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Alzheimer's disease and the Blood-Brain Barrier: Past, Present and Future

Gene L. Bowman, N.D. and Joseph F. Quinn, M.D.

NIA-Layton Aging & Alzheimer's Disease Center, Oregon Health & Science University, Portland.

1.1. Normal Physiology of the Blood-Brain Barrier

In 1885 Ehrlich reported that the brain, unlike other organs, failed to retain dyes that were injected systemically. Subsequent investigation by Goldman demonstrated that dyes will in fact stain the CNS if injected into the brain ventricular system, suggesting that Ehrlich's observation was due to a barrier between blood and brain tissue (1,2). Since blood vessels in the brain make intimate contacts with astrocytic foot processes, the astrocyte was presumed to represent the structural basis of the blood-brain barrier until the 1960s when Brightman (3) and others (4,5) demonstrated that tight junctions between endothelial cells are the basis of the barrier function. (Figure 1) (6). An intact blood brain barrier (BBB) restricts all molecules dependent on molecular weight and lipid solubility, with lipid soluble agents able to cross the BBB more readily than water-soluble agents. The intact BBB prevents the passage of water-soluble drugs with a molecular weight greater than 180 (7). This is exemplified by albumen and immune globulin (IgG), which constitute the majority of high molecular weight components in peripheral circulation and are largely restricted from brain tissue by this blood-brain barrier. Selective pinocytosis and other transport mechanisms permit specific agents to cross an otherwise intact BBB, so that some investigators have emphasized that the BBB has both "barrier" and "carrier" functions. For example, glucose and ascorbic acid are transferred from circulation to the brain by active transport mechanisms (8,9). The present review is focused on the barrier function in Alzheimer's disease.

1.2. Methods for Assessing Blood-Brain Barrier Integrity

1.2.1. Direct examination of brain tissue

Animal models of BBB function typically involve intra-arterial infusion of a marker normally excluded by a healthy BBB. Post-transfusion examination of the brain tissue identifies the presence of the marker allowing some conclusion regarding BBB integrity. A marker commonly used is the dye Evans blue. This dye binds tightly to albumen and forms a large molecular weight complex restricting its passage across the BBB. In the presence of BBB disruption the brain parenchyma will be stained blue. An analogous approach can be taken with post-mortem human tissue by probing in brain parenchyma for plasma markers normally excluded by a healthy BBB. These studies typically probe for IgG or albumen. Post-mortem studies of human subjects with AD have relied in part on these methods for evaluating BBB integrity in AD.

1.2.2 Clinical assessment of BBB integrity in living patients: the albumen index

Since cerebrospinal fluid (CSF) reflects the composition of extracellular fluid in the brain, CSF levels of large molecular weight blood borne markers are dependent on the integrity of the BBB. Albumen is synthesized only in the liver, so any albumen in the brain and CSF is derived from the peripheral circulation. The assumption that albumin found in the CSF is derived from the periphery is supported by studies in different laboratories failing to prove its synthesis in the CNS (11–13). Albumin has a molecular weight of about 67,000 Daltons, a typical CSF

concentration about 200 times lower than serum, and is the most abundant protein component of the CSF in humans (14). The ratio of albumen in CSF compared to serum, the “CSF albumen index” has been utilized as a marker of BBB integrity in living human subjects (14,15).

1.2.3. Imaging techniques for the assessment of BBB integrity

However, the invasive nature of lumbar puncture limits the utility of the CSF albumen index, so non-invasive neuro-imaging methods are attractive alternative methods for assessing BBB integrity. Routine clinical brain CT and MRI scans demonstrate regions of BBB impairment as focal areas of “contrast enhancement.” Brain tumors, brain abscesses, sub acute strokes, and active multiple sclerosis lesions all are recognized by local “contrast enhancement” due to BBB impairment. In these instances the “signal to noise” ratio for the contrast agent is very high in the region of localized BBB impairment. Detection of subtler or more diffuse BBB dysfunction is not possible with routine clinical brain scans, and imaging modalities for examining BBB integrity have been sought for decades. Positron emission tomography with radio-labeled EDTA was one method used in the past for tracking BBB integrity in living subjects (16), and CT scanning with the iodinated compound meglumine iothalamate (17,18) was another. These methods have been supplanted by an advanced MRI imaging method known as “dynamic susceptibility contrast” imaging, which involves serial imaging of an IV bolus of gadolinium contrast. While this method is most often used to determine rates of cerebral perfusion by tracking the appearance of contrast agent in parenchyma, it may also be used to determine BBB dysfunction. Prolonged retention of post-bolus contrast material in brain parenchyma may reflect BBB dysfunction (19,20). In addition to the advantage of non-invasiveness, imaging methods using tracers with relatively low MW (gadolinium ≤ 1 kD) are potentially more sensitive to BBB dysfunction than biochemical methods dependent on a much larger tracer (albumin~67,000 kD).

