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Is Alzheimer's disease amyloidosis the result of a repair mechanism gone astray?

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Abstract

We synthesize several lines of evidence supporting the hypothesis that at least one function of Aβ is to serve as a part of the acute response to brain hemodynamic disturbances intended to seal vascular leakage. Given the resilient and adhesive physicochemical properties of amyloid, an abluminal hemostatic repair system might be highly advantageous if deployed on a limited and acute basis in young individuals. However, in the aged, inevitable cardiovascular dysfunction combined with brain microvascular lesions may yield global, chronic hypoperfusion that may lead to continuous amyloid deposition and consequential negative effects on neuronal viability. A large body of experimental evidence supports an Aβ rescue function gone astray. Preventing or inducing the removal of amyloid in Alzheimer's disease (AD) has been simultaneously successful and disappointing. Amyloid deposits clearly play major roles in AD, but may not represent the preeminent factor in dementia pathogenesis. Successful application of AD preventative approaches may hinge on an accurate and comprehensive view of co-morbidities, including cardiovascular disease, diabetes and head trauma.

Introduction

A recent report from Alzheimer International projects that if existing trends continue, 115 million individuals worldwide will have Alzheimer's disease (AD) by 2050 [1]. Despite a wealth of fundamental discoveries regarding AD pathogenesis, translation of potentially promising findings into clinically useful treatments has been repeatedly stymied.

Alzheimer's disease is classically explained by a reductionist pathogenic mechanism positing amyloid deposition as the primary toxic entity in this dementia. The amyloid cascade hypothesis was reinforced by the discovery of familial cases of AD caused by mutations in the amyloid-beta precursor protein (APP) and in the presenilin (PS) genes which produce abundant amyloid deposition and early-onset dementia. Further support for the amyloid cascade hypothesis has also been provided by the engineering of transgenic (Tg) mouse models which mimic some aspects of AD amyloid pathology using mutant human APP and PS transgenes. Data revealing the significance of amyloid to AD pathology culminated in the therapeutic disruption of amyloid deposits in Tg mouse models and in AD patients. Despite the promising results in Tg mice, the successful disruption of amyloid plaques failed to yield commensurate effects on dementia in clinical trials [2-7].

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Extrapolating Tg mouse model observations directly to humans while neglecting significant evolutionary and biological differences between the two species may have played an important role in the lack of success against dementia [8;9]. Despite the clear mitigation of amyloid plaque pathology in some patients, the striking lack of concurrent effect against dementia expression suggests the disappointing prospect that we have underestimated the complexity of the underlying pathology and thereby failed to address critical facets of the problem. Viewed as a whole, the results obtained with Tg mice and clinical trial experiences reveal that AD pathology involves more than amyloid accumulation and conquering dementia demands something more than eliminating amyloid plaque deposits once cognitive impairment becomes evident. Enticed by the clear abundance of amyloid deposits in AD brain tissue and vasculature, these neuropathological features have been the dominant target in therapeutic interventions. However, the fundamental question of why amyloid accumulates in the elderly brain has yet to be answered.

In this position paper, we explore the possibility that sustained cardiovascular disease or head trauma leads to amyloid deposition, a process intended to ensure vessel repair and integrity at specific sites of injury or leakage. However, this vital protective function becomes inadvertently deleterious when chronically activated in the elderly, creating excessive amyloid deposits around the brain vasculature and an anti-angiogenic environment which generates hypoxia/ischemia. In addition, during the aging process, evolving cardiovascular decline inevitably reduces brain perfusion. Coupled with escalating brain microvascular damage, these conditions may establish a vicious cycle of anomalous and excessive vascular amyloid deposition promoting capillary and arteriole wall strangulation and luminal occlusion, eventually producing blind capillary remnants and free extracellular amyloid cores which are manifested prior to the clinical onset of the disease [10]. The concept of amyloid serving as a hemostatic patch for leaky brain microvessels was first postulated in 1993 by Roher et al. [11] and further advanced by Atwood et al. [12] and Cullen et al. [13]. Our assumptions are compatible with recent observations postulating a series of events initiated by hypoxia/ischemia and followed by vascular injury, disruption of the blood-brain barrier (BBB) and vascular amyloid deposition which is complicated by a failure in Aβ clearance and potential increase of Aβ up-take from the circulation [14]. These series of biological events are conducive to neurovascular dysfunction, neuroinflammation and neurodegeneration [15].

