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The Blood-Brain Barrier and Cerebrovascular Pathology in Alzheimer's Disease

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ABSTRACT: **The pathology of Alzheimer's disease (AD) is not limited to amyloid plaques and neurofihrillary tangles. Recent evidence suggests that more than 30% of AD cases exhibit cerebrovascular pathology, which involves the cellular elements that represent the blood-brain barrier. Certain vascular lesions such as microvascular degeneration affecting the cerebral endothelium, cerebral amyloid angiopathy and periventricular white matter lesions are evident in virtually all cases of AD. Furthermore, clinical studies have demonstrated blood-brain barrier dysfunction in AD patients who exhibit peripheral vascular abnormalities such as hypertension, cardiovascular disease and diabetes. Whether these vascular lesions along with perivascular denervation are coincidental or causal in the pathogenetic processes of AD remains to be defined. In this chapter, I review biochemical and morphological evidence in context with the variable but distinct cerebrovascular pathology described in AD. I also consider genetic influences such as apolipoprotein E in relation to cerebrovascular lesions that may shed light on the pathophysiology of the cerebral vasculature. The compelling vascular pathology associated with AD suggests that transient and focal breach of the blood-brain barrier occurs in late onset AD and may involve an interaction of several factors, which include perivascular mediators as well as peripheral circulation derived factors that perturb the endothelium. These vascular abnormalities are likely to worsen cognitive disability in AD.**

INTRODUCTION

Alzheimer's disease (AD) is the most common cause of dementia in the elderly. The underlying processes that lead to dementia in this disorder are not understood but late onset AD is very likely acquired by the interaction of both hereditary and environmental factors. AD is pathologically defined by the presence of senile plaques and neurofibrillary tangles. The presence of other pathologies including vascular lesions is usually ignored or regarded as insignificant. Brains of subjects with AD often bear cerebrovascular pathology consisting of degenerative microangiopathy, cerebral amyloid angiopathy (CAA), cerebral infarcts and intracerebral hemorrhages. "Pure AD" is typically considered as plaque and tangle pathology, but does

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TABLE 1. **The variety and percentage of distribution of cerebrovascular lesions** in AD[a]

Vascular Lesions	Specific feature(s) or markers involved
Degeneration of cerebral microvessels (100%)	Loss of endothelial markers, CD34, GLUT1 Thickening of basement membrane, collagen IV
Localization of serum proteins (80%)	P component, complement, ApoE in AD lesions
Presence of cerebral amyloid angiopathy (CAA) (98%)	Aβ peptides, Cystatin C protein, inflammatory markers
Presence of lobar and intracerebral hemorrhages (10%)	CAA-related intracerebral hemorrhages
Large cerebral infarcts and cortical micro-infarcts (36%)	Variably distributed and sized
Diffuse white matter disease (35%)	Periventricular and deep white matter lesions

[a]Data (%) derived from series published previously (Premkumar et al., 1996)[5] and unpublished results (Kalaria et *al.*) on 300 cases.

such clear-cut pathology exist in the elderly? Interestingly, even Alzheimer in his original report' describing the pathology in the brain of Auguste D had written that besides "one or several fibrils in otherwise normal cells", and "numerous small miliary foci . . . and .. storage of peculiar material in the cortex, one sees endothelial proliferation and also occasionally neovascularisation." Is it likely that Alzheimer described degeneration of the cortical microvessels as the seat of the blood-brain barrier (BBB) evident by modern methods rather than angiogenesis or was it that Auguste D had suffered cerebral infarcts and the "endothelial proliferation" was a consequence of the infarction? Both of these possibilities and the fact that there was moderate athersosclerosis in the basal brain arteries of Auguste D provide a basis for thinking that vascular pathology was also evident in the original case of Alzheimer, which we use today to define AD. Nevertheless, it remains to be known whether the brain vascular pathology found in AD is coincident with the disease process or whether peripheral vascular abnormalities including those that alter cerebral perfusion are causal factors in AD. Indeed, BBB abnormalities may also be caused by vascular factors linked to cardiovascular disease. These include hypertension, atria1 fibrillation, and aortic and carotid atherosclerosis that may decrease cerebral perfusion and increase risk of stroke or transient ischemic attacks in AD

