

Vascular pathology in the aged human brain

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Abstract Cerebral atherosclerosis (AS), small vessel disease (SVD), and cerebral amyloid angiopathy (CAA) are the most prevalent arterial disorders in the aged brain. Pathogenetically, AS and SVD share similar mechanisms: plasma protein leakage into the vessel wall, accumulation of lipid-containing macrophages, and fibrosis of the vessel wall. CAA, on the other hand, is characterized by the deposition of the amyloid β -protein in the vessel wall. Despite these differences between CAA, AS and SVD, apolipoprotein E (apoE) is involved in all three disorders. Such a pathogenetic link may explain the correlations between AS, SVD, CAA, and Alzheimer's disease in the brains of elderly individuals reported in the literature. In addition, AS, SVD, and CAA can lead to tissue lesions such as hemorrhage and infarction. Moreover, intracerebral SVD leads to plasma protein leakage into the damaged vessel wall and into the perivascular space resulting in a blood–brain barrier (BBB) dysfunction. This SVD-related BBB dysfunction is considered to cause white matter

lesions (WMLs) and lacunar infarcts. In this review, we demonstrate the relationship between AS, SVD, and CAA as well as their contribution to the development of vascular tissue lesions and we emphasize an important role for apoE in the pathogenesis of vessel disorders and vascular tissue lesions as well as for BBB dysfunction on WML and lacunar infarct development.

Keywords Atherosclerosis · Small vessel disease · Cerebral amyloid angiopathy · Brain infarction · Hemorrhages · White matter lesions

Introduction

The three most important vessel disorders in the elderly brain are cerebral atherosclerosis (AS), small vessel disease (SVD), and cerebral amyloid angiopathy (CAA). All three disorders can lead to infarction and hemorrhage [56, 87, 102]. SVD is also associated with white matter lesions (WMLs) [48]. Infarction, hemorrhage, and WMLs cause the destruction of brain tissue and, thereby, frequently cause neurological symptoms.

This review is aimed at identifying pathogenetic mechanisms involved in AS, SVD, and CAA that may explain their correlation with one another and with vascular lesions, such as hemorrhage, infarction, and WMLs. To address this aim, we will first summarize the current knowledge about these vessel disorders. Second, we will discuss the correlation between these vessel diseases and the proteins involved in the pathogenesis of all three disorders. Third, we will summarize the current concepts about the involvement of apolipoprotein E (apoE) in these vessel disorders, and discuss potential pathogenetic mechanisms that may represent a link among them. Then,

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the relationship between the vessel disorders and vascular brain lesions will be reported and pathogenetic mechanisms will be discussed.

Pathology of major vessel disorders in the aging brain

Atherosclerosis

Atherosclerosis is a degenerative vessel disorder that frequently affects large- to medium-sized arteries. In the brain, the vessels of the circle of Willis are often involved [5, 66]. The occurrence and the severity of AS in the circle of Willis increase with age (Table 1). AS changes in small arteries overlap with those found in SVD. Atherosclerotic plaques are prone to rupture with subsequent thrombosis [119, 120]. The thrombus resulting from plaque rupture can either lead to vessel occlusion or it can embolize and occlude a smaller artery [73]. Embolism is most frequently originated from the extracerebral parts of the vertebral artery and the common and internal carotid arteries [73]. Atherosclerotic aneurysm is a consequence of cerebral vessel wall destruction, rarely leading to subsequent rupture and hemorrhage [56].

Intima thickening and accumulation of blood-derived lipids in the intima initiate the development of AS [66, 121]. Further intima proliferation, splitting of the lamina elastica interna and the accumulation of cholesterol-laden macrophages lead to the generation of atherosclerotic plaques [119–121] (Fig. 1a, b), which is accompanied by further destruction of the vessel wall and the accumulation of T-lymphocytes and macrophages [42, 119–121]. In later stages, AS plaques exhibit a necrotic core, cholesterol clefts and calcifications [119]. AS plaque rupture is associated with (1) inflammation, including the secretion of cytokines [e.g. interleukin (IL)-1 α , IL-12, IL-18], (2) collagen-degrading enzymes, such as matrix-metalloproteinases (e.g. MMP-1, MMP-9) and the neutrophil elastase, which are involved in

