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Aging and cerebrovascular dysfunction: contribution of hypertension, cerebral amyloid angiopathy, and immunotherapy

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Abstract

Age-related cerebrovascular dysfunction contributes to ischemic stroke, intracerebral hemorrhages, microbleeds, cerebral amyloid angiopathy (CAA), and cognitive decline. Importantly, there is increasing recognition that this dysfunction plays a critical aging secondary role in many neurodegenerative diseases, including Alzheimer's disease (AD). Atherosclerosis, hypertension, and CAA are the most common causes of blood brain barrier (BBB) lesions. The accumulation of amyloid beta (A β) in the cerebrovascular system is a significant risk factor for intracerebral hemorrhage (ICH), and has been linked to endothelial transport failure and blockage of perivascular drainage. Moreover, recent anti-A β immunotherapy clinical trials demonstrated efficient clearance of parenchymal amyloid deposits, but have been plagued by CAA-associated adverse events. While management of hypertension and atherosclerosis can reduce the incidence of ICH, there are currently no approved therapies for attenuating CAA. Thus, there is a critical need for new strategies that improve BBB function and limit the development of beta-amyloidosis in the cerebral vasculature.

Keywords

Alzheimer disease; cerebral amyloid angiopathy; blood brain barrier; immunotherapy; hypertension

Introduction

The majority of elderly have brain pathology, and those with multiple brain pathologies have a greater risk of developing dementia [1,2]. The common co-occurrence of Alzheimer's disease (AD) and vascular pathology suggest that many vascular risk factors may also be risk factors for brain atrophy and dementia [3,4]. Moreover, cerebral amyloid angiopathy (CAA) along with hypertension, are the two most common causes of intracerebral hemorrhage (ICH), and CAA has also been correlated with microbleeds in the elderly. Age-related alterations in transport across the BBB, as well as a reduction in the efficacy of the perivascular drainage pathway have been proposed to enhance accumulation of parenchymal and cerebrovascular amyloid deposits in the elderly [5–10]. Interestingly, modeling suggest that vessel pulsations provide the force to drive perivascular drainage, and age-related stiffening of arteries has been hypothesized to reduce flow thereby enhancing A β

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deposition in the perivascular space thereby further slowing the clearance of A β from the CNS [8,9].

There is at least some hope for CAA-induced neuropathology because in a subset of patients with a diagnosis of CAA where there were clinical manifestations of the CAA-related inflammation there was significant clinical improvement following anti-inflammatory therapy. The clinical symptoms were subacute cognitive decline or seizure rather than hemorrhagic stroke. Of six inflammatory CAA patients with available follow-up information, five demonstrated clinical and radiographic improvement after immunosuppressive treatment [11]. Additional studies have found associations between CAA, inflammation and dementia [12–14]. One conundrum of epidemiological studies linking anti-inflammatory drugs to favorable clinical outcomes [15] and studies of human diseases in animal models [16] is that they often fail in subsequent clinical trials. A likely critical factor in the success of anti-inflammatory drugs in treating diseases with associated inflammation is when the therapy is actually administered. For example, in a recent report where induction of autoimmune tolerance eliminated relapses, but failed to halt disease progression in a animal model of multiple sclerosis [17], suggesting that secondary disease processes were responsible for the continued decline in behavioral measures.

The remainder of this review we will focus on the pathological implications of CAA under normal aging conditions and in the presence of anti-A β immunotherapy in humans and in transgenic animal models. We will also discuss potential therapies to minimize the accumulation of CAA and reduce CAA-induced pathological complications.