THE BLOOD-BRAIN BARRIER AND CEREBROVASCULAR PATHOLOGY IN AD

At least a third of the patients with AD may exhibit a variety of brain vascular lesions (TABLE 1). These are often ignored as coincidental findings at autopsy. The cerebrovascular pathology of AD encompasses a variety of lesions including changes in endothelial and vascular smooth muscle cells, macroscopic and micro-infarction, hemorrhage and white matter changes related to small vessel disease.[2,3] In addition, amyloid β protein is involved in the degeneration of both the larger perforating arterial vessels as well as the cerebral capillaries that represent the BBB. While these microvascular changes imply that the integrity of the cerebral vasculature is impaired in AD as a result of the progressive cortical pathology, they also entail the long-term influence of peripheral vascular factors. These include long-standing hypertension, atria1 fibrillation, coronary or carotid artery disease, and diabetes: conditions that may promote cerebral hypoperfusion during aging. Whether, vascular and neurodegenerative pathologies are additive in the way in which they influence clinical presentation or progression of dementia[4,5] is the subject of some debate. It also remains to be known whether each of these lesions are simple manifestations of brain aging or intrinsic to the pathogenesis of AD and the cause of dementia.[6,7]

BBB-ASSOCIATED PROTEINS IN AD

Selective biochemical changes, not necessarily related to aging, are evident in the cerebral microvasculature of AD and Down's syndrome subjects (TABLE 2). We previously reported impairment of the BBB-associated glucose transporter (GLUT1) in isolated brain microvessels and in cortical membrane fractions obtained from subjects with AD and age-matched controls.[8] The rationale for this study was based on evidence from positron emission tomography studies showing that in AD the brain has a low metabolic rate for glucose, especially in those regions which are most affected pathologically.[9,10] This may implicate impaired GLUT1 in AD although under normal conditions, glucose transport across the BBB is not rate limiting. However, under pathophysiological conditions such as in seizures and perhaps aging, transport of glucose can become a limiting factor for brain oxidative metabolism. Using the binding properties of [^{3}H]cytochalasin B and immunochemical methods,[8] we also confirmed that many collagen IV positive capillaries were absent in GLUT1 immunoreactivity.[11,12] These findings, along with unchanged binding in the cerebellum and putamen indicated somewhat selective abnormality of the GLUT1 in AD, particularly at the BBB. The reduction of the GLUT1 protein in AD subjects could not be attributed to either aging or postmortem factors[8] and suggested abnormalities in the post-translational modification of the protein. Whether amyloid β deposition in cerebral microvessels in AD impairs synthesis or increases degradation of the GLUT1 protein remains to be shown. Our recent preliminary studies in microvessels suggest that GLUT1 mRNA is also decreased in AD. It is more likely that the decreased GLUT1 in AD is related to the morphological alterations in the cerebral endothelium as described above. Since the expression of GLUT1 is limited to the endothelium-bearing tight junctions[13] these results imply increased permeability of the BBB with consequent down regulation of the GLUT1. Our observations were recently corroborated by positron emission tomography studies showing that the transport of glucose (kinetic parameter k_1) into brains of AD subjects is diminished.[14] It is also of interest that Marcus et al.[15] observed decreased uptake of 2-deoxy-D-glucose uptake implying reduced hexokinase activity in isolated cerebral microvessels of AD subjects. This decreased activity directly relates to our reduced GLUT1 findings and suggests that microvessels deprived of glucose may be using other sources of metabolic fuel.

