocytes, whose function is neuroprotection and recovery of injured neural tissue, are accumulated around diffuse amyloid deposits or amyloid plaques. Astrocytes present dense layers of processes as if forming small scars around plaques (perhaps as a neuroprotective barrier function) and, eventually, release cytokines, interleukins, nitric oxide, and other cytotoxic molecules, increasing neuroinflammatory response (Fig. 5) (Heneka et al. 2015; Sofroniew and Vinters 2010).

Table 1 The Boston criteria

Criteria	Method	Features
Definite CCA	Postmortem examination	Lobar, cortical-subcortical hemorrhage, absence of another diagnostic lesion, and severe CAA with vasculopathy
Probable CCA	Utilizing clinical data and pathologic tissue samples	Hemorrhages, pathological evidence of CAA, and absence of any other diagnostic lesion
Probable CCA	Analyzing clinical and imaging data	Multiple hemorrhages in cortical/lobar/subcortical regions, in patients less than 55 years old
Possible CCA	Imaging and clinical data	Single hemorrhages restricted to same regions or superficial siderosis, absence of any other lesion, in patients less than 55 years old

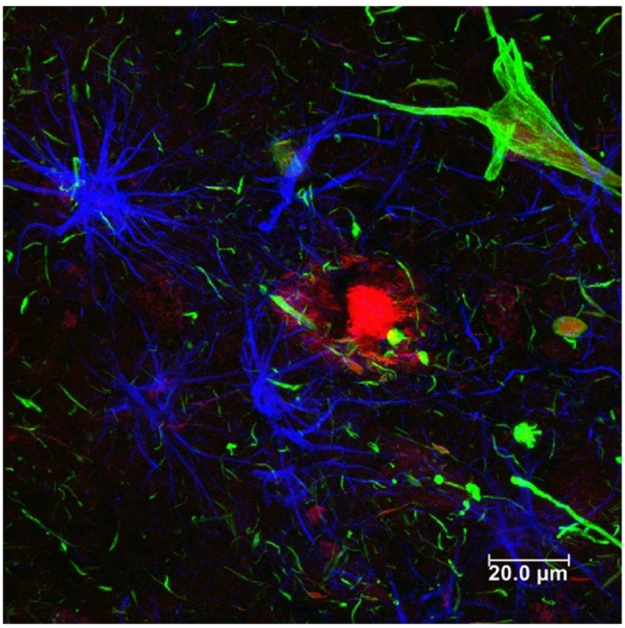

Fig. 5 Glial cells are associated with a mature neuritic plaque (NP). The mature NP is bordered by several glial cells (blue channel) and cytoplasmic processes into the amyloid deposit. Phosphorylated tau (green channel), thiazine red (red channel), and GFAP (blue channel). Immunofluorescence and analysis by confocal microscopy. SP8 LEICA confocal Microscopy

Cerebral microvessels from genetic and sporadic AD patients secrete high amounts of cytokines, which generates an insufficient microglial phagocytic capacity by downregulating Aβ phagocytosis receptors (Hickman et al. 2008), and also contributes to NVU damage (Zlokovic 2011).

Together, these events create a pro-inflammatory environment that could promote amyloid deposition throughout the entire vasculature leading to CAA, tissue damage, and eventually indicate the beginning of all the pathogenic processes of AD. However, these pathological events may be the opposite, which means that vascular amyloid deposits could trigger the neuroinflammation environment, the extracellular Aβ accumulation, and the tau protein phosphorylation, as we will describe in the next section.

On the other hand, synapse loss and dysfunction are present in most neurodegenerative diseases at the very first stages. It is estimated that a 25–35% decrease in synapse density occurs before cognitive and memory deficits occur (Cisternas et al. 2020; Jackson et al. 2019). Although misfolding of the tau protein has been associated with neuronal and synaptic dysfunction (Tracy and Gan 2018), growing evidence suggests that CAA can also lead to these events. The neuropathological mechanism involved could be blocking the clearance of soluble vascular Aβ, which can indirectly affect neurons and synapses (Cisternas et al. 2020; Weller et al. 2009).

NVU dysfunction and vascular amyloid deposits as an early stage in AD

The NVU is an anatomical structure composed of several cells, including neurons, glial cells (microglia, astrocytes, and oligodendrocytes), brain endothelial cells, pericytes, and smooth muscle cells. The NVU promotes an effective CBF, maintains neuronal metabolic activity and a functional BBB (Soto-Rojas et al. 2021b).