the degradation of the vessel wall [20, 21, 23, 71, 72], (3) anti-oxidative stress response as indicated by the presence of glutathione-S-transferase omega [65], and (4) endothelial/intimal alteration as indicated by the occurrence of plasma proteins [e.g. α 2-macroglobulin (A2M; Fig. 1), neutrophil elastase] in the AS plaque [70, 117]. Arterial hypertension is a well-known risk factor for AS [76] and may foster plasma protein leakage into the vessel wall. Other risk factors are increased homocysteine plasma levels found in AS patients [148] and the 677C-T mutation in the MTHFR gene (methylene-tetrahydrofolate reductase—an enzyme that is involved in the remethylation of homocysteine, the mutation results in increased plasma homocysteine levels) [32].

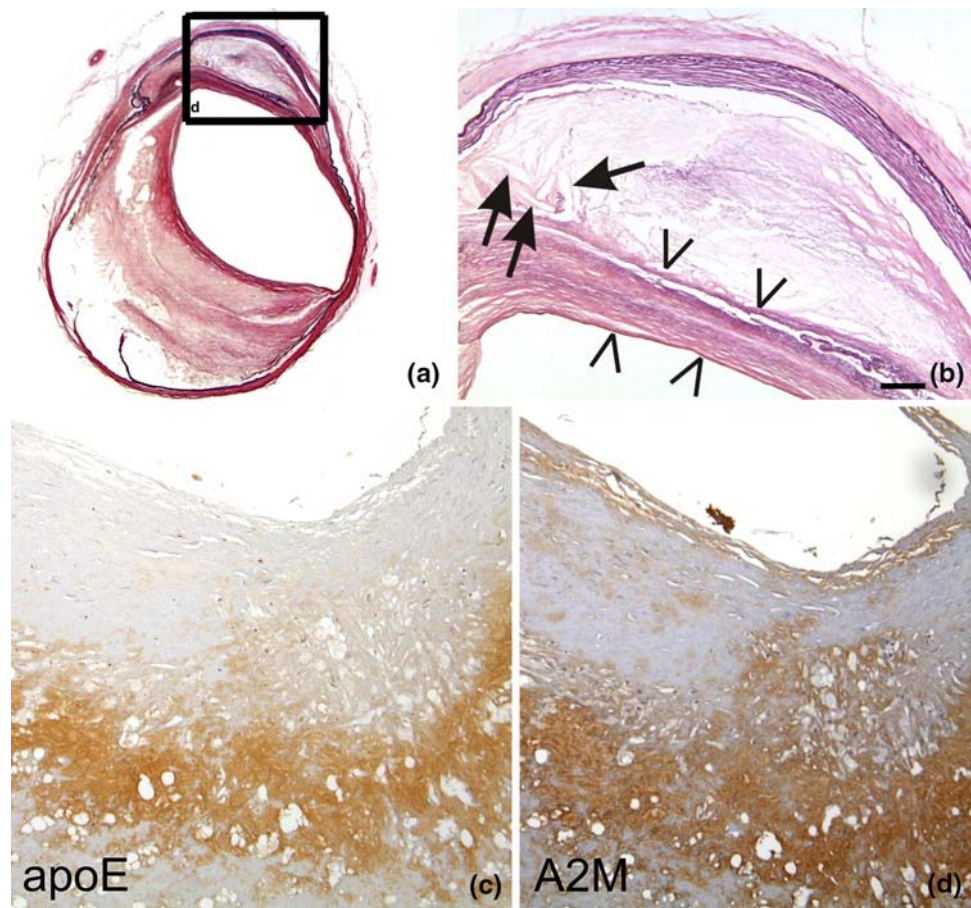
ApoE and its receptors are critically involved in the pathogenesis of AS. ApoE-knockout mice and low-density lipoprotein (LDL) receptor knockout mice develop AS [8, 156]. Dysfunctional uptake of LDLs may, thereby, lead to the accumulation of oxidized LDLs in the atherosclerotic vessel wall [9]. Thus, oxidized LDLs may be candidates to trigger the development of atherosclerotic plaques. ApoE and LDL receptors [e.g. LDLR and A2M receptor/LDL receptor-related protein (LRP = CD91)] were found in AS plaques (Fig. 1c) [8, 43]. The apoE ϵ 4 allele is controversially discussed as a possible genetic risk factor for AS [64, 75, 116]. The second ligand of LRP, the plasma protein A2M, also accumulates within AS plaques (Fig. 1d) [117] and an association of its deletion/insertion polymorphism with the expansion of AS plaques within the circle of Willis has been reported [70]. The accumulation of A2M within the AS plaque did not correlate with the type of the AS lesions [71] suggesting that plasma protein influx including A2M may play a role in the initiation of AS plaques but not for plaque rupture. In summary, apoE, LDL receptors and A2M are involved in the pathogenesis of AS. Leakage of plasma apoE and A2M possibly contributes to the development of AS plaques.