Further studies were pursued to determine if different proteins associated with BBB transport functions were affected in AD.[13] We assessed γ-glutamyl transferase along with other enzymes known to be associated with the endothelium in isolated

TABLE 2. Features of the BBB and markers in AD[a]

Cellular Feature	Specific Markers Found to be Affected
Cerebral endothelium	Loss of glucose transporter, Na^+/K^+ ATPase
Endothelial membranes/ microvascular endfeet	Moderate loss of AlkP, GGT, AChE, BChE
Basement membrane	Increase in collagen proteins and perlecans
Endothelial mitochondria	Loss of carnitine aceytltransferase
Cerebral endothelium (oxidative stress)	Increased glucose-6-phosphatase
Vascular smooth muscle cells	Loss of alpha actin and accumulation of amyloid β

'Data derived from series published previously (Kalaria, 1992)[2] and unpublished results (Kalaria et *al.*) on 300 cases.

ABBREVIATIONS: AChE, acetylcholinesterase; AlkP, alkaline phosphatase; BuChE, butrylcholinesterase; GGT, gamma glutamyl transpeptidase.

brain microvessels (TABLE 2). There were no statistically significant changes in the activities of plasma membrane-associated enzymes including angiotensin-converting enzyme and alkaline phosphatase between AD and age-matched controls, but the activities were consistently lower in vascular fractions from AD subjects. Previous morphological evidence has shown that the cerebral endothelium is enriched in mitochondria[16] and that cerebral microvessels of a number of species are enriched in monoamine oxidase localized to the outer membrane of mitochondria. We measured monoamine oxidase activities in cerebral microvessels from AD subjects and age-matched controls. We found no significant changes in total monoamine oxidase in microvessels although carnitine acetyltransferase activity, an enzyme also localized to the mitochondria but not necessarily restricted to them, was significantly reduced in microvessels from AD subjects. Cholinesterases previously known to be localized in the cerebral microvasculature were also assessed. We found that activities of both acetylcholinesterase and butrylcholinesterase were significantly reduced in cerebral microvessels from AD subjects compared to age-matched controls (TABLE 2). These differential alterations cannot be readily explained but may relate to the deposition of amyloid β in the vasculature since cholinesterases interact with amyloid and associated proteins. However, these findings support the notion that selective or focal BBB changes may occur in the neocortex in AD.

Previous studies have suggested that the cerebral microvasculature is immunologically activated in AD. Cell adhesion molecules such as the intercellular adhesion molecule (ICAM-1) induced during inflammatory processes are upregulated in response with amyloidotic pathology[17–19] and are increased in brain capillaries and perivascular cells in AD subjects.[20] We reported that ICAM-1 immunoreactivity within capillary profiles associated with amyloid β plaques and soluble ICAM-1 determined by immunoassay were significantly increased in frontal and temporal cortex of AD subjects compared to age-matched controls.[21] Similarly, the vascular cellular adhesion molecule was increased in both capillaries and neocortical extracts from brains of AD subjects (Kalaria et al., unpublished observations). These findings support the activation of the cerebral endothelium that may lead to increased permeability to circulating cells and therefore alterations in the BBB.

THE BBB AND SERUM PROTEINS IN AD LESIONS

The localization of proteins originating in or extravasated from the circulation is considered an index of BBB breakdown and provide support for microvascular abnormalities in AD. This is particularly important if the factors or proteins derived from the circulation are not produced by the brain cellular elements. Both amyloid β deposits and neurofibrillary pathology in AD acquire several specific proteins whose role is unclear in these lesions. One of the first studies[22] reported positive albumin and IgG immunoreactivity in amyloid plaques and tangles contained in brains from AD patients. More recent studies showed that these diffuse deposits of serum proteins were also evident in aging controls and concluded that such localization was not proof of BBB breakdown in AD.[23] However, antemortem factors may explain the lack of clear differences between aging controls and AD subjects.[6,13] To elucidate this issue of BBB permeability in AD, we showed that circulating proteins that particularly localize with amyloidotic lesions may accumulate over a protracted period during focal and transient leaks in the BBB. The abundance of pentraxins such as P component and C-reactive protein immunoreactivities in cerebral lesions in AD but lack of their mRNA in brain suggested that these relatively large circulation-derived proteins and possibly others, as yet uncharacterized, originate from the liver during the pathogenetic process. The specific binding of P component and amyloid β could explain the localization of some but not the more common serum proteins such as albumin and immunoglobulins in cerebral amyloid β deposits.[24] It is feasible that proteins, which do not characteristically interact with amyloid β, would either be sequestered or readily removed via the brain drainage systems. Nonetheless, these observations provide indirect evidence for an immunological link between the brain parenchyma and the circulation.