Cerebral amyloid angiopathy

CAA is a collective name for the several diseases of different etiology sharing similar pathology. They are characterized by congophilic deposition of amyloid formed by different peptides such as A β , cystatin C, gelsolin, prion protein, ABri and ADan within the walls of small and medium size cerebral blood vessels and sometimes in the microvasculature [18–21]. However, the most frequent form of CAA is caused by cerebrovascular accumulation of A β in sporadic disorders in the elderly and is present in 80–100% of AD patients, and 100% of individuals with Down Syndrome [19,22–25]. The incidence of CAA in the elderly population without AD or other neuropathological abnormalities is age dependent and increases from 13.8% of people between 60 and 69 years to 44.8% of those 80 years and older [26]. CAA is not restricted to humans only and can be easily found in aged mammals: dogs and non-human primates [27–29]. In humans hereditary CAA is often complemented by hemorrhages and stroke and initiated by vasculotropic autosomal dominant mutations in A β sequence of Dutch, Iowa, Flemish, Arctic and Italian types [12,30–33]. Other familial mutations associated with increased risk of CAA also connected with extra copies of APP as in French families with APP duplication [34], trisomy 21 [23], or APP processing-related enzymes presenelin-1 or -2 [35–39].

Cerebral amyloid angiopathy and hypertension

CAA is, along with hypertension, the most common cause of ICH in the elderly. CAA-ICH is characterized by a high rate of recurrence, estimated at 21% at two years, with in-hospital mortality of 24% and six month mortality of 32% [40]. Given the high recurrence rates and devastating consequences of CAA-ICH, it is remarkable that there are currently no treatments available to prevent CAA-ICH. Clinical interventions usually consist of blood pressure control (i.e., hypertension treatment), as well as avoidance of medications that increase systemic hemorrhage risk (e.g. aspirin). However, there are currently no available treatments to specifically reduce the risk of CAA-ICH.

CAA may be an important predisposing factor for hemorrhagic complications of recombinant tissue-type plasminogen activator therapy for ischemic stroke [42]. Moreover, CAA is a well-described accompaniment of white matter disease of the elderly [50]; the latter is a near-universal accompaniment of aging and is regarded as a cerebrovascular disease variant. Another area of importance for CAA is its coexistence with ischemic stroke, ranging from large vessel occlusive disease to small vessel disease. In this setting, the clinician is faced with the highly problematic task of preventing brain infarction in a patient at high risk for brain hemorrhage. Ischemic stroke prevention almost always relies on pharmacotherapies that interfere with clotting pathways. Thus clinicians are faced with a profound dilemma in which prevention of ischemic stroke may exacerbate risk of hemorrhagic stroke.

Recently Schneider et al. [41] reported that the majority of elderly have brain pathology, however those that had multiple brain pathologies (AD, PD/LBD, or infarcts), had greatly increased odds (3 fold) for dementia. The common co-occurrence of AD and vascular pathology mesh with epidemiologic data showing that many vascular risk factors are also risk factors for brain atrophy and dementia [3,4]. Thus, there is increasing recognition that dysfunction in the cerebral vasculature plays a critical role in many neurodegenerative diseases, including AD where approximately 80–95% of the cases have cerebral vascular pathology [42,43]. Finally, Lippa and Knopman in an editorial on the Schneider et al. study proposed “that we may want to maximize medical management of vascular risk factors in the elderly, regardless of whether cognition is still normal [44].

Amyloid component of cerebral amyloid angiopathy pathogenesis

While there are multiple forms of amyloid deposits found in AD brain parenchyma, which include dense core plaques, neuritic plaques, diffused plaques and pre-amyloid aggregates [45,46], the amyloid deposits on the cerebral blood vessels are more uniform and always well organized and structured. Vascular amyloid deposits assembled in β -sheet structures and are easily stained with Thioflavin S (Figure 1) or Congo Red, which provides an additional name, “conophilic amyloid angiopathy”, for vascular deposits.