Table 1 Distribution of frequencies of autopsy cases with a given extent of atherosclerosis (AS) within the arteries of the circle of Willis (CaW) among different age groups

Extent of AS	Frequency of cases/% in the age group		
	60–70 years	71–80 years	81 years and older
No AS	20.69	3.57	4.00
1–25% of CaW vessels with AS	17.24	7.14	12.00
26–50% of CaW vessels with AS	20.69	32.14	8.00
51–75% of CaW vessels with AS	24.14	35.71	40.00
76–100% of CaW vessels with AS	17.24	21.43	36.00

The table presents the percentage of cases without AS and with AS in a given extent in the age groups 60–70, 71–80, and 81 years and older. This observation is based on the data obtained from 82 non-selected autopsy cases. The circle of Willis was observed macroscopically for the presence or absence of the 11 arteries of the circle of Willis as previously described [70]. The extent of AS was calculated as: number of AS-affected vessels \times 100/number of investigated vessels of the circle of Willis [70]. The cases analyzed here were already included in other studies under other aspects [65, 70]

Fig. 1 a, b The left internal carotid artery of a 79-year-old man exhibits severe atherosclerotic changes (Type 5 according to Stary [119]). There is a thinning of the lamina media, proliferation and lipid accumulation in the intima including cholesterol clefts (*arrows*). The necrotic core is covered by a fibromuscular tissue layer (*arrowheads*) indicative for Stary Type 5 lesions. **b** Corresponds to a high magnification view of the boxed area in (a). ApoE (c) and A2M (d) occur in the plaque core of an AS plaque. Staining in (a, b) Elastica van Gieson (EVG), c anti-apoE [Covance (Dedham, USA), D6E10, 1/500, formic acid and microwave pretreatment], d anti-A2M [BioMac (Germany, Leipzig), polyclonal rabbit, 1/5,000]. The calibration bar in (b) corresponds to: a 400 μ m, b 90 μ m, c, d 70 μ m



Small vessel disease

Small vessel disease encompasses degenerative alterations in the vessel wall of the small arteries and arterioles that are assumed to be pathogenetically linked [51, 67, 142]. SVD includes changes also described as small vessel arteriosclerosis/atherosclerosis, arteriolosclerosis, and lipohyalinosis [51, 67, 142]. These three subforms of SVD and how they are pathogenetically linked to one another will be discussed hereunder. CAA is not included in this group basically because of differences in the pathogenesis and the location of affected vessels.

Small vessel arteriosclerosis/atherosclerosis constitutes AS in small intracerebral and leptomeningeal arteries (200–800 μ m in diameter). The vessels show endothelial proliferation, splitting of the lamina elastica interna (Fig. 2a), small plaque-like accumulations of plasma proteins, lymphocytes and macrophages (microatheroma) [31, 67]. The pathogenesis is similar to that of AS including the role of apoE leakage and the mechanisms responsible for thrombosis and hemorrhage development [67]. Smaller arteries (40–300 μ m) exhibit asymmetric areas of fibrosis/hyalinosis associated with foam cells and leakage of plasma proteins such as apoE, A2M, and immunoglobulin