2. Pathophysiology of Alzheimer’s disease

2.1. Amyloid Hypothesis

About a hundred years ago Dr. Alois Alzheimer reported his observation of fibrils that were coiled and twisted and a central core with a diffuse halo during pathologic examination of brain tissue from a patient with a presenile dementia (21). These neurofibrillary tangles and amyloid plaques have become the pathologic hallmarks of the disease, which now bears Alzheimer’s name. Nearly 80 years later the sticky amyloid β -peptide ($A\beta$), which is the chief component of the amyloid plaque was sequenced (22,23). The gene that encodes the β -amyloid precursor protein (APP) was subsequently mapped to chromosome 21 (24–27).

The central premise of the amyloid hypothesis is that the neurodegenerative cascade in AD is due to a neurotoxic form of $A\beta$. Since monomeric $A\beta$ is synthesized and present in healthy brains, and since large plaques are immobile and somewhat inert, the current amyloid hypothesis argues that soluble oligomeric $A\beta$ is the toxic form. However, this hypothesis remains unproven and hotly debated (Figure 2).

Perhaps the largest concern with this hypothesis is that the number of $A\beta$ deposits in the brain does not correlate well with the degree of cognitive deficits in AD (28). The degree of dementia in AD correlates much better with $A\beta$ assayed biochemically than histologically determined plaque counts and the concentration of soluble $A\beta$ species (which are invisible to immunohistochemistry) appear to correlate with cognitive impairment (29–31).

Arguably the strongest evidence in favor of the amyloid hypothesis is that mutations in the APP heighten the self-aggregation of $A\beta$ into amyloid fibrils and these are sufficient to produce clinical and pathological AD. The remarkably high incidence of AD pathology in Down’s syndrome, which involves a duplication of APP on chromosome 21, is another point in favor

of the amyloid hypothesis. The plausibility of the hypothesis is illustrated by the large number of clinical trials aimed at reducing the production or promoting the clearance of A β (e.g., secretase inhibitors, secretase modulators, anti-A β immunotherapy).

The amyloid hypothesis typically considers the neurotoxicity of only parenchymal A β , ignoring vascular A β which is seen in most cases of AD. Vascular A β , or “conophilic angiopathy” (32) is a well established cause of intracerebral hemorrhage. Some investigators have suggested that silent micro-hemorrhages may contribute to the global cognitive decline in AD (33), and others have demonstrated neurotoxicity of endothelial cells exposed to A β (34), suggesting that A β may contribute to dementia by way of vascular mechanisms. Amyloid angiopathy is therefore one possible cause of blood-brain barrier impairment in AD.

2.2. Non-amyloid cerebrovascular disease and AD

Atherosclerosis is another possible cause of blood-brain barrier impairment in patients with a clinical diagnosis of AD. The diagnosis of AD is made on clinical grounds, and in the vast majority of cases diagnosed carefully, the pathologic changes of AD (plaques and tangles) are confirmed at autopsy. However, concomitant atherosclerosis and arteriosclerosis are also commonly seen at brain autopsy, so that many patients with autopsy-confirmed AD also have cerebrovascular disease.

Several epidemiologic studies have highlighted a synergistic effect of AD pathology and vascular pathology in producing the clinical phenotype of dementia. One of particular interest is the Nun study (35). Here the prevalence of dementia was compared in nuns dying with equivalent AD pathologic burden but differing in the amount of cerebrovascular pathology. The nuns with cerebrovascular disease were significantly more demented than those with equal amounts of plaques and tangles but no vascular disease. Other studies have confirmed the impression that occult cerebrovascular disease contributes to the expression of late life dementia. For example, the Rotterdam scan study demonstrated that clinically silent brain infarcts more than doubled the risk of dementia and were associated with more rapid cognitive decline than seen in subjects without infarcts (36). Other studies have confirmed that “white matter hyperintensities” are more common in AD than in control subjects, with MCI subjects intermediate between the two groups, again supporting the hypothesis that otherwise silent cerebrovascular disease may contribute to the phenotype of AD-type dementia.

In summary, even when vascular dementia is excluded, and when vascular risk factors are minimized by exclusion of elevated Hachinski ischemia scores, many AD patients have clinically silent cerebrovascular disease, which represents another possible cause of BBB impairment.

