Interaction between AD and Cerebral Small Vessel Disease

Subjects: Neuroimaging

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Alzheimer's disease (AD) is characterized by the presence of β-amyloid (Aβ) and tau, and subcortical vascular cognitive impairment (SVCI) is characterized by cerebral small vessel disease (CSVD). They are the most common causes of cognitive impairment in the elderly population. Concurrent CSVD burden is more commonly observed in AD-type dementia than in other neurodegenerative diseases. The developments in Aβ and tau positron emission tomography (PET) have enabled the investigation of the relationship between AD biomarkers and CSVD in vivo.

Keywords: subcortical vascular cognitive impairment ; Alzheimer's disease ; ß-Amyloid ; tau ; cerebral small vessel disease ; positron emission tomography

1. Introduction

Dementia is a progressive and deteriorative syndrome that affects memory and other cognitive domains, which interferes with a daily living [1]. Alzheimer's disease (AD) and vascular dementia (VaD) are the two most common causes of dementia in the elderly [2]. AD is characterized by senile plaques formed by β-amyloid (Aβ) and neurofibrillary tangles (NFTs) formed by hyperphosphorylated tau. These changes, along with loss of neurons, contribute to the symptoms of dementia [3]. Based on these core AD pathological features, including Aβ [A], tau [T], and neurodegeneration [N] biomarkers, the National Institute on Aging—Alzheimer's Association (NIA-AA) proposed the AT(N) classification system [4]. A and T biomarkers are specific for the Aβ plaques and tau NFTs that constitute the hallmark neuropathologic signs of AD, respectively, while biomarkers of (N) (such as atrophy on magnetic resonance imaging, MRI) are not disease specific [4][5]. Brain atrophy is indicative of the considerable loss of neurons and synapses in the cerebral cortex [6]. Although the assessment of atrophy lacks specificity to determine whether the cause is cell loss or synaptic loss, cortical thickness is widely used as a surrogate marker for neuronal loss [7][8]. The NIA-AA research framework defines AD biologically based on neuropathologic change or biomarkers and considers cognitive impairment a symptom or sign of the disease rather than the definition of the disease [4].

Further, Alzheimer's disease is frequently associated with other aging-related disorders such as cerebrovascular disease, Lewy body disease, transactive response DNA-binding protein of 43 kDa (TDP-43) proteinopathies, and argyrophilic grain disease [6]. AD pathology mixed with vascular disease is more frequent in the elderly population (also known as mixed pathology in dementia or mixed dementia) [9]. Vascular diseases include arteriolosclerosis, cerebral amyloid angiopathy (CAA), atherosclerosis, macroinfarcts, and microinfarcts [10]. In fact, previous studies have shown that AD combined with vascular disease is the most prevalent mixed pathology [9][11][12].

Vascular dementia is caused by ischemic or hemorrhagic brain lesions that are characterized by numerous clinical syndromes [13]. The most common forms of VaD in the elderly are subcortical vascular dementia (SVaD), strategic infarct dementia, and multi-infarct dementia [14]. VaD is generally known to be the second most common cause of dementia in later life among Caucasian populations, although it may be the most common cause in East Asia [15][16][17]. SVaD, one of the main forms of VaD, is characterized by extensive cerebral small vessel disease (CSVD), including white matter hyperintensities (WMHs) and multiple lacunes [18]. Vascular risk factors, such as age, hypertension, and diabetes mellitus, contribute to the development of CSVD MRI markers. These markers gradually form deposits in subcortical regions over several decades, eventually resulting in SVaD [19]. Thus, SVaD shows a progression pattern similar to that of AD, which reveals an insidious onset and gradual progression; however, it is dissimilar to that of multi-infarct dementia (another major form of vascular dementia). From this perspective, there is a prodromal state of SVaD, referred to as subcortical vascular mild cognitive impairment (svMCI). Subcortical vascular cognitive impairment (SVCI), which incorporates SVaD and svMCI, refers to cognitive impairment caused by subcortical vascular lesions [20][21][22][23][24].

2. Frequency of AD Imaging Markers in SVCI

AD markers are more commonly observed in patients with SVCI than in cognitively unimpaired individuals. Specifically, in svMCI patients, the frequencies of Aβ positivity have been reported to be about 30% [25][26][27]. SVaD patients tend to display more frequent Aβ positivity than svMCI patients, ranging from 30% to 53% [25][28][29]. In terms of the tau marker, it has been shown that tau positivity is 70% (14/20) in Aβ (+) ADCI patients, 25.9% (7/27) in Aβ (+) SVCI patients, and 6.1% (2/33) in Aβ (−) SVCI patients. [30].