G (IgG) (Fig. 2b–f) termed *lipohyalinosis*. The initial lesion is a fibrinoid necrosis of the vessel wall in the absence of inflammation [67]. High arterial pressure and blood–brain barrier (BBB) breakdown are implicated in plasma protein leakage and fibrinoid necrosis in this disease [68, 91, 92]. Lipohyalinosis is different from concentric hyaline thickening of small arteries (40–150 μ m in diameter) leading to a concentric stenosis of the vessel lumen (Fig. 2g) [67] termed *arteriolosclerosis*. Due to the high blood pressure, plasma proteins, such as albumin, A2M and apoE, leak into the vessel wall and into the perivascular brain parenchyma [1, 139] (Fig. 2h–i). These changes are usually seen in white matter arteries [84, 140, 151].

SVD is first seen in the arteries of the basal ganglia, mainly in the putamen and the globus pallidus, which exhibit small vessel AS and lipohyalinosis. Secondly, small white matter arteries become affected by arteriolosclerosis or lipohyalinosis. Leptomeningeal arteries of the hemispheres and the cerebellum develop small vessel AS in parallel. Brain stem arteries, including those located between the pontine nuclei, usually develop lipohyalinosis or arteriolosclerosis only in the end stage of SVD [129]. Cortical vessels are usually free of SVD [129]. Enlarged