Despite the fact that vascular deposits in humans, all other mammal species and APP/Tg mice and consists predominantly of A β 40, CAA must be initiated, or “seeded”, by A β 42. The pivotal role of A β 42 in CAA formation was demonstrated in classical experiments by Todd Golde’s group using Tg mice selectively expressing only human A β 40 or A β 42 peptides in Bri-A β expressing cassette and crosses between those mice and Tg2576 [47,48]. While mice expressing high levels of A β 40 peptide did not develop parenchymal, nor vascular amyloid deposits, at the same time, mice expressing low levels of A β 42 over time started to accumulate not only parenchymal compact plaques and diffused deposits, but also vascular, mainly leptomeningeal, deposits, resembling amyloid angiopathy in humans [47]. Additional support for a role for A β 42 in seeding CAA comes from FAD mutations in presenilin-1 (PS-1), which alters cleavage of A β from the less amyloidogenic and more soluble A β 40 towards aggregation prone A β 42. Despite the shift in A β 40/A β 42 production towards A β 42, which on average increased from 10% of total A β in wild type PS-1 to 20.6 $\pm$ 9.6% in different PS-1 mutants [49,50] and dramatic cotton wool, diffused and dense core amyloid deposition in parenchyma, individuals carrying these mutations always have extensive CAA pathology [35,38,51]. It is important, that CAA A β is always organized in β -sheet Congo Red positive structures. In FAD of Dutch type A β accumulates predominantly in the small vessels of leptomeninges and cerebral cortex. It is deposited in the parenchyma mainly in the form of pre-amyloid Congo Red negative deposits, while mature neuritic plaques and neurofibrillary tangles, hallmark of AD, are characteristically absent [52,53]. At the same time Congo Red positive A β deposits associated with cerebrovasculature remained

consistent with the AD pathological features. Interestingly, in aged dogs parenchymal A β deposits are predominantly of Congo Red negative diffuse type, while canines develop congophilic angiopathy with age (Figure 1) [54–56]. Also, in aged squirrel monkeys cerebrovascular amyloid is the most abundant form, even in the cases of severe cerebral amyloidosis [57]. APP transgenic mice we also found only Thioflavin S positive fibrillar amyloid deposits associated within the cerebral vasculature (Figure 1).

Ultrastructural analysis of CAA location revealed that in large leptomeningeal arteries amyloid deposits consists of clusters of fibrils in the outmost part of the basement membrane at the media-adventitia junction [58]. In small leptomeningeal arteries and arterioles amyloid found in the outer portion of the basement membrane, with smaller deposits surrounded by the intact smooth muscle cells (SMC), while the bigger, more advanced deposits are surrounded by degenerative SMC. In capillaries smaller deposits are also associated with abluminal basement membrane, which often abnormally folded and layered. Astrocytes foot processes and activated microglia is associated with such deposits [58]. Natta et al. using gold-labeled anti-A β 40 and anti-A β 42 specific antibodies on sections from hereditary cerebral hemorrhages with amyloidosis, Dutch type (HCHWA-Dutch) patients revealed possible molecular mechanism of CAA formation [59]. It starts with non-fibrillar A β 42 deposits associated with reticular and electron dense structures on capillaries. Further, there were very few A β 42+40- deposits of fibrillar structure, while the majority of deposits were larger and always fibrillar A β 42+40+, often extended in the surrounding neuropil. A β 40 was not detectable at the capillary basement membrane without A β 42+ presence, suggesting that vascular amyloidosis as well as parenchymal plaques, is a nucleation-dependent phenomena and require fibrillar A β 42+ as a seed [60]. Multiphoton microscopy analysis of CAA development in mouse AD model demonstrated a stereotypical pattern, with vessels over the dorsal surface of the brain showing an anterior-to-posterior and large-to-small vessel gradient of involvement. Higher magnification imaging showed that CAA began with a banding pattern determined by vascular smooth muscle cells. Later on, gaps between amyloid bands shrink and disappear, gradually reaching a confluent structure. Also CAA deposits are propagating by expansion of the already formed plaques rather than forming new “eyes” of the deposition [61,62]. However, which factors promote A β 42 adherence to the basement membrane and initiate the chain reaction of A β assembly and proliferation into fibrillar form remains to be investigated.