3. Blood-Brain Barrier and Alzheimer’s disease

3.1. Histological evidence of BBB disruption in *post-mortem* AD brain tissue

Immune globulin, a high molecular weight protein which does not cross an intact BBB, has been repeatedly identified in brain tissue from AD patients (37,38, Mann 1982?), presumably due to extravasation from blood vessels. In one study, the immune globulin was only present in the parenchyma in proximity to blood vessels which were damaged by arteriosclerosis (Mann?). Subsequent studies have also demonstrated extravasated albumen in the AD brain, again primarily in the vicinity of damaged blood vessels, but in this case the blood vessels were involved by amyloid angiopathy or surrounded by amyloid plaques {Wisniewski, 1997 #56, 39}. Serum amyloid protein, another large molecular weight marker, has also been localized to amyloid plaques in AD (40), and is also presumed derived from peripheral blood in the absence of any evidence that it is synthesized in the CNS (41). The morphology and

ultrastructure of endothelial cells in AD brain tissue is also suggestive of BBB dysfunction (37,38,42,43).

3.2. BBB dysfunction in living AD patients: The CSF albumin index

Post-mortem studies, however, necessarily represent a late stage of AD when BBB dysfunction may represent an epiphenomenon in a badly damaged brain. If the pathogenesis of AD includes BBB dysfunction then it should be detectable at earlier stages of the disease in living patients. Several studies have examined BBB integrity in AD subjects compared to controls using the CSF albumen index, with mixed results (Table 2). Of the 10 studies reported, six found evidence of BBB dysfunction in AD (44–49) and four did not (50–53). These and other studies consistently find elevated CSF albumin index in subjects with vascular dementia, but only intermittently in subjects with AD (Table 2). This implies that either AD populations in these studies included subjects with un-diagnosed cerebrovascular disease, or that sub-populations of AD subjects exist with BBB damage due to AD per se.

Most of these studies have used the National Institute of Neurological and Communicative Disorders and Stroke /Alzheimer's Disease and Related Disorders Association criteria to diagnose probable AD (45–54), but the manner in which these studies controlled for vascular contribution to dementia has varied. We recently added to this literature by describing the CSF albumen index in a population of AD subjects with rigorous exclusion of vascular disease and vascular risk factors. This included a Hachinski ischemia score limitation and absence of vascular disease on brain MRI.

Despite rigorous exclusion of vascular disease, we found BBB impairment in 22% of 36 subjects with mild to moderate AD. The absence of significant vascular disease in our sample was supported by brain autopsy in 13 of the 36 subjects, with pathologic confirmation of the diagnosis of AD in all cases.

In summary, the literature on CSF albumen index in AD indicates that a sub-population of rigorously diagnosed AD subjects has BBB impairment. We will consider the etiology and consequence of BBB impairment in AD below, after reviewing other types of evidence of BBB impairment in living subjects with AD.

3.3. Imaging studies of BBB integrity in AD, MCI and non-impaired elderly

The first imaging method applied to the question of BBB integrity in AD was PET imaging with radiolabeled EDTA (Table 3). A study of 5 AD and 5 control subjects with this method found “no evidence that intravascular tracer entered the brain in either the dementia or control group”(58). This small study was followed by two studies of dynamic CT imaging comparing AD patients and controls. In the first study, 26 AD patients and 15 control subjects were studied with a bolus injection of iodinated contrast, followed by serial CT images which were quantified in 16 regions of interest (ROI)(59). In this method, delayed washout of contrast agent is considered evidence of BBB dysfunction. A non-significant trend toward delayed washout of contrast was seen in AD compared to control subjects in 11 of 14 ROIs. However, a subsequent study with dynamic CT scanning which compared 14 AD and 9 control subjects failed to find a difference between groups and concluded that “there is no generalized abnormality of BBB in AD” (60). More recently, a small study of 11 subjects with Mild cognitive impairment (MCI) and 11 age and sex-matched control subjects examined BBB integrity with dynamic contrast-enhanced MRI (61). One region typically involved by AD pathology (hippocampus) and one region spared by AD pathology (cerebellum) was studied. Contrast material was retained for a longer period of time in the hippocampi of AD subjects compared to controls, suggesting that BBB integrity is impaired in this area even at this very early “pre-dementia” stage of pathology. The absence of any difference between MCI and

controls in cerebellum suggests that the differences observed are specific to brain regions affected by AD pathology.

In contrast to the CSF albumen index studies described above, imaging studies of BBB integrity in AD has not included vascular dementia patients as a “positive control” group. Imaging studies of vascular dementia have also not used dynamic contrast imaging per se, but have examined contrast enhancement at the site of white matter lesions at “optimal” times after contrast administration. One study found increased contrast enhancement in diabetic patients with white matter lesions (62); one study found no contrast enhancement in dementia patients with white matter lesions (56), and one study found increased contrast enhancement in patients with “Binswanger’s” type of vascular dementia (63).