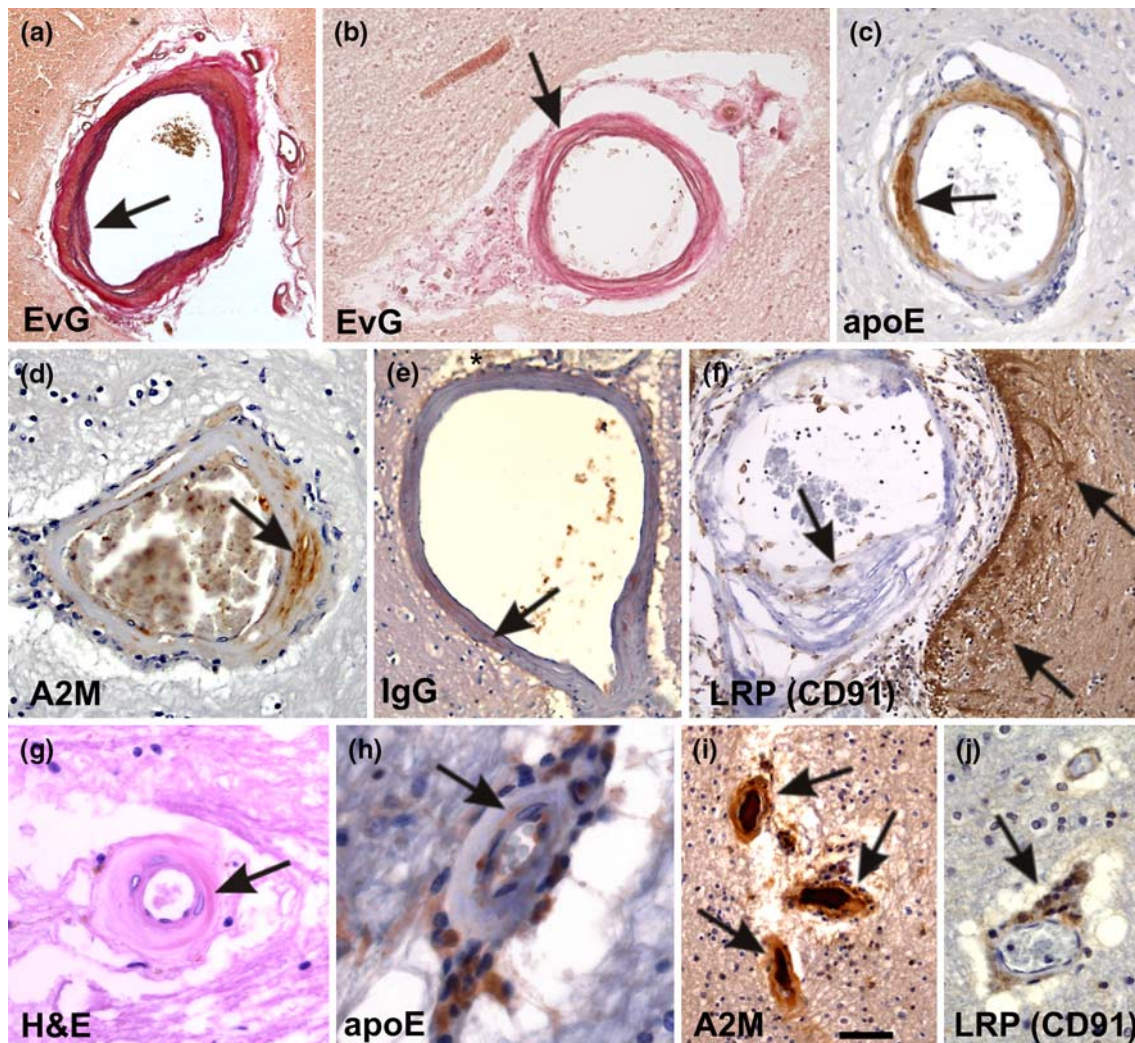


Fig. 2 Small vessel disease-related changes. **a** A leptomeningeal artery shows intima proliferation and a splitting of the internal elastic lamina (*arrow*). These changes are related to small vessel arteriosclerosis/atherosclerosis. **b** A white matter artery exhibits fibrosis, lipohyalinosis of the vessel wall, and fibrinoid necrosis (*arrow*). Lipohyalinosis affected vessels exhibit the plasma proteins apoE (**c**), A2M (**d**), and IgG (**e**) within the vessel wall (*arrows* in **c–e**) indicating the leakage of plasma proteins into the vessel wall and into the perivascular space (*asterisk* in **e**). **f** Macrophages within the lipohyalinotic lesions and perivascular astrocytes strongly exhibit the A2M and apoE receptor LRP (CD91) (*arrows*) indicating that these cells are capable of taking up A2M and apoE. **g** Arteriosclerosis of a white matter artery shows severe hyalinization (*arrow*) of the vessel wall. **h–j** ApoE and A2M were observed within the vessel wall of arteriosclerotic vessels (*arrows* in **h, i**). Within the enlarged perivascular spaces

high numbers of apoE (**h**), A2M (**i**), and LRP-positive cells (*arrow* in **j**) were observed indicating that these perivascular cells accumulate apoE and A2M due to an insufficient perivascular drainage. These perivascular macrophages are often Prussian blue negative and do not necessarily represent hemorrhagic residues [129]. Stainings in **a–j** as indicated. Anti-apoE and anti-A2M staining was performed as indicated in Fig. 1. For anti-IgG and anti-LRP immunohistochemistry the following antibodies were used [anti-IgG: polyclonal goat; Biomedical, Foster City, CA; 1/100; microwave pretreatment; anti-LRP (anti-CD91): α 2-M-R-II2C7; BioMac, Leipzig, Germany; 1/150; microwave and protease pretreatment]. The calibration bar in **i** corresponds to: **a** 300 μ m, **b** 80 μ m, **c** 40 μ m, **d, j** 35 μ m, **e, f** 60 μ m, **g** 20 μ m, **h** 16 μ m, **i** 50 μ m. **a** and **b** are reproduced from Thal et al. 2003 [129] with kind permission

perivascular spaces are often associated with SVD-affected vessels. As such, all subforms of SVD contribute to this hierarchical expansion of SVD changes throughout the brain and seem to be pathogenetically linked.

Arterial hypertension and diabetes mellitus are risk factors for SVD [69]. However, this association is lacking in a significant number of cases [69]. Plasma protein leakage into the vessel wall including apoE and A2M is a

common feature in all three subforms of SVD (Fig. 2c–e, h, j). Genetically, an association between SVD and the apoE ϵ 4 allele has been reported [154].