Non-amyloid components of cerebral amyloid angiopathy pathogenesis

Besides A β , which is the major component of senile plaques these lesions also accumulate other factors. The most common proteins detected in senile plaques, include proteoglycans [63], apolipoprotein E [64]; protease inhibitors α 1-antichymotrypsin [65], α 2-microglobulin [66]. Additionally Amyloid P, complement components C1q, C3d, C4d and membrane attack complex C5b-9, and complement inhibitors vitronectin, protectin and clusterin have also been reported to be in plaques [67,68], growth factors and signaling molecules like cytokine-inducible adhesion molecule-1 [69]. Among the multiple proteins associated with senile plaques there is possibly a group of mainly inert molecules, while the majority of the proteins continue to be functionally active, thus attracting surrounding microglial cells and astrocytes and inducing their activation [68], which may occur independently of the chemoattractant and stimulatory properties of the fibrillar forms of A β .

Similar to the non-amyloid composition of senile plaques, there is robust presence of complement factors C1q, C3c, C4D and C5b-9 in the CAA [70,71]. Verbeek et al. reported especially strong staining for C4d and C3c factors, while C1q was present in CAA with variable intensity [71]. Exceptionally strong staining of CAA was also detected for MAC C5b-9, compared with less intensive deposition in senile plaques, which suggests classical

activation of the complement system and formation of membranolytic complex in CAA, and together with non sufficient complement inhibitory activities indicates extensive inflammation and degeneration of the vascular cells in CAA.

Analysis of the complement deposition in APP23 mouse AD model indicated a relatively weak complement response compared with AD, with similarly weak activation of microglia [72]. Antibodies against C1q, C3, C3d and C5 recognize parenchymal amyloid deposits weakly with more prominent cerebral vessels staining [72]. Microglial cells also express lower levels of complement CD11b receptor. In another AD mouse model TgSwDI with vasculotropic A β Dutch and Iowa mutations, with characteristic deposition of fibrillar A β in microvessels of the thalamus and hippocampus, and Thioflavin negative diffuse A β deposits throughout the frontal cortex [73], C1q, C3 and C4 were elevated in the regions of fibrillar A β deposits, e.g. thalamus and hippocampus, while the frontal cortex was free of complement deposition [74]. We found low levels of C1q and C3b complement factors associated with parenchymal plaques and vascular amyloid deposits in Tg2576 mice (Figure 2). Overall, in AD the strong deposition of complement and the co-localization of the membrane attack complex with damaged neurites and cerebral vasculature has led to speculation that complement activation is responsible for considerable neurodegeneration and cerebrovascular dysfunction [75].

Experiments with mice deficient in complement components has produced mixed results regarding the possible role of complement in A β pathology and AD [76]. Inhibition of C3 activation with complement receptor-related protein significantly reduced reactive microgliosis, increased A β deposits in hAPP mice and was accompanied by a prominent accumulation of degenerating neurons [77]. Similar results were obtained in C3 deficient APP/C3^{-/-} mice, which developed significantly increased total A β and amyloid plaque burden, significant loss of neuronal markers and differential activation of microglia towards the alternative phenotype [78]. APP mice deficient in C1q, APPQ^{-/-}, also had strong reduction in glial activation biomarkers similar to APP/C3^{-/-} mice, but they did show any differences in A β deposits [79]. Moreover, APPQ^{-/-} mice demonstrated reduced neurodegeneration based on immunostaining for synaptophysin and MAP2 compared with their C1q sufficient APP counterparts.