The Role of Cardiovascular Disease, Diabetes and Head Trauma in AD

The cardiovascular system is pre-eminent in the development of the brain maintenance of its vital functions. The brain consumes a disproportionate share of total oxygen and metabolic resources. By age 80, the human heart and vessels have beaten, stretched and contracted about 3 billion times to propel approximately 200 million liters of blood through the vasculature. This situation may explain why AD rates expand almost exponentially with advancing age in parallel with an increased incidence of morbidity and mortality resulting from cardiovascular disease [16-21]. As time elapses, the cumulative harmful effects of wear and tear on cardiovascular function become more apparent. This is well illustrated by a significant decline in cardiac output and cardiac index with advancing age [22;23]. Numerous cross-sectional and longitudinal studies, using various imaging and ultrasound techniques, have shown that in AD there is an statistically significant reduction in total and regional cerebral blood flow when compared to age matched controls [24-32]. Echocardiographic investigations demonstrated that AD subjects exhibited a statistically significant diastolic dysfunction revealed by increased transmitral vortex formation time [33]. Likewise, duplex Doppler carotid ultrasound showed a consistent and significant decrease in diastolic flow along the path of the carotid artery in AD patients, suggesting a loss of arterial elastic capacity [34]. These parameters can be construed as risk factors for

pathologic brain aging and, by extension, potential harbingers of AD. Aging imposes alterations in both the intracranial resistance of arterioles and capillaries [35-39] thus reducing cerebral blood flow and inducing cognitive dysfunction [40;41]. Recent hemodynamic studies using transcranial Doppler ultrasound confirmed decreased arterial mean flow velocity and increased pulsatility index in probable AD patients compared to non-demented controls [34], revealing that diffuse microvascular pathology, increased arterial rigidity and vascular resistance contribute to overall cognitive decline.

Brain hemodynamic alterations due to severe stenosis and hardening of the neck and intracranial arteries will impact brain perfusion while promoting lacunar infarcts and strokes. By age 80 atherosclerosis of the circle of Willis, carotid and vertebral arteries is widespread. These arteries exhibit a significantly increased degree of atherosclerosis in AD subjects compared to age-matched controls [42]. Chronic hypoxia/ischemia can lead to gross disruption of the BBB integrity [43-45], conditions that may be accentuated by hypertension and diabetes. These prevalent and progressive pathologies eventually exert negative effects on energy metabolism and neuronal transmission that are detrimental to memory and cognition.

Hypertension is an important risk factor for AD due to its microangiopathic effects on the brain [21;46] and its relationship to brain microhemorrhages [47]. This condition affects approximately 25% of the adult population in the USA [48], and increases to 60-65% in those older than age 65 [21;49]. As a highly perfused organ offering low resistance to blood flow, hypertension will ultimately elicit difficult-to-repair vascular injuries and irreversible structural and functional damage in the brain [50;51]. With aging, systolic and pulse pressure increases result in endothelial cell tearing, breaches in the BBB, smooth muscle cell disruption, small arterial dilations, vascular fragility, lipohyalinosis and fibrinoid necrosis [52]. As age advances, there is a direct relationship between stiffening of large elastic arteries and brain microvascular disease [50] as well as with increased pulse pressure and pulse velocity which are correlated to cognitive decline [53].

