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Blood-Brain Barrier Permeability in Aging and Alzheimer's Disease

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Alzheimer's disease (AD) is a complex illness characterized pathologically by accumulation of protein aggregates of amyloid and tau in the brain (1). While most studies of AD focus on patients with AD alone, recent pathological and imaging studies show that other proteins and disease mechanisms may also be important (2). With the failure of several large trials of treatments designed to lower the amyloid load in the brain of patients with AD, a shift has occurred in thinking and vascular factors are emerging as a major focus of research interest (3). While early investigators identified “hardening of the arteries” as one of the major causes of dementia, interest in vascular disease waned until the seminal “Nun Study” indicated that vascular disease was a co-factor in AD, leading to a large number of articles emphasizing the overlapping roles of the two diseases (4-6). With the recognition that AD and vascular cognitive impairment (VCI), the new name for vascular dementia, rarely occur in a pure form, and that the majority of patients have so-called “mixed dementia”, there is renewed interest in the interaction between the two diseases, and rekindled interest in identifying treatments for VCI, which may open a new treatment window for AD.

Vascular disease progresses relentlessly with aging, intersecting with AD after age 70 with an increasing number of normal people showing amyloid and tau deposits and microinfarcts at autopsy; this is consistent with the large number of patients with mixed dementia (7). Normal changes in the vasculature that are part of the aging process are exaggerated by the major vascular risk factors, hypertension, diabetes mellitus, hyperlipidemia, smoking, and on rare occasions by genetic factors. The cerebral blood vessels are critical for normal brain function; they form a blood-brain barrier (BBB) that restricts fluid and entrained molecules from being transported into the brain from the systemic circulation. Several cell types interact to form the BBB, which is now referred to as the “neurovascular unit (NVU)”, and is composed of the cerebral endothelial cells, basal lamina, astrocytic foot processes, and pericytes (8). Tight junction proteins, such as claudin, occludin, and zona occludin, provide the initial barrier with the blood. Basal lamina containing type IV collagen, fibronectin, heparan sulfate, and other molecules, provides the second barrier, which is thought to act as a molecular weight filter. Finally, the pericytes provide a macrophage, smooth muscle-like function, and the astrocyte end-feet contain proteases, neurotransmitters along with other essential molecules (9).

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With aging there are alterations in the BBB that are thought to contribute to the pathological processes in VCI and possibly also in AD (10). Studies of the effect of aging on the BBB, while not conclusive, suggest an increase in NVU permeability occurs over time. The earliest studies of the role of aging on cerebral permeability showed an increase in albumin in the cerebrospinal fluid (CSF), indicating that the large protein molecule, albumin, which is produced exclusively in the liver and restricted to the blood compartment, was abnormally transported across the cerebral vessels into the CSF. Ratios of albumin levels in the CSF to those in the blood were highest in patients with vascular causes of dementia (11). Albumin ratio was normal in AD, suggesting that the vascular disease was the cause of the increased permeability and not the presence of the amyloid and tau proteins, which were known to be present in AD. Although the data was conflicting, a recent meta analysis suggested that the albumin ratio rose with increased age (10).

Interpretation of studies on the BBB in dementia requires a careful scrutiny of the patients selected, the animal models used and the methods chosen to measure the leakage. Separation of the different pathophysiologies involved in AD and VCI is in general not possible in the early stages of either disease, and combination of a number of biomarkers is needed (12). Patients with VCI can have slowly progressive symptoms at the onset that suggest a neurodegenerative disease rather than a strokelike vascular process. To overcome the problems related to diagnosis in the early stages of a neurodegenerative process require combining results of advanced imaging with MRI and PET, CSF studies and clinical evaluations; this approach has made it possible to separate patients at earlier stages and to better characterize the underlying disease process based on pathologically relevant biomarkers. However, these advanced imaging and CSF studies have only recently become available, and most of the earlier studies have not been able to separate those patients carefully into AD, VCI and mixed, making interpretation of earlier studies problematic.

There are several methods to measure the leakage across the BBB. Measurements of cerebral permeability can be done by CSF albumin ratio or with imaging methods, such as positron emission tomography (PET), magnetic resonance imaging (MRI) and computed tomography (CT). An earlier PET study, using [68Ga] ethylenediaminetetraacetic acid ([68Ga]EDTA), in only 5 AD patients and 5 controls, failed to show any BBB opening in the AD patients (13). In addition, CT and MRI studies failed to show an increase in permeability in AD, although the number of subjects was very small, little information was available on controls, and whether mixed patients were included was not specified (14 15). Thus, it can be concluded that the current information from studies in humans does not support disruption of the BBB in AD, but the studies were most likely inadequate.

The presence of vascular disease increases BBB permeability, particularly those with white matter lesions on CT or MRI. Measurements of albumin ratio clearly demonstrate elevated permeability in VCI, which is further increased in aging (16). MRI studies likewise indicate an increase in permeability when vascular disease is present; both qualitative and quantitative MRI studies indicate that the BBB is open in the presence of vascular disease (17, 18). Our group used dynamic contrast-enhanced MRI (DCEMRI) with a quarter dose of Gadolinium to study the permeability in a well-characterized group of patients with VCI. We found that those with extensive white matter hyperintensities (WMHs) and clinical and

neuropsychological evidence of subcortical ischemic vascular disease (SIVD) of the Binswanger type had the highest levels of increased BBB opening as measured in the white matter (19). This suggests that the human studies showing disruption of the BBB in AD may have included those patients with both AD and VCI, and a study in patients that have only AD without vascular disease, using the more accurate DCEMRI method, will be very important to resolve this issue.

There is very little information on the BBB in the frail elderly. Albumin ratio in the CSF appears to be elevated, but whether this is sufficient to lead to pathological changes is uncertain. Clearly, this is an important area to investigate with quantitative MRI methods, particularly in the patients that do not have evidence of amyloid deposition.

Animal studies suggest that the presence of amyloid is a factor in the opening of the BBB. In experimental animals and cell cultures, amyloid proteins induce MMP-9 (20). Genetically modified mice with human amyloid proteins show disruption of the BBB (21). Furthermore, transgenic mice with apoE4 demonstrate BBB breakdown by activating the pro-inflammatory cyclophilin A-matrix metalloproteinase-9 (MMP-9) pathway in brain pericytes, which in turn results in degradation of the BBB tight junctions and basal lamina proteins (22). Mice overexpressing Aβ-precursor protein, have pericyte loss, elevating brain Aβ40 and Aβ42 levels and accelerating amyloid angiopathy and cerebral amyloidosis (23). These studies in animals are mirrowed in human studies showing that MMP-9, which disrupts the BBB by attacking basal lamina and the tight junction proteins, is elevated in patients with SIVD, but not AD (24, 25).

While data from animal models supports a role for BBB disruption in AD, the human data is less convincing. One possible explanation is that amyloid deposition in the early stages in patients with vascular disease has little impact on the BBB, which would lead to the conclusion that the disruption of the BBB is not a major factor. However, in those patients with blood vessels damaged by vascular disease, the activation of the MMPs is accelerated by the presence of amyloid, making the patients with the mixed dementia most likely to be affected. This would lead to the hypothesis that patients with vascular disease and amyloid deposits would have more severe disruption of the BBB. If this hypothesis could be shown to be true, it would justify a collaborative study to reduce vascular risk factors combined with an agent known to reduce amyloid deposition. Technology to test this hypothesis is available in research centers with the capability to perform amyloid PET studies, MRI BBB measurements, and protein and MMP measurements in the CSF. This could lead to clinical trials to reduce BBB disruption and amyloid deposits with agents that reduce neuroinflammation.

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