Another important component of both CAA and parenchymal A β deposits is apolipoprotein E [64,80,81]. There are three allelic variants of ApoE in humans, ApoE2, ApoE3 and ApoE4, and individuals with one or two ApoE4 alleles have progressively higher risks and younger age of AD onset [82,83]. The ApoE4 allele also increases the odds ratio for moderate or severe CAA by 2.9-fold if present as one allele, and 13.1-fold if present in two copies relative to the non-epsilon 4 carriers [84]. Individuals with ApoE4 alleles also have higher risks and earlier age of incidence for lobar hemorrhages [85]. ApoE4 genotype defines not only the risk of AD onset, but also the specific pathological feature of A β CAA deposits. Thal et al.[86] defined two forms of sporadic CAA. CAA-type1 is characterized by immunohistochemical detection of A β in cortical capillaries, leptomeningeal and cortical arteries, arterioles, veins and venules [86]. The CAA-type2 also exhibits A β deposits in leptomeningeal and cortical vessels, with the exception of cortical capillaries. The ratio of CAA-type1 and CAA-type2 were independent of severity of AD-related beta-amyloidosis, CAA-severity or increasing age, which suggested two different types of CAA pathology. At the same time, the ApoE4 allele constituted a 4-times higher risk of CAA-type1 and neuropil-associated vascular A β deposition in capillaries [86].

The question of how ApoE affects the risk of developing AD and how it contributes to A β deposition has been addressed with an ApoE knockout mouse model [87]. The cross between the PDAPP mouse AD model [88] with mice deficient in ApoE^{-/-}, demonstrated

that ApoE^{-/-} mice had dramatically decreased immunoreactive A β deposits, which were present in the form of diffuse plaques, thus suggesting an important role of ApoE in facilitating A β peptide deposition [89]. Further analysis of these mice revealed a role for ApoE in the anatomical distribution of A β and APP processing. Lack of ApoE produced altered levels of full-length APP and elevated levels of A β in an age and region-dependent manner [90,91]. Nilsson et al. demonstrated that ApoE facilitates both diffuse and fibrillar amyloid deposition and promotes cognitive impairment in PDAPP mice [92]. ApoE^{-/-} mice were also crossed to another mouse model of AD, Tg2576 with a Swedish mutation [93,94], which is known for an age-related progressive cerebral vascular amyloid accumulation in leptomeningeal and cortical vessels. Once again there was a robust reduction of parenchymal and vascular A β deposits, and in neuritic degeneration, thus further demonstrating the role of ApoE in pathological formation of not only neuritic but also CAA [95,96]. In TgSwDI mice, substitution of the endogenous mouse ApoE for human ApoE3 or ApoE4 led to a strong shift from primarily microvascular fibrillar A β deposits towards parenchymal fibrillar deposition, however the ApoE4 isoform remained more vasculature-prone than the ApoE3 [97].

Cerebral amyloid angiopathy and anti-A β immunotherapy

In 1999, Dale Schenk, and colleagues, at Elan reported that immunization of PDAPP transgenic mice with a vaccine containing fibrillar A β induced anti-A β antibodies that inhibited A β plaque deposition, dystrophic neurites and astrogliosis in the brains of the mice [114]. Importantly, when older mice that had already developed A β plaques were immunized with A β peptide, the amyloid plaques were cleared from the brain. Subsequently, other researchers showed that anti-A β immunotherapy improved behavioral measures in APP-transgenic mice [115]. Thus Anti-A β immunotherapy represents a potentially powerful strategy for reducing pathological forms of A β , and possibly aberrant forms of tau, in the brains of AD patients [98–104]. Although results from the Phase I trial showed good safety and tolerability, the phase IIa portion of the AN1792 immunotherapy vaccine trial was halted because approximately 6% of the volunteers developed symptoms of an adverse inflammatory response in the brain [105]. Postmortem analysis of two cases with meningoencephalitis showed robust glial activation, T-cell infiltration and clearance of A β . Speculation on the cause of the meningoencephalitis has focused on A β -reactive T cells and adjuvant-induced inflammation in the brain [106,107].

In addition, both active and passive immunotherapy increase the risk of adverse cerebral vascular events, including increased densities of cortical microhemorrhages and microvascular lesions, white matter abnormalities and vasogenic edema [103,108–112]. Interestingly, transgenic mouse models of Alzheimer's disease amyloidosis have actually been good predictors of anti-A β immunotherapy-induced adverse events in the cerebral vasculature.