Diabetes is an additional important risk factor for AD because of its vascular pathological repercussions and impact on energy metabolism [54-57]. By age 60 years and older, about 23% of Americans have diabetes [58]. A large body of research supports the contention that diabetes is more frequent in patients with AD [59-61]. Diabetics face a considerably higher risk of developing cardiovascular disease, hypertension, atherosclerosis and obesity [57;62] as well as brain microvascular changes leading to dysfunctional BBB associated with hypoperfusion and cognitive deficiencies [63-65]. It has been suggested that sporadic AD should be classified as type-3 diabetes due to insulin resistance and reduced expression of insulin and insulin-like growth factors in the AD brain [54-57;62].

Acute head trauma is a risk factor for AD development [66-68]. In comparison to the general population, AD and other memory loss-related diseases are 19- and 5-fold more frequent in National Football League players 30-49 and 50 plus years of age, respectively [69]. Both APP and amyloid-beta (Aβ) levels increase after acute brain injury [70-73], suggesting an acute phase protein response involved in brain salvage function. The capacity of Aβ to produce vasoconstriction [74;75], coupled with its potent anti-angiogenic activity [76;77] and the ability of the Aβ peptides to act as metal chelating agents [78-80] may reduce the generation of deleterious reactive species [81;82] from extravasated hemoglobin-bound iron [83;84] resulting from concussive microhemorrhages. Thus, while amyloid deposition may increase the probability of surviving acute brain injury, it also confers a threat for future dementia development. Despite evidence for clearance of trauma-associated Aβ [12], even minute remnants of vasculature-associated deposits could act as seeding

templates for the future propagation of widespread amyloid pathology analogous to the chain reaction expansion characteristic of prion diseases [85].

In summary, cardiovascular dysfunction, common in middle age and elderly individuals, whether due to hypertension, intrinsic cardiac diastolic and systolic failure, lost of vascular compliance, atherosclerotic stenosis/thrombosis, brain diffuse microvascular disease and/or damaged BBB will eventually cause brain hypoxia/ischemia. These perturbations could be synergistically aggravated by respiratory disease, diabetes or by concussive head trauma. A disturbed microvasculature will need to be efficiently repaired to maintain the integrity of the BBB and an efficient blood flow to prevent energy metabolism failure and ultimately dementia.

Amyloid as a vascular repair mechanism

From a structural viewpoint, amyloid filaments exhibit high mechanical strength, are highly insoluble and resistant to degradation [86;87]. In addition, amyloid filaments are plastic, have cement-like bonding properties [86] and readily interact with the extracellular matrix [88] as well as with a reduced turnover suitable for vascular injury repair. Animal cements, based on amyloid polymerization aid in wound healing, maintenance of tissue integrity and exhibit biochemical processes analogous to blood clotting [89;90]. An abluminal amyloid molecular lattice would permit continued vascular blood flow while sealing breaches in the BBB [11;12]. This putative function would prevent the classical coagulation cascade from blocking the lumen of the capillaries and arterioles [12]. Moreover, Aβ may also act as an anti-microbial peptide capable of inhibiting and entrapping invading bacteria that otherwise could have harmful consequences for brain survival [91].

The above properties suggest that amyloid deposits may act as dynamic hydrophobic, insoluble sealants to halt vascular leakage due to vascular disease, trauma or intrinsic agingfailure of the brain vasculature [11;12] as well as serving as an acute phase protective function by sequestering excess heme, iron and other metal ions [92;93]. Blood components and their breakdown products free in the brain tissue have grave functional and pathological consequences as amply illustrated by the effects of hemorrhagic stroke [94] and brain edema [95]. Hypothesizing a brain-specific microvascular repair mechanism has important pathophysiological implications. A breached BBB will permit the infiltration of plasma proteins directly into the parenchyma or the creation of overt microhemorrhages. Small vascular lesions resulting in blood permeation into the neuropil are documented in AD by imaging techniques [96] and histological studies [97]. High levels of thrombin and matrix metalloproteinase-2 participate in the disruption of the BBB [98-101]. Hemin can generate oxidative stress through the production of superoxide and hydroxyl radicals by redox-active iron moieties resulting in membrane peroxidation attack, reduction of NADPH and depletion of glutathione levels [102]. Morphological studies have demonstrated a physical overlap between heme deposits and vascular-associated amyloid cores in the AD brain [13;103]. In brief, the grave consequences of extravasated plasma proteins and free-hemoglobin in the brain parenchyma, produced by a breached BBB and brain microhemorrhages, may be remediated by amyloid deposition.