Several reports support that NVU dysfunction is an early and key event in the pathophysiology of AD and CAA (Fig. 6), as well as a reliable predictor of cognitive impairment (Boyle et al. 2015; Thal et al. 2003). In addition to NVU dysfunction, the cerebral vascular and perivascular deposits of Aβ have been associated with the deterioration in the gliovascular unit, decrease in the cerebral lymphatic flow, and CBF (Bakker et al. 2016; Kimbrough et al. 2015; Louveau et al. 2017). Together, these pathological events could lead to decreased cerebral Aβ clearance, neuroinflammatory environment, and finally, neurodegeneration.

Likewise, the vascular two-hit hypothesis of AD, stipulates that in an early phase or before neurodegeneration there could be a decrease in CBF as a result of genetic predisposition and vascular risk factors (Fig. 6, step 1) such as smoking, hypertension, dyslipidemia, diabetes, obesity, and metabolic syndrome (Winkler et al. 2014) Concerning genetic predisposition, it has been observed that APOE4 carriers present significant reductions in CBF, even before brain atrophy and Aβ accumulation (Kim et al. 2013; Sheline et al. 2010). This CBF decrease (Fig. 6, step 2) can lead to a state of chronic hypoxia (Fig. 6, step 4) and, in turn, to the following pathological events: a) BBB dysfunction (Fig. 6, step 3); b) infiltration of plasma-derived neurotoxins (including fibrin, thrombin, plasmin, and hemoglobin-derived iron and ROS) and peripheral immune cells (Fig. 6, step 5); c) decrease in ATPase activity, interfering with action potentials and cellular transport; d) reduction in the transport of glucose and other nutrients; e) defective Aβ clearance (Soto-Rojas et al. 2021b; Winkler et al. 2014). Together these pathological events could converge in the tau protein hyperphosphorylation, neuroinflammation (Fig. 6, step 6), Aβ accumulation in the parenchyma and cerebral vasculature, as well as in neuronal dysfunction and degeneration (Fig. 6, step 7).

Interestingly, it has been suggested that one of the causes of chronic hypoxia in the initial AD stages could be the accumulation and clearance failure of the vascular Aβ, as a consequence of pericytes degeneration (Winkler et al. 2014). Pericytes are cells similar to smooth muscle cells and constitute the NVU and the BBB (Zhang et al. 2020). Thier main functions are to regulate angiogenesis,