Overall, there was significant reduction in cortical A β plaque load and gliosis, and a reduction in dystrophic neurites in patients immunized with fibrillar A β . However, initial reports did not detect a change in neurofibrillary pathology in response to immunotherapy [101]. More recent analysis with a larger group of cases have reported a significant reduction in neuropil threads and dystrophic neurites in areas cleared of amyloid plaques, i.e. cerebral cortex, CA1 hippocampus, subiculum and entorhinal cortex [104,113]. However, the phospho-tau accumulation in the neuronal cell bodies, contributing to neurofibrillary tangles, appeared not to be affected [104]. We previously reported a similar finding regarding the persistence of established tangles even with high titers of anti-A β antibodies in the 3xTgAD model [114]. Importantly, relatively high and chronic anti-A β antibodies titers appear to be required to maintain amyloid clearance in the brain [103].

As mentioned above, APP transgenic mice have proven to be good predictors of anti-A β immunotherapy-induced adverse events in the cerebral vasculature. In both mice and humans CAA for the most part has remained refractory to immunotherapy [98,99,103,115–117]. Moreover, the decrease of parenchymal A β plaques due to anti-A β immunization has been accompanied by a corresponding increase in vascular amyloid deposition. This has been interpreted to be due to immunotherapy-induced mobilization of A β in plaques, consisting of mostly A β 42, which then travels with the flow of interstitial fluid to the basement membranes of cerebral capillaries and arteries where the A β accumulates [7]. Evidence in support of this hypothesis has come from further analysis of the CAA in patients that were vaccinated, which showed a prominent increase in the amount of A β 42 in the cerebral vessels. Whether the immunotherapy-induced adverse cerebral vascular events can be clinically managed remains to be determined. For example, during the phase II stage of Elan's Bapineuzumab (AAB-001) passive immunotherapy clinical trial 10 out of 12 patients that developed vasogenic edema were ApoE 4 positive, and ApoE 4 is found in 40% of the AD population, however lower dosing with the antibody appears to reduce the risk. Regarding the mechanism underlying the immunotherapy-mediated increase in CAA, Carare and colleagues have proposed that antibody-A β immune complexes may actually interfere with perivascular drainage when they are located specifically in the basement membranes, but at later time points perivascular drainage actually recovers due to clearance of immune complexes [Carare R et al., 9th International Alzheimer's Congress / Parkinson's Congress (AD/PD) 2009 Prague, Czech Republic]. Recent neuropathological data from the AN1792 clinical trial also provides support for the possibility that long-term immunotherapy may be able to clear A β from the cerebral vasculature. Analysis of two cases where the immunized patients lived for an extended period of time (four to five years) with the persistent presence of anti-A β antibodies had virtually complete absence of both plaques and CAA [103].

Reducing CAA and the incidence of pathological complications

In old canines immunized with aggregated A β 42 monthly for 25 months we were able to induce high levels of anti-A β antibodies. Immunotherapy initiated a robust reduction in parenchymal amyloid plaques in the absence of detectable CAA deposition, further supporting idea that the increase in CAA in response to immunotherapy may be transient [103,118].

Another significant adverse event associated with immunotherapy and redistribution of A β from the parenchyma towards cerebral vasculature is the increased density of microhemorrhages, initially described in the mouse model of AD [115] and subsequently reported in AN1792 clinical trials [103,119]. We also reported a significant increase in cerebrovascular microhemorrhages after active immunization of old Tg2576 mice [120], with involvement of leptomeningeal vessels and cortical arteries. Moreover, the concurrent increase in CAA and microhemorrhages was accompanied by significant co-localization of complement factors C1q and C3b at sites of CAA and microhemorrhages (Figure 3). Interestingly, in very old Tg2576 mice the cognitive benefits of immunotherapy persisted in spite of increased risks of CAA and microhemorrhages [121].

In preliminary studies we have tested the hypothesis that immunotherapy-induced microhemorrhages are caused by inflammation from antibody-A β immune complex formation at the sites of the CAA. In very old (20+ months) Tg2576 APP transgenic mice with substantial CAA we co-administered minocycline, which can suppress activation of microglia and monocytes, together with passive immunotherapy. While minocycline significantly attenuated microglial activation, it did not affect the number of microhemorrhages in the brains of the mice. However, minocycline did modestly decrease the size of microhemorrhages (Figure 4).