The deleterious effects of excessive amyloid deposition

Vascular amyloid deposition ultimately evolves into a devastating condition resulting in progressive hypoxia/ischemia, failure in energy metabolism and permanent brain injury [97;104]. It is tempting to speculate that these consequences manifested in the aging brain are the ultimate tradeoff for a pathway selected through evolutionary processes to safeguard vascular continuity in younger individuals, but becomes progressively destructive under physiologic conditions in the elderly [105].

Microscopic examination of whole-mounted vascular specimens revealed that in AD, the cortical microvascular network harbors abundant fibrillar amyloid deposits at different degrees of condensation (Figure 1). At higher magnification, some microvessels appear constricted, particularly at sites surrounded by large cores of fibrillar amyloid [11;13]. Continuous Aβ accretion around the microvessel wall should generate increasing pressure on the expanding deposit, eventually occluding the vascular lumen. Conceivably, luminal occlusion is followed by degeneration and disappearance of the vessel wall, leaving insoluble amyloid cores apparently 'floating' free within the brain parenchyma entirely detached from the remaining vascular stumps (Figure 2). The chemical composition and post-translational modification similarities between microvasculature-attached and 'free' amyloid plaque Aβ peptides, rich in insoluble Aβ42 with abundant post-translational modifications [11;106-108] as well as the tenacious association of developing amyloid deposits with the brain vascular walls support this tenet. In advanced vascular amyloidosis, heavy amyloid deposition within the cortical arteries' periarterial spaces compromises interstitial fluid removal from the white matter, dilating the periarterial spaces (etat criblé) [109-111]. Retention of interstitial fluid and poisonous metabolic waste may negatively compound the severe demyelination present in two-thirds of patients with AD [109]. Furthermore, it may also explain gross ventricle enlargement, a nearly universal signature of this type of dementia. From a hydrodynamic point of view, relentless enlargement of the ventricles will drastically compress the white matter, thereby promoting degeneration of this tissue.

Global therapeutic implications of amyloid removal

Immunotherapy has disrupted amyloid plaques in humans and Tg animal models. Although amyloid deposition creates noxious conditions and amyloid plaques have been correlated with AD dementia, this association is relatively weak [112;113]. The remarkable physical impact of immunotherapy coupled with the striking lack of corresponding effect on dementia suggests that amyloid plaques are not the sole or perhaps even primary pathogenic factor of AD.

The postmortem data from immunotherapy trial subjects reveal that although the disruption of amyloid plaques has been dramatic in some cases, the elimination was not total and persistent remnants may still harbour toxic Aβ peptides or other noxious molecular species [2;3;114]. In addition, plaque removal cannot reverse a legacy of destroyed vascular elements or neurons. The inability of Aβ immunization to totally eradicate amyloid plaques coupled with the failed or slow exit of amyloid from the brain [2;3;114] due to a congested vasculature means that the amyloid hypothesis *per se* has yet to be tested rigorously. Furthermore, additional findings suggest that amyloid plaques might reconstitute swiftly as soon as antibody levels decline [3]. Taken together, these observations strongly suggest that to avoid amyloid toxicity, applying interventions on a preventative rather than a therapeutic basis may be more efficacious.