4. Blood-Brain Barrier Dysfunction: Cause, Effect, or Epiphenomenon in AD?

The literature reviewed above indicates that at least some patients diagnosed with AD have BBB impairment, but the literature is much less clear about the causes and consequences of BBB impairment in this setting. Some have suggested that BBB impairment could actually be an initiating event in the generation of AD pathology, with serum proteins like plasma amyloid or SAP providing a nidus for amyloid aggregation (32). Others have argued that BBB impairment is simply a marker of a brain damaged by amyloid deposition, and others have argued that BBB impairment is independent of amyloid pathology altogether, and is instead a marker of arteriosclerotic vascular damage. Probably the most critical question is whether BBB impairment contributes to pathogenesis or rate of neurodegeneration in AD. If it does promote neurodegeneration, then it represents a potential therapeutic target, and discerning the cause of BBB impairment is important to those therapeutic efforts. If BBB impairment does not impact the course of the disease, then it probably represents an epiphenomenon which is largely irrelevant to therapeutic efforts. Imaging evidence of BBB impairment during the “preclinical” MCI stage (61), and evidence that BBB impairment correlates with rate of disease progression (54) each support the hypothesis that the BBB may serve as a therapeutic target.

5. Future Research Direction

In order to determine if BBB impairment contributes to neurodegeneration in AD, prospective studies of outcomes in patients with and at risk of AD will need to be performed. Imaging modalities for assessing BBB integrity are preferred to the CSF albumen index for this purpose, so further development and validation of these imaging modalities is a high priority for this area of research. If prospective studies then support our observation that the rate of disease progression is correlated with the degree of BBB impairment, then the next logical stop would be to intervene with measures that “strengthen” the BBB, in order to definitively determine cause and effect. However, since we have not yet identified such interventions, this will require further research as well.

One candidate strategy is lowering of serum homocysteine. Hyperhomocysteinemia precedes and increases the risk of AD and is associated with age-related cognitive decline (64–66). Since elevated homocysteine is known to promote vascular disease and endothelial toxicity (67–72), it is possible that homocysteine imparts an increased risk of dementia by promoting BBB impairment. A report showing that a homocysteine-lowering intervention resulted in “normalization” of elevated CSF albumen index in MCI patients provides support for this hypothesis (73). Similarly, hypercholesterolemia increases both vascular risk and risk of dementia. The effect of hypercholesterolemia and cholesterol-lowering strategies upon BBB integrity and neurologic outcomes is another potential area for investigation. And finally, it is possible that amyloid-lowering strategies may act on the BBB. There is very good clinical evidence that immunotherapy with monoclonal antibodies reduces the amyloid burden in blood

vessels as well as in brain. The success of these strategies now entering clinical trials however, may depend on their effects on the BBB.

In summary, the priorities for future research in this area in descending order are:

1. Development and validation of imaging modalities for assessment of BBB.
2. Prospective studies of the effect of BBB integrity upon cognitive outcomes in patients at risk or with AD
3. Development and application of nutritional and anti-amyloid interventions directed at “strengthening” the BBB.

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Figure 1.
Blood-Brain Barrier anatomical orientation (10)

Age dependent changes in production or clearance, or missense mutations in APP, PS1, or PS2 genes

Increased A β 42 production and accumulation

A β 42 oligomerization and deposition as diffuse plaques

Subtle effects of A β oligomers on synapses

Progressive synaptic and neuritic injury

Dementia

Figure 2.
Amyloid cascade hypothesis

Table 2

Summary of comparison between AD and Vascular Dementia versus Controls

Study reference	Population		CSF Albumin Index [□]	
	Controls	AD	Vascular Dementia	Vascular dementia
Alafuzoff, 1983 (44)	16	20	23	23
Blennow, 1990 (55)	50	118	50	118
Blennow, 1995 (45)	32	45	19	45
Elovaara, 1987 (47)	22	22	29	29
Frolich, 1991 (50)	25	25	25	25
Kay, 1987 (51)	14	31	14	31
Mecocci, 1991 (52)	17	46	20	46
Skoog, 1998 (48)	29	13	14	13
Sun, 2003 (53)	11	141	11	141
Wada, 1998 (49)	7	14	7	14

* Statistically significant difference relative to controls

[□] Derived from CSF/serum albumin ratio and reported as mean and standard deviation

Table 3**Summary of Imaging Techniques for Assessing Blood-Brain Barrier Integrity**

Reference	Method	Population	Result
Schlageter, 1987 (58)	EDTA PET	5 AD; 5 control	No difference between groups, no evidence of BBB impairment in either group
Dysken, 1990 (59)	Dynamic contrast-enhanced CT	26 AD, 15 control	Non-significant trend to delayed washout (i.e., BBB dysfunction) in 11 of 14 ROI's
Caserta, 1998 (60)	Dynamic contrast-enhanced CT	14 AD, 9 control	No difference between groups, no evidence of BBB dysfunction
Wang, 2006 (61)	Dynamic contrast-enhanced MRI	11 amnesic MCI 11 controls	Increased BBB permeability in MCI in hippocampus but not cerebellum