While the BBB is accepted to be unconditionally impaired in vascular dementia, it has been proposed that BBB dysfunction is involved in the aetiology and pathogenesis of AD.[13,25,26] The cerebrospinal fluid (CSF):serum albumin ratio is a generally accepted method of assessing BBB function in living subjects. Increased CSF:serum ratios have been reported in AD patients, particularly in those exhibiting peripheral vascular disease,[13,27,28] but are not apparent in others.[29,30] However, Skoog et *al.*[31] reported that 85-year-olds with AD had a higher CSF:serum albumin ratio than nondemented individuals, and that there were indications of a disturbed BBB function even before onset of the disease in a population-based study. It is noteworthy that chronic hypertension, considered a strong risk factor for AD, is another factor which could cause increased vascular permeability with protein extravasation. A relative BBB dysfunction may increase the possibility that substances from serum penetrate the BBB and reach the brain, where they may interact with neurons, perhaps initiating a cascade with amyloid accumulation and Alzheimer encephalopathy.

ENDOTHELIAL DEGENERATION AND BASEMENT MEMBRANE PATHOLOGY

In addition to CAA and associated intracerebral hemorrhage, AD subjects exhibit profound changes in cerebral microvessels often independent of amyloid deposition.[2] Several elegant studies using morphological and biochemical methods have

demonstrated abnormalities in various cellular elements of cerebral microvessels or capillaries that relate to **BBB** function. These include degeneration of vascular smooth muscle cells,[32,33] focal constrictions and degenerative changes in smooth muscle cells,[34] degeneration and focal necrotic changes of the endothelium," vascular basement membrane alterations accompanied by accumulation of collagen,[26,35] loss of perivascular nerve plexus,[36] decreased mitochondrial content and increased pinocytotic vesicles,[37] and loss of tight junctions.[16] Using differential immunocytochenical methods, we[11,38] have further defined the convolutional abnormalities and "collapsed" or attenuated capillaries in cortical lobes of AD subjects.[39] The differential labeling was characterized by selective degeneration of the endothelium in capillary profiles, which yet retained their basement lamina, as evidenced by markers such as collagen IV. This phenomenon was observed in virtually all amyloid B-laden cortical lobes of more than 95% of the AD as well as Down's syndrome subjects.[11] Both the length and number of degenerated microvessel profiles were significantly correlated with neocortical amyloid β deposits, but there was no apparent relationship between the degenerated microvessels and neurofibrillary tangles or existing pyramidal neurons. This vascular phenomenon along with a profound microangiopathy is concomitant with amyloid β deposition and implies abnormalities in the patency of the brain microvasculature in AD.[2] The observations support previous conclusions on disturbances in local perfusion and oxygen tension as a consequence such that neurons furthest away from the capillaries are divested.[36] However, it should be realized that the brain is a dynamic organ and that reactive or compensatory responses are presumably not limited to neurons or glia[38] but that the cerebral endothelium must also be constantly changing even in aging.* It is conceivable that the BBB may be able to sustain subtle damage within certain regions and that the deposition of extracellular amyloid predisposes the endothelium to further degeneration. Although, these vascular abnormalities combined with the vascular amyloid deposition imply breach of the BBB in AD, clear functional evidence to support this is not apparent from non-invasive imaging and permeability studies (see Kalaria, 1992[2]). However, it is possible that breakdown of the BBB occurs focally and transiently over a protracted period in association with reactive mechanisms that direct repair and growth.[38]