3. Correlation between AD and CSVD Imaging Markers

Molecular imaging studies have enabled people to investigate the relationship between AD markers and CSVD MRI markers throughout the whole brain. There is increasing evidence from these studies showing that AD marker uptake is correlated with WMH volume, which is a characteristic MRI marker of CSVD. This has been observed prominently in the posterior regions of the brain. In the previous study of 53 SVCI patients, a relationship between Aβ uptake and WMH volume was observed in *APOE4* non-carriers [31]. WMH volume is correlated with Aβ uptake in the posterior cerebral regions. Another study using clustering analyses classified SVCI patients and AD patients into the Aβ occipital-predominant and Aβ occipital-sparing groups. The frequency of the occipital-predominant group has been shown to be higher in SVCI patients (62.2%) than in AD patients (37.8%) [32]. Furthermore, the Aβ spreading pattern in patients with SVCI is quite different from in patients with ADCI. Specifically, the Aβ spreading pattern of patients with SVCI demonstrates that Aβ accumulates in the occipital area before the temporal and frontal regions, whereas in patients with ADCI, the parietal and fronto-temporal regions precede the occipital region. [32][33][34][35][36]. The predominant Aβ deposition in the occipital region, mainly observed in patients with SVCI, may be related to the distribution pattern of CAA or ischemic vulnerability of the posterior circulation [31]. CAA is primarily found in the occipital region [31][37]. Moreover, ischemic injury and dysfunction of the endothelial layer may lead to disruption of the blood–brain barrier (BBB), which in turn leads to the deposition of Aβ. Since the vertebrobasilar system, which is responsible for the posterior circulation, may be vulnerable to ischemia, SVCI patients may show Aβ deposition primarily in the posterior region [31].

In terms of the relationship between CSVD and tau, previous studies have suggested that ischemia might increase tau burdens regardless of the amyloid pathway [38]. Animal studies have also shown an association between increased cerebrovascular pathology and tau formation [39]. In vivo imaging studies have shown that CSVD burden may be associated with higher tau accumulation in the inferior temporal regions regardless of Aβ positivity [40]. Furthermore, in terms of tau spreading order, patients with SVCI are quite different from patients with ADCI. Unlike in ADCI, tau accumulates earlier in the fusiform gyrus and inferior temporal gyrus than in the parahippocampal cortex in SVCI [40][41].

4. Potential Distinct Pathobiology of AD Markers in SVCI

Considering that SVCI and ADCI patients show different spreading patterns of AD imaging markers, there may be differences in the potential pathobiology of AD biomarkers between SVCI and ADCI patients. In patients with SVCI, vascular risk factors may lead to Aβ deposition. Several cohort studies have reported an association between vascular risk factors and Aβ deposition [42][43][44][45][46][47]. This Aβ deposition is increased by impaired Aβ clearance via a deficit in perivascular drainage of Aβ and breakdown of the BBB [48][49]. BBB breakdown causes faulty transport of Aβ through reduced levels of low-density lipoprotein receptor-related protein 1 (LRP1) and increased levels of receptor for advanced glycation end products (RAGE). These changes eventually lead to impaired clearance of toxic Aβ species [50][51]. Furthermore, Aβ accelerates the tau hyperphosphorylation by mediating the activation of protein kinases, including cyclin-dependent kinase 5 (CDK-5) and glycogen synthase kinase 3β (GSK-3β) [52][53]. In addition, Aβ induces the activation of caspase-3 and calpain-1 and the cleavage of tau, generating neurotoxic tau fragments [54][55]. The link between Aβ and tau aggregation may involve microglial activation [56]. Soluble Aβ oligomers are known to activate microglial cells [57]. Mouse studies on transgenic AD have revealed that the microglial activation precedes tau aggregation [58] and facilitates tau hyperphosphorylation through cytokine release with subsequent NFT formation [59]. There are two potential mechanisms that may explain how vascular risk factors induce tau accumulation. One hypothesis is that ischemia may activate CDK-5 and GSK-3β, resulting in tau phosphorylation [60]. Activation of CDK-5 occurs when ischemia inhibits the pumping of calcium ions out of cells and raises intracellular calcium levels [61][62]. GSK-3β is activated by ischemia through decreased activity of the phosphatidylinositol 3-kinase/Akt pathway [63][64]. Moreover, vascular risk factors and the accumulation of Aβ plaques lead to oxidative stress [65][66][67]. Oxidative stress may also be caused by several mechanisms, such as mitochondrial dysfunction or inflammatory responses [67]. It may manifest as damage to synapses and changes in Ca^{2+} homeostasis, resulting in an apoptotic cascade and neurotoxicity [67].

Notably, there are distinct effects of *APOE* genotyping on Aβ deposition between patients with SVCI and ADCI. Specifically, apolipoprotein E4 (*APOE4*) is a risk factor for Aβ positivity in patients with ADCI and SVCI. Apolipoprotein E2 (*APOE2*) is a protective factor in ADCI (OR = 0.43); however, it is a risk factor in SVCI (OR = 2.26) [68]. Thus, *APOE2* might accelerate apolipoprotein E leakage in the vessel walls of patients with SVCI, which in turn leads to impaired vascular drainage of Aβ. This impaired drainage eventually results in increased Aβ burdens in the brain parenchyma [68]. Alternatively, *APOE2* may contribute to the development of CAA, which in turn leads to increased CSVD [68].