Other approaches aimed at minimizing adverse events at sites of CAA include utilizing deglycosylation of the Fc portion of anti-A β immunoglobulins to reduce complement activation and Fc receptor-mediated inflammatory functions. APP transgenic mice that received the deglycosylated anti-A β (de-2H6) showed significant reductions in total A β immunohistochemistry and Congo red. Significantly fewer vascular amyloid deposits and microhemorrhages were observed in mice administered the de-2H6 antibody compared with mice receiving unmodified 2H6 antibody. Thus deglycosylated anti-A β antibodies may be preferable to unmodified IgG for anti-A β immunotherapy [122,123]. Finally, intracerebroventricular delivery of low levels of anti-A β antibodies, as oppose to high doses delivered peripherally, reduces CAA and associated microhemorrhages, while preserving amyloid-clearing and behavior benefits in Tg2576 mice [124].

Conclusion

Recognition that cerebral vascular dysfunction plays a critical secondary role in many neurodegenerative diseases, and that the blood brain barrier appears to be particularly susceptible to age-related functional decline presents a significant challenge to researchers and clinicians. We envision two areas that should be targeted for future therapeutic intervention, endothelial cell transport and the perivascular drainage pathway, because both are involved in removing metabolic waste products from the brain. In this review we have focused on the clinical problems, such as intracerebral hemorrhage, deficits in endothelial transport, clogging of perivascular drainage, and increased microhemorrhages associated with the accumulation of one particular waste product, the A β peptide, which is the primary component of CAA in the vascular system. We also addressed the issue CAA-associated adverse events linked to anti-A β immunotherapy, and provided some examples of potential therapies to minimize the accumulation of CAA and reduce CAA-induced pathological complications.

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Figure 1.

In canines fibrillar A β preferentially accumulates in the cerebral vasculature. (A) Prefrontal cortex of 15 years old border collie was stained with anti-A β antibodies. A β accumulates in the cerebral vessels as fibrillar Thioflavine S positive deposits and co-localizes with activated glial and endothelial cells. (B) Amyloid beta was detected with pan-A β antibodies (red color) and fibrillar A β forms were visualized with Thioflavine S staining (green) in 7- and 12-months old TgSwDI and 18 months old Tg2576 mice. (C) Activated glial and endothelial cells were detected with anti-CD14 antibodies (red) and fibrillar A β was detected with Thioflavine S (green) in 18 months old Tg2576 mice.

Figure 2. Complement factors C1q and C3b are more strongly associated with vascular A β deposits than the parenchymal ones. Brain sections from 18 months old Tg2576 mice were immunostained with anti-C1q or C3b specific antibodies.

Figure 3. Anti-A β immunotherapy in very old Tg2576 mice is associated with the increased incidents of vascular failure. 18 months old Tg2576 mice were treated with mannan-A β_{28} conjugate vaccine, which significantly reduced amyloid load and gliosis, but also increased CAA, microhemorrhages and complement deposition. (A) Thioflavine S positive meningeal vessel (green) decorated with C1q (red). (B) Parenchymal arteries of immunized mice are often immunopositive for complement factor C3b. (C) Cerebral blood vessels of immunized mice showing microhemorrhages (blue).

Figure 4.

Preliminary studies with minocycline as an adjunct anti-inflammatory therapy to anti-A β immunotherapy in very old Tg2576. Twenty months old Tg2576 were injected weekly with anti-A β antibodies and supplemented with minocycline diet for 9 weeks. (A) Passive immunotherapy reduced amyloid plaque load. (B) Passive immunotherapy reduced glial activation and was further attenuated by minocycline. (C) Anti-inflammatory minocycline therapy had no effect on microhemorrhage occurrence, but (D) minocycline modestly decreased the size of microhemorrhages.