CEREBRAL AMYLOID ANGIOPATHY, INTRACEREBRAL HEMORRHAGE AND APOLIPOPROTEIN E

Amyloid p-associated CAA has been reported to be present in 62-97% of AD subjects and is consistently always present in Down's syndrome.[3] Our recent analysis on isolated cerebral vessels in parallel with brain tissue from a series of 300 cases of AD indicates that CAA is more frequent in AD than previously thought.[5] It involves the leptomeninges, small pial vessels, intracortical arterioles as well as brain capillaries.[39] The lesion was characterized by sporadic focal deposits in surface vessels to complete infiltration of numerous meningeal and intracortical vessels throughout all cortical lobes.[39] There can be little doubt that cerebral vascular amyloid deposition resulting in CAA compounds the aging-related microvascular abnormalities in AD.[2] However, amyloid B-associated CAA may coexist with other

neurodegenerative disorders such as Creutzfeldt-Jakob disease,"' and it may be exclusive to certain disorders such as hereditary cerebral hemorrhage or hemorrhagic stroke with amyloidosis of the Dutch type and the Flemish type. CAA was frequently prominent in the occipital lobes and more profound in the sulci compared to the gyri of the neocortex. Vascular amyloid β deposits were rare in the large cranial arteries or muscular vessels of peripheral organs even in patients with relatively high degree of cerebral amyloid β burden. CAA could result from head injury or sporadic hemorrhagic strokes causing vascular amyloid accumulation when cerebral vessels are subjected to trauma, oxidative stress, or hemodynamic stress.[41] The characteristic cerebral distribution of CAA also implies that the process may be largely limited to brain vessels associated with a tight or continuous endothelium and when exposed to molecular triggers which may include soluble amyloid β itself that may even originate in perivascular plaques.[2] An intriguing hypothesis has been proposed to explain the mechanism of CAA and accumulation of amyloid β in brain. Weller et *al.*[42] have suggested that the characteristic vascular deposition of amyloid is related to the lack of clearance of amyloid β via the interstitial drainage pathways. Irrespective of the mechanism of CAA, it is highly likely that the characteristic vascular deposition in AD and the other amyloid angiopathies compromise BBB function and promote chronic hypoperfusion.[43]

CAA is considered an important cause of intracerebral and lobar hemorrhages. We have estimated that up to 10% of AD subjects exhibit CAA-related intracerebral hemorrhages.[5,44] We have moreover shown that AD subjects with evidence of intracerebral hemorrhage exhibit higher proportions of the more pathogenic amyloid β(42) compared to amyloid β(40) in the vasculature (Kalaria *et al.*, unpublished observations). Whereas intracerebral bleeds characterize the Dutch and Flemish variants of cerebral hemorrhage with amyloidosis, it can cause premature death in the elderly and AD patients. Consideration of the Dutch disease provides certain clues to a link between CAA and stroke. It is thought that the first stroke-like episode triggers multiple cerebral bleeds, which may be accompanied by white matter lesions that in turn lead to rapid decline of cognitive functions.[45] We have previously proposed that certain routinely classified AD cases with predominant microvascular lesions and vascular amyloid β deposition might in fact be CAA variants of AD.[38] This would be consistent with the pathological features of the Dutch hereditary disease where severe CAA is present in the absence of profound cortical pathology.

Previously implicated as a susceptibility factor for cardiovascular disease, the inheritance of the ε4 allele of the apolipoprotein E gene (*APOE)* is considered to be the most important genetic factor in nonfamilial AD. A three- to fourfold increased frequency of the *APOE*-ε4 allele is not only linked to late-onset AD, but also to middle-aged individuals with coronary heart disease[46] and atherosclerosis.[47] In accord with the implications that apolipoprotein E might promote pathological alterations in the vascular wall, it is intriguing that the *APOE*-ε4 allele is also a strong factor in the development of CAA in AD.[5,48] We examined the frequencies of *APOE*-ε4 alleles in age-matched controls and subgroups of 200 AD subjects exhibiting CAA and other frequently associated vascular lesions. *APOE*-ε4-allele frequency (48%) in AD subjects with moderate to severe CAA was six times higher than those who exhibited mild CAA. In the subjects with severe CAA, the occurrence of an ε4 allele was increased by a factor of more than 15. This was despite the fact that neocortical amy-