5. Clinical Effects of AD and CSVD Markers in SVCI Patients

There has been some debate related to the clinical effects of Aβ and CSVD imaging markers. In fact, among patients with extensive WMHs, some tend to show severe dementia symptoms, while others have no symptoms. In this regard, the previous studies investigated which imaging markers might affect the clinical features of SVCI and found that AD biomarkers and CSVD independently affect cognition, abnormal behavior, and gait disturbances [26][29][40][69][70][71][72]. A cross-sectional study has reported that Aβ uptake is only associated with memory dysfunction, whereas CSVD burden is associated with memory, visuospatial, and frontal executive functions [70]. Longitudinal cohort studies have also shown that Aβ positivity is associated with faster cognitive decline in patients with SVaD [29] and higher conversion to dementia in patients with svMCI [69]. In terms of abnormal behavior, Aβ predicts the signs of delusions and irritability, while CSVD burdens are associated with other behavioral symptoms, such as apathy and depression [73]. In addition, periventricular WMHs are the most important predictor of gait disturbances [74].

SVCI patients show distinct brain structural and cognitive trajectories based on AT (Aβ/tau) biomarker profiles [30]. A previous study showed that patients in the A+T+ group predicted a more rapid decline in structural and cognitive trajectories than those in the A+T− group, followed by those in the A−T− group [30]. Moreover, AD markers and CSVD burden have a synergistic effect on cognitive decline. In a cross-sectional study, significant interactions between WMHs and Aβ uptake were apparent in visuospatial function, suggesting that CSVD and Aβ synergistically affect cognitive impairment [26]. A longitudinal study comparing patients with SVCI and ADCI who had similar tau levels has shown that as Aβ turns positive, SVCI shows a steeper cognitive decline compared to the ADCI group [75]. In addition, as tau levels increase, the SVCI group shows a steeper cognitive decline than the ADCI group [75]. These findings indicate that there are interactive effects between AD markers and CSVD on cognitive decline.

Furthermore, Aβ and CSVD affect specific downstream imaging markers, such as network changes and brain atrophy in specific regions, which in turn lead to the development of these corresponding clinical outcomes [69][71][76]. Specifically, Aβ uptake is associated with cortical thinning in the medial temporal regions including hippocampal changes, which in turn leads to memory dysfunction. In contrast, CSVD burdens are primarily associated with frontal thinning [77] and white matter network disruption [71], which in turn leads to frontal dysfunction. In addition, a three-year longitudinal study has shown that time-varying Aβ and CSVD affects the temporoparietal and frontal thinning, respectively, which in turn contributes to the corresponding cognitive decline [69]. Another cross-sectional study has demonstrated that Aβ positivity and CSVD severity are independently associated with higher tau uptake in the medial and inferior temporal regions, respectively [40]. Moreover, increased tau uptake can mediate the relationship between Aβ and CSVD uptake and cognitive impairment, indicating that tau is another important common downstream marker of Aβ and CSVD burdens.

6. Hemorrhagic Markers in Cerebral Amyloid Angiopathy (CAA) and the Clinical Effects

CAA is characterized by Aβ deposition in the small arteries of the meninges and cortex, which causes vascular dysfunction and brain injury [78]. CAA is clinically and radiologically characterized by lobar intracerebral hemorrhage (ICH), strictly lobar cerebral microbleeds (CMBs) and cortical superficial siderosis (CSS) [79]. CAA is generally related to Aβ parenchymal aggregates, such as neuritic and diffuse plaques, although it can also occur pathologically without evident AD neuropathological changes [80].

Generally, the anatomical location of CMBs reflects their underlying etiology. Specifically, deep CMBs are presumed to be due to hypertensive CSVD, whereas lobar CMBs may reflect CAA [81]. In a cross-sectional study, consistent with previous studies, Aβ uptake has been shown to be associated with lobar CMBs [23]. CSVD is also associated with lobar CMBs as well as deep CMBs [23]. Aβ uptake and CSVD synergistically affect the development of lobar CMB [23]. Furthermore, a longitudinal study demonstrated that longitudinal measures of Aβ uptake and lacunes synergistically affect the development of lobar CMBs [44]. According to Thal's CAA pathologic stage, CAA pathology extends sequentially from leptomeningeal and cortical vessels to cerebellar vessels and eventually to the striatum and brainstem vessels [82]. Patients with both cerebellar and lobar CMBs are more likely to present with CAA features, whereas deep CMBs,

regardless of the presence of both lobar and cerebellar CMBs, are more likely to represent underlying hypertensive angiopathy than CAA features [83]. Interestingly, restricted superficial cerebellar CMBs refer to CAA imaging markers, whereas the involvement of the cerebellar dentate nucleus might be equivalent to deep CMB [83].

The previous study showed that the frequency of *APOE4* was higher in Aβ (+) CAA than in Aβ (−) CAA, whereas *APOE2* was associated with overt hemorrhagic markers of CAA, such as lobar ICH and CSS [84]. These findings are consistent with other studies showing that *APOE4* is related to the deposition of Aβ burdens [85][86], and *APOE 2* is related to the breakdown of blood vessel walls [87]. In addition, the number of lobar CMB and the presence of CSS can predict Aβ (+), whereas ischemic CSVD markers can predict Aβ (−) [84].

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