If amyloid deposits perform a vascular rescue function or simply accumulate steadily with age and produce localized damage, specifically removing them may inadvertently promote BBB breaches. However, explaining this assumption as the consequence of the simple removal of an essential vascular patch [12] is not straightforward. Microhemorrhages are frequently observed in AD patients [97], implying that the unchecked accumulation of vascular amyloid can itself be intrinsically destructive. Postmortem examinations of AN-1792-immunized individuals revealed that vascular amyloid deposits were partially refractory to immune disruption [2;114;115]. In some AD patients, vascular amyloid may have increased as a consequence of immunotherapy [2;114;115]. Amyloid-β immunotherapy has induced deleterious side effects such as microhemorrhages [115-118], as well as

vasogenic edema and aseptic meningoencephalitis (reviewed in: [119]) in some recipients. In these patients, it is possible that essential amyloid depositional processes in the vasculature were active when therapy commenced and the removal of functional amyloid "scabs" [12] breached the vessels directly or created failure-prone areas. Recognizing that amyloid accumulation may precede the onset of dementia by a substantial margin [10;120] and the empiric discovery that patient ApoE genotype exerts considerable influence over the type and emergence of lesions, suggest that careful patient selection, precise treatment timing and individual titration of immunotherapy may be essential for optimal efficacy.

An additional complication of Aβ immunotherapy is its potential interference with the coagulation cascade, a complex and highly conserved hemostatic mechanism that repairs injured blood vessels. Multiple, interdependent proteins participate in a chain of events terminating in the formation of an adhesive clot, mainly made of platelets and cross-linked fibrin. Although a well functioning coagulation cascade is essential for survival, the requirements for vascular integrity maintenance and repair in the brain may be more stringent than those of peripheral organs. The brain is an exceptional organ with finely tuned electrical activities generated by neurons assisted by glial cells that need to be maintained in a semi-secluded molecular compartment secured by the integrity of the BBB. While rapid coagulation mediates vascular recovery in many organs, severe microvascular damage within the brain may follow a fundamentally different response strategy to ensure adequate blood flow while minimizing the prospect of neuronal injury.

In AD, a breached BBB would release fibrinogen into the extracellular space of the brain microvasculature where it will contact Aβ peptides. In addition, damaged endothelial cells produce thrombin [121]. Recent *in vivo* and *in vitro* experiments demonstrate that the interaction between these two molecules results in altered thrombosis and fibrinolysis and generates lysis-resistant clots that may contribute to vascular constriction, brain hypoperfusion and neuroinflammation [122;123].

It is important to recognize that the production and distribution of Aβ is not restricted to the brain [124]. The long-term effects of chronic immunotherapy administration on vital cell signaling pathways and the coagulation system are not known. The available data suggest that potential interactions between protease nexin-2 (PN-2), an APP molecule carrying a Kunitz-type serine protease inhibitory domain, and anti-Aβ antibodies may have negative effects on the coagulation cascade resulting in thrombosis. Although antibodies against Aβ are directed against amino acid sequences within the Aβ peptide, the possibility of interactions with APP in patients undergoing immunotherapy remains open. Intriguingly, in recent clinical trials several AD patients treated with bapineuzumab, a monoclonal antibody against the N-terminal domain of Aβ, developed deep venous thrombosis (3.2%) or pulmonary embolism (0.8%), while none of these coagulation cascade-associated adverse events occurred in the placebo branch [125]. For comparison, acute venous thromboembolism has an annual incidence of about 1-2 cases for 1000 individuals in the general population [126;127]. The observation that Aβ immunotherapy in AD patients and APP Tg mice induces microhemorrhages [115;116;118;128] further suggests that the normal coagulation cascade may be perturbed. This may be a manifestation of PN-2 inhibition, steric hindrance effects or conformational changes induced by high titers of circulating anti-Aβ antibodies. Protease nexin-2 blocks the IXa, Xa and XIa factors and tissue factor:factor VIIa in the prothrombinase complex cascade, supporting the hypothesis that PN-2 functions in the focused regulation of the coagulation process at sites of vascular injury [129]. The net effects of such induced alterations may be more profound in the periphery, but unfortunately no data exist to settle the matter.