loidβ plaque densities in the advanced and mild CAA groups were similar and that all the subjects had met the accepted neuropathological criteria for AD. More remarkably, the ε4-allele frequency was highly associated with AD subjects exhibiting lobar or intracerebral hemorrhage, all of whom had advanced CAA. These findings suggested that the *APOE*-ε4 allele is a significant factor in the development of CAA in AD and revealed the possibility that *APOE* is a factor in CAA and other vascular abnormalities associated with AD. Our observations on the relationship between *APOE*-ε4 allele and CAA-related intracerebral hemorrhage were confirmed by others,[49–52] but it was later demonstrated that the ε4 allele does not appear to be an independent risk factor for CAA-related hemorrhage. Surprisingly, recent studies implicate *APOE*-ε2 allele as the strong factor for intracerebral hemorrhage in amyloid-laden vessels that may cause rupture of the vessel walls by inducing specific cellular changes.[50,53,54]

Recent observations suggest *APOE*-ε4 allele frequency also increases the risk of dementia in stroke survivors[55] and that the allele frequency is similarly increased in vascular dementia.[56] Bronge et *al.*[57] have recently reported that *APOE*-ε4 homozygotes have extensive white matter lesions seen upon magnetic resonance imaging in the deep white matter than those with the ε3/ε3 genotypes. These reports are in accord with our postmortem studies showing that the ε4 allele frequency in 36% of the AD subjects, who exhibited concomitant cerebrovascular pathology resulting from single infarcts, multiple microinfarcts, ischemic white matter lesions, or petechial hemorraghes, was significantly higher than in those without such pathology. That additive effects of peripheral vascular disease and *APOE* may also be important in AD has been implied by some studies.[58–60] We found that 77% of the patients with AD had cardiovascular disease defined by the presence of variable arteriosclerosis of the aortic blood vessels at autopsy. We also reported that *APOE* frequencies in patients who exhibited cardiovascular disease were significantly different from those who did not and over 60% of the AD subjects with arteriosclerosis carried at least one *APOE*-ε4 allele. Interestingly, those who carried the *APOE*-ε4 allele were almost three times likely to have had both AD and cardiovascular'disease. These findings are consistent with those of Hofman et *al.*[58] implicating an interaction between carotid artery thickening and *APOE* ε4 in the progression of AD.

APOE is considered to have more widespread effects than any other genetic factor implicated in AD, but the mechanism(s) by which it exerts its effect remain largely unknown. However, several scenarios involving molecular events in brain pathology and physiological actions on the cardiovascular system have been proposed. An increased reutilization of apolipoprotein E-lipid complexes may explain our recent finding that apolipoprotein E in CSF is decreased both in AD and vascular dementia.[61,62] Both hypertension and hyperlipidemia are major risk factors for atherosclerosis.[63] Since high serum cholesterol level during middle age was associated with an increased risk for AD in old age, it is conceivable that a part of the effect of the *APOE*-ε4 allele on the risk for AD is mediated through high serum cholesterol concentrations. Alternatively, it can have direct effects on the endothelium rendering it leaky and leading to compromise of BBB functions.[63] In view of these developments, it remains to be seen whether cholesterol-lowering drugs will be useful to prevent or slowdown progression of AD. Indeed, the outcome of such an approach may help to define the nature of the interaction between apolipoprotein E, atherosclerosis,[58] and ischemic white matter lesions[61,64] in the etiology of AD.