Cerebral amyloid angiopathy

Deposits of amyloid β -protein (A β) in the cerebral and leptomeningeal vessel walls are characteristic of CAA in

both sporadic and A β -related familiar forms [34, 55, 108]. A β deposits occur in arteries, veins and capillaries [141] (Fig. 3a, b). A β_{40} is more predominant in vascular A β deposits than in parenchymal ones [45, 110]. In the sporadic form of CAA, vascular A β deposition is strongly associated with AD-related pathology and around 80–100% of all AD patients have CAA [3, 4, 51, 55, 108, 126, 129, 132, 141]. Morphologically, two types of CAA can be distinguished: CAA with capillary involvement (CAA-type 1) and CAA lacking capillary A β deposition (CAA-type 2) [130]. Capillary CAA is more common in AD patients [4, 132] and it can induce capillary occlusions resulting in disturbances of cerebral blood flow [128]. The severity of CAA is related to the degree of vessel wall destruction [144]. Intracerebral hemorrhage, cerebral infarction [14, 79, 132, 141], and CAA-related angiitis [62, 78, 107] are complications of CAA (Fig. 3c).

CAA begins in cortical and leptomeningeal vessels of neocortical areas and then, expands into vessels of allocortical areas and the cerebellum. In single cases, even white matter arteries and vessels of the basal ganglia, the diencephalon, and/or the brain stem exhibit CAA [129, 132]. This hierarchical pattern resembles the one described for A β plaques [2, 131, 134].

Physiologically, brain-derived A β is drained along the perivascular space [15, 147] and the vascular basement membranes [16, 146]. Alterations of this clearance pathway may result in the deposition of A β near the basement membrane [146]. In addition, smooth muscle cell-derived A β is potentially capable of contributing to the deposition of A β in the vessel wall [85, 86]. ApoE plays an important role in the pathogenesis of CAA. It is found in vascular A β deposits [93] and it is physiologically drained along the perivascular space co-occurring with A β [133, 139]. ApoE binds A β [123]. Alterations of the perivascular drainage of A β and apoE likely lead to CAA [133, 146, 147]. CAA, especially capillary CAA, is associated with the apoE ϵ 4 allele [37, 100, 103, 126, 130, 132]. This finding points to an important role of apoE for the development of CAA because apoE4 is less effective in the receptor-mediated clearance of A β when compared to apoE3 [19]. This property of apoE4 presumably results in capillary A β deposition in apoE ϵ 4 carriers as soon as alterations in the perivascular drainage occur. In addition, the apoE ϵ 4-genotype promotes A β aggregation in vascular smooth muscle cell cultures [85]. Finally, CAA-related hemorrhage is reported to be associated with the apoE ϵ 2 and ϵ 4 allele [37, 88, 95, 97].

In familial cases, other amyloidogenic proteins can also aggregate in the cerebral blood vessels and cause other forms of CAA, i.e., ABri, ADan, transthyretin, gelsolin, cystatin D, and prion protein [108]. Unlike A β -related