Summary statement and conclusions

The supreme challenge is to set the impressive knowledge regarding brain Aβ biochemistry into a larger physiological context that takes account of established AD systemic co-morbidities such as cardiovascular disease and diabetes. This is no small task since the normal function(s) of APP/Aβ, an evolutionarily-conserved molecule, remains nebulous. Several lines of evidence suggest that at least one function of Aβ might be as a part of the acute response to brain vascular trauma and degeneration intended to seal capillary and small vessel leakage. A brain vascular repair system mitigating ischemia/hypoperfusion might be highly advantageous deployed on an acute basis in young individuals. However, in the aged, inevitable cardiovascular dysfunction combined with microvascular lesions may yield chronic conditions that are misinterpreted as requiring repair which promotes a self-synergizing global cascade of insidious vascular occlusion and ultimately negative effects on cognition. Although amyloid deposits deployed in the acute response to brain vascular trauma are apparently reversed, especially in younger more functionally vigorous individuals, past head injuries are a recognized risk factor for AD development, suggesting that the salvaged regions of the brain harbour potential nucleation sites that may promote amyloid propagation in the future.

Confronting hypothesis with data, it seems likely that the long-prevailing view of AD pathogenesis may be too limited. The brain is heavily dependent on cardiac output and the functional integrity of the arterial and venous networks. The brain is unique among the organs in its extreme perfusion demands, energy requirements and strictly maintained biochemical separateness from the circulatory system. Considering the brain and its age-related AD in isolation, we may have overlooked the fact that all aspects of brain function ultimately depend on the cardiovascular system and adequate energy metabolism. The genesis of dementia is multifactorial and heterogeneous; its mitigation may be a complex undertaking as well.

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List of Abbreviations

Aβ	amyloid-beta
AD	Alzheimer's disease
ApoE	apolipoprotein E
APP	amyloid-beta precursor protein
BBB	blood-brain barrier

PN-2	protease nexin-2
PS	presenilin
RBC	red blood cell
Tg	transgenic
WBC	white blood cell