OTHER PATHOLOGY IN AD: WHITE MATTER LESIONS AND CEREBRAL INFARCTION

Although white matter lesions may influence the course of AD there is no clear consensus to suggest that volume or localization of the lesions is predictive of AD. Ischemic white matter lesions associated with lipohyalinosis and narrowing of the lumen of the small perforating arteries as well as arterioles which nourish the deep white matter, have also been amply described in AD.[64–66] Neuropathological correlative studies comparing magnetic resonance imaging (MR) findings with post-mortem neuropathological examination have determined that the hyperintense deep white matter lesions, identified in more than 60% of AD patients as well as dementia with Lewy bodies,[67] consist mainly of demyelination, reactive gliosis and arteriosclerosis.[68] In late-onset AD subjects, white matter lesions are differently distributed than in early-onset AD[66] and in vascular dementia patients[69] and that they have more severe leaukoariosis.[70] In a recent study of nondemented individuals with extensive neuropathology of AD, de la Monte[71] suggested that the white matter degeneration precedes the cortical atrophy in AD. It is known that long-standing hypertension causes lipohyalinosis and thickening of the vessel walls.[72] In this context, it is intriguing that AD-type pathology may be precipitated by hypertensive insults. For example, Sparks et *al.*[73] found an increased amount of neurofibrillary tangles and senile plaques in the brains of nondemented individuals with hypertension. However, knowledge about risk factors for the development of ischemic white matter lesions, their progress over time, influence on the clinical course of AD and their relationship with other vascular pathologies remains to be still clarified.

Individuals with AD may be at increased risk for stroke and cerebral infarction, the main diagnostic features in vascular dementia. Current findings suggest that almost 35% of AD subjects bear evidence of cerebral infarction at autopsy.[5,44] Cortical lobar infarcts as well as microinfarcts, which generally tend to be more frequent and invariably localized in the temporal and occipital lobes, occur in AD (TABLE 1). Both remote and recent infarcts have been evident at autopsy. The microinfarcts may or may not be associated with petechial hemorrhages. Multiple microinfarcts may occur as a result of endothelial damage or luminal blockage or thrombotic events induced in microvessels. CAA may also increase the tendency of cerebral infarction in AD. Neither the strategic location nor the volume of such infarcts has been precisely determined in AD and correlated with measures of cognitive decline. It is not understood whether the isolated infarcts are a consequence of or responsible for triggering the classical pathological lesions in AD. However, certain features or conditions may rapidly precipitate strokes in AD patients. This is corroborated by circumstantial evidence suggesting that rapid development of cerebral infarctions in some AD patients occurs because of a strong interaction between severity of cerebral amyloid angiopathy-i.e., amyloid infiltration of the media and adventitia of cerebral vessels, and hypertension.[5,44] Conversely, recent longitudinal clinical and epidemiological studies suggest that stroke episodes may lead to characteristic degenerative changes of AD demonstrated by the progressive onset and course of dementia.[74,75] Kokmen et *al.*[75] suggested that stroke may account for as cause of AD in as many as 50% of demented cases in older age groups. Such studies have also emphasized that AD is three times likely to precipitate in the elderly after a stroke episode or a transient ischemic attack. While the substantial presence of strokes is likely to influence the processes

that cause dementia in AD, prospective follow-up studies are necessary to evaluate their exact role in AD, especially where preexisting stroke episodes or cardiovascular disease are not considered as an exclusion criteria for the diagnosis of AD.

CONCLUSIONS

Cerebrovascular abnormalities underscore the role for the blood-brain barrier in the etiopathogenesis of AD. There are profound morphological and biochemical changes such as that in the glucose transporter of the cortical microvasculature in subjects with late onset AD. In addition, amyloid β protein is involved in the degeneration of both the larger perforating arterial vessels as well as the cerebral capillaries that represent the BBB. These vascular changes not only imply that the integrity of the cerebral microvasculature is impaired in AD but may relate to long-term peripheral influences associated with cardiovascular disease or peripheral vascular disease. Genetic factors such as *APOE* and the ε4 allele may modify or attenuate cerebrovascular function during aging and increase the susceptibility to pathogenetic processes in AD. I suggest the microvascular disease causes transient and focal breach of the BBB in late onset AD and it results from an interaction of several factors, which include perivascular mediators and circulation derived damage to the endothelium. These may collectively contribute to the deterioration of cognitive functions in AD.

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