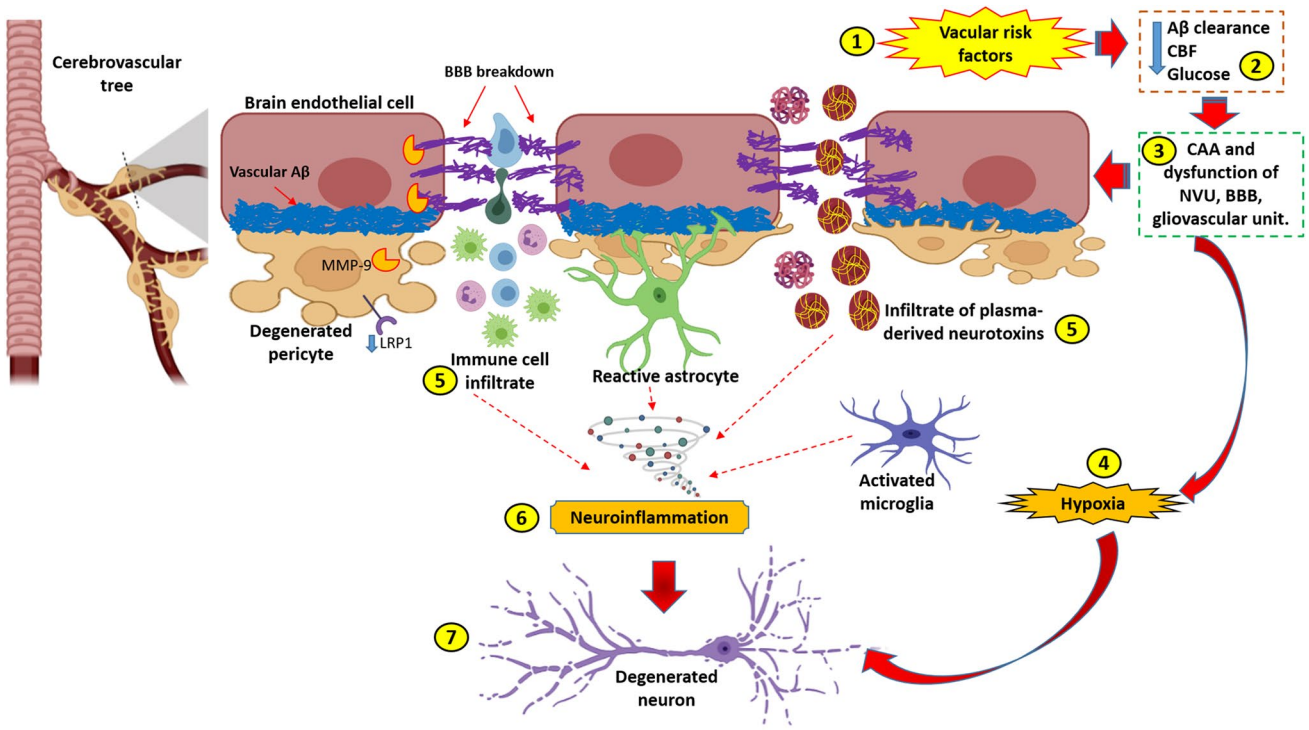

Fig. 6 Cerebral amyloid angiopathy (CAA) and dysfunction of neurovascular (NVU)/ blood–brain barrier (BBB) as an early stage in Alzheimer´s Disease (AD). Vascular risk factors (step 1), could trigger reduction of Aβ clearance, CBF, and glucose (step 2), and subsequently to CAA and dysfunction of NVU, BBB, and gliovascular unit (step 3). Those last events could cause hypoxia (step 4) and infiltration of immune cells and of plasma-derived neurotoxins (step 5) leading to neuroinflammation (step 6), and finally both events to neurodegeneration (step7). Abbreviations: Aβ, beta-amyloid; BBB, blood–brain barrier; CAA, cerebral amyloid angiopathy; CBF, cerebral blood flow; LRP1, LDL receptor-related protein-1; MMP-9, matrix metallopeptidase 9; NVU, neurovascular unit

CBF (through capillary constriction), support permeability of microcirculation and stability to the BBB, and act as immunoregulatory cells (Maier and Pober 2011; Thomas 1999; Zhang et al. 2020). Both animal models and brains of AD patients have shown an apparent and accelerated degeneration of the pericytes in the hippocampus and cortex (Baloyannis and Baloyannis 2012; Farkas and Luiten 2001; Halliday et al. 2016; Ma et al. 2018; Sengillo et al. 2013; Winkler et al. 2012). In addition to BBB dysfunction, multiple studies have associated APOE4 with pericytes degeneration (Bell et al. 2012; Halliday et al. 2016; Hultman et al. 2013; Zipser et al. 2007). Notably, the loss or degeneration of the pericytes has been associated with the following pathophysiological events: 1) BBB breakdown, which increases vascular permeability (Winkler et al. 2014); 2) dysfunction of the scavenger LDL receptor-related protein-1 (LRP-1), a receptor closely associated with Aβ clearance (Sagare et al. 2013a); 3) chronic hypoperfusion that could trigger neuronal damage; and 4) Aβ accumulation, tau pathology and early neuronal loss (Sagare et al. 2013a).

In this context, BBB dysfunction has been suggested as an early biomarker of cognitive impairment (Nation et al. 2019), as well as early AD stages (Montagne et al. 2015; van de Haar et al. 2016). Likewise, a postmortem histopathological study of MCI and AD patients revealed that there was early apoptosis and progressive loss of the pericytes and a vascular decrease of LRP1 in the retina. These events were correlated with early vascular Aβ accumulation, brain pathology, and cognitive impairment (Shi et al. 2020). Therefore, understanding the roles of pericytes in healthy conditions and AD patients, the therapies could be focused on preventing the decrease in CBF, rupture of the BBB, amyloid vascular accumulation and, thus, preserve neuronal functionality.

Conclusion

AD is characterized by NFTs, NPs composed of extracellular Aβ deposits, and CAA. CAA is a cerebrovascular disorder characterized by Aβ deposits in the walls of small to medium cerebral blood vessels, which might induce cognitive impairment and dementia. A growing number of studies suggest that a synaptic dysfunction resulting from vascular Aβ deposition may lead to CAA, a subsequent exacerbated

neuroinflammation, and eventually the early events in the onset of AD. These vascular and genetic risk factors could predispose the NVU dysfunction and generate an incorrect cerebral Aβ clearance, neuroinflammatory environment, and finally, neurodegeneration. Therefore, it is essential to understand the early pathophysiological mechanisms associated with NVU / BBB dysfunction, cerebral amyloid deposits, and pericyte degeneration to establish early biomarkers and timely therapeutic targets for AD and others dementias.

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Data availability Confocal images.

Code availability Software confocal LEICA SP8.

Declarations

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional (UNPHU number: 014–2020) and national research ethics committee (CONABIOS number: 025–2020) and with the 1964 Helsinki declaration. Informed consent was obtained from all individual participants included in the study.

Conflict of interest The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Disclaimer The opinions presented here are those of the authors. The information in these materials is not a formal dissemination of information by the US FDA and does not represent agency position or policy.

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