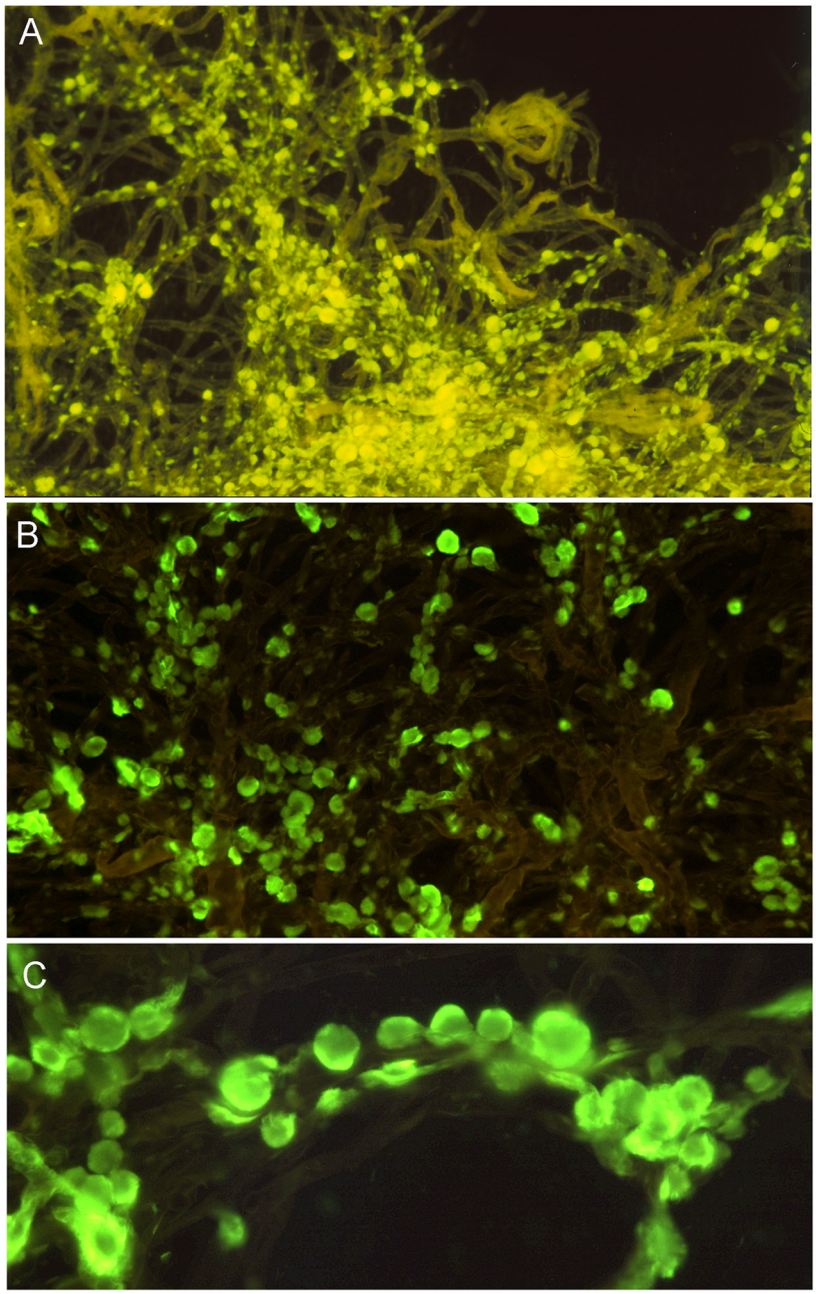

Figure 1. Alzheimer's disease whole-mount preparations of isolated microvessel-associated amyloid deposits stained by thioflavine-S

A) A tuft of cortical microvessels walls revealed as detergent (SDS) insoluble cross-linked extracellular matrix remnants demonstrating a wide range of amyloid core deposits intimately associated with the basal lamina. The early amyloid deposits are small, flat and ellipsoidal. In more advanced deposits, the amyloid deposits become spherical and completely surround the vascular wall. The continuous accretion of fibrillar Aβ onto the surface of the amyloid sphere by glial cells may eventually obliterate the microvessel, thereby compromising blood supply. **B** and **C)** Tufts of capillaries and arterioles with numerous amyloid cores attached to the vascular basal lamina. Note that in some instances the spherical amyloid cores are sparse while in other instances they are distributed in a

rosary-like succession. For detailed technical information and interpretation see reference [11]. Figure **A** reproduced with permission from the Publisher: Proceeding of the National Academy of Sciences, USA. Magnification: A = 100X; B = 200X; C = 400X.

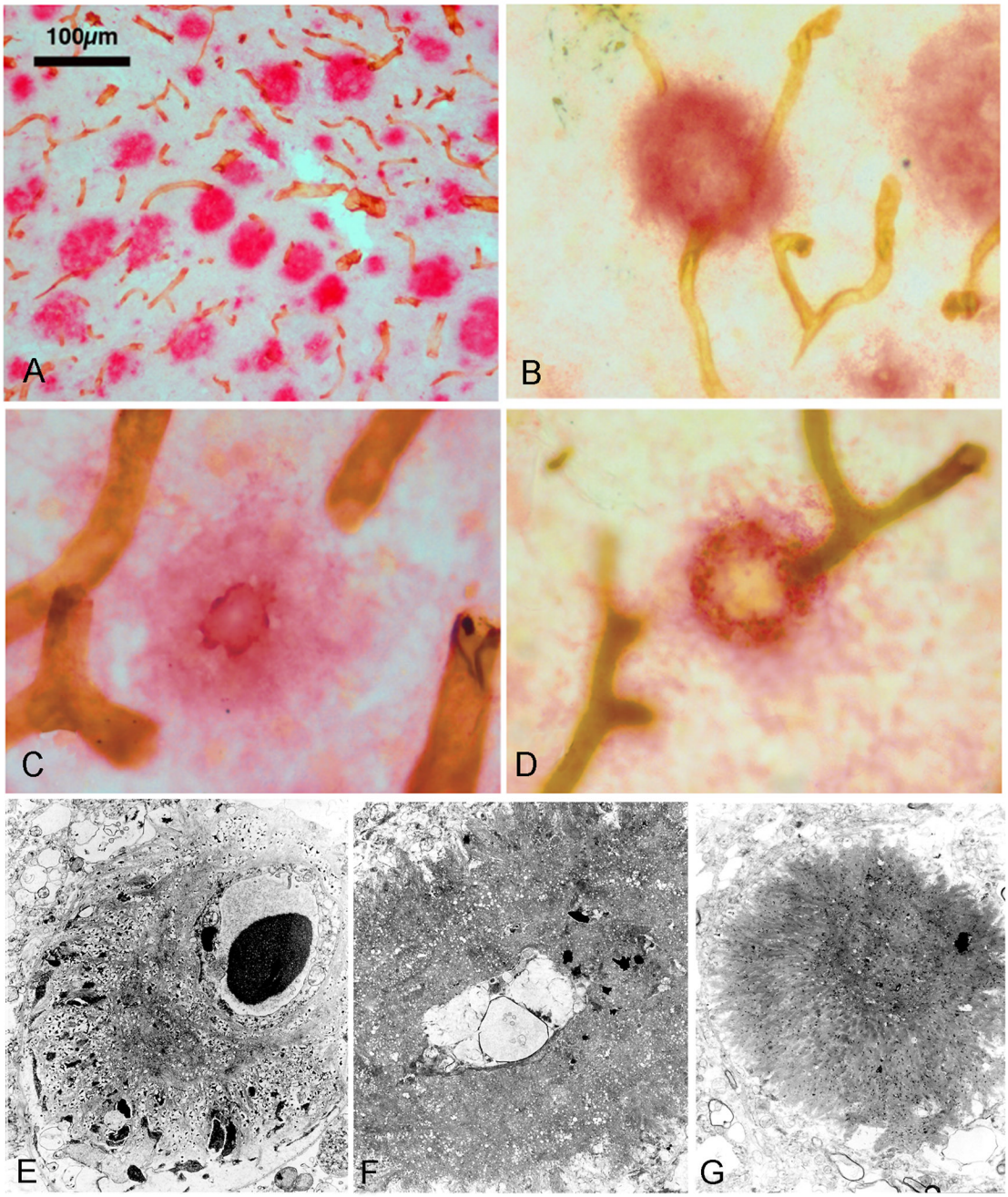

Figure 2. Spatial associations between amyloid plaque cores and microvessels in AD cortical areas

A) Digital image of entorhinal cortex of amyloid deposits stained with anti-Aβ (red) and microvessels (brown) stained with anti-collagen IV monoclonal antibody demonstrating the association between the two structures. **B**, **C** and **D)** These images demonstrate the close relationship between amyloid plaques and the cerebral microvessels. In some instances, the vessel is surrounded by the amyloid plaque or the amyloid plaque appear to be 'floating' free in the neuropil surrounded by remnant vascular stumps. For complete technical description and interpretation of data for **A**, **B**, **C** and **D** see Cullen et al 2006 [13]. Figures **A**, **B**, **C** and **D** reproduced with permission from the Publisher: Elsevier Inc. **E)** Electron

micrograph showing a core of amyloid attached to the surface of a cortical microvessel. The wisps of amyloid fibrils are inter-digitated with the extracellular matrix and cellular debris. **F)** As amyloid deposition advances, the swollen remnants of the blood vessel are entrapped at the center of an amyloid core. **G)** Once the blood vessel is totally obliterated and the vascular stumps retract, a dense core of radiating amyloid fibrils represent the ultimate permanent lesion. Magnification: E = 5500X; F = 5500X; G = 2500X.