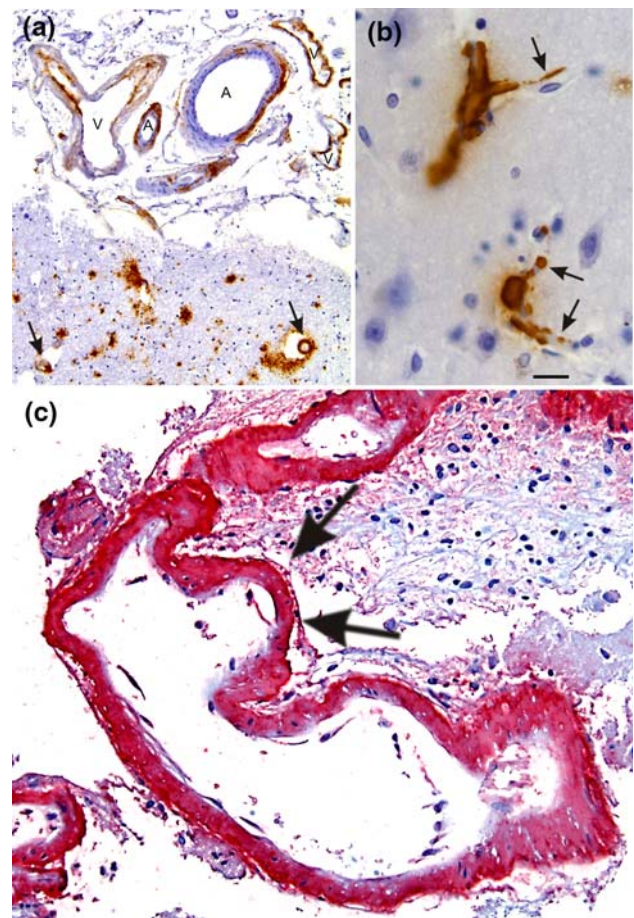


Fig. 3 Cerebral amyloid angiopathy (CAA). **a** A β deposition in the vessel wall of leptomeningeal arteries (A) and veins (V) as well as in cortical arteries (arrows). **b** Capillary CAA is characterized by A β deposits at the basement membrane of cortical capillaries (arrows). **c** Severe CAA in a case of CAA-related hemorrhage. The CAA-affected artery exhibits multiple aneurysmal dilations of the vessel wall as indicated by arrows. A β deposits are stained in red (permanent red; DAKO, Glostrup, Denmark) with an antibody against A β_{17-24} (4G8, Covance, Dedham, USA, 1/5,000, pretreatment with formic acid). The same antibody was also used in figures **a** and **b** but 3,3-diaminobenzidine–HCl was used as chromogen. The calibration bar in **b** corresponds to: **a** 85 μ m, **b**, **c** 20 μ m

CAA, these forms of CAA are usually not restricted to the cerebral and leptomeningeal vessels [108].

Relationship between SVD subforms, AS, and CAA

Although AS, SVD, and CAA are distinct disease entities, they correlate with one another as well as with AD except for AS, which did not correlate with CAA [5, 13, 109, 129]. In our own sample, we confirmed the correlation between AS and SVD, SVD and CAA, SVD and AD, and CAA and AD whereas there was no significant correlation between AS and CAA, and AS and AD (Table 2). In the

Table 2 Correlations between extent of cerebral atherosclerosis (AS), small vessel disease (SVD), cerebral amyloid angiopathy (CAA), and Alzheimer's disease (AD)

Correlation between	<i>r</i>	<i>p</i>	<i>n</i>
AS–SVD	0.475	0.003	36
AS–CAA	−0.109	0.488	43
AS–AD	0.15	0.175	83
SVD–CAA	0.252	0.025	79
SVD–AD	0.177	0.022	166
CAA–AD	0.575	0.001	87

The extent of AS was obtained as described in the legend of Table 1. The extent of SVD and CAA was measured by the stage of SVD and CAA distribution throughout the entire brain [129]. AD was diagnosed in the event that the pathology of the demented cases showed a moderate or high likelihood for AD according to the NIA-Reagan criteria [135]. Non-AD controls were all cases that did not match the NIA-Reagan criteria and did not develop dementia

r Spearman rho correlation coefficient, *p* probability, *n* number of cases analyzed

light of these correlations, it is tempting to speculate that AS, SVD, and CAA share common or linked pathogenetic mechanisms.

SVD and AS exhibit similar morphological alterations. For example, atherosclerotic lesions in small arteries are defined either as AS or as SVD (subform: small vessel arteriosclerosis/atherosclerosis). Partly, this overlap is explained by the similarities of the pathogenetic mechanism of AS in large- and medium-sized vessels as well as in small vessels [67], such as plasma protein leakage into the vessel wall. On the other hand, there are morphological differences that justify the distinction between AS and the SVD subform small vessel arteriosclerosis/atherosclerosis: AS plaques in large- and medium-sized vessels often contain cholesterol clefts and calcifications, which are usually not seen in small vessel arteriosclerosis/atherosclerosis.

SVD itself is subclassified into small vessel arteriosclerosis/atherosclerosis, arteriolosclerosis, and lipohyalinosis/fibrinoid necrosis. Despite morphological differences, plasma protein leakage into the vessel wall and/or into the perivascular space are common features of all three subforms (Figs. 2, 4a). The hierarchical expansion of SVD, encompassing all of its subforms, throughout the brain, as described in detail in “[Small vessel disease](#)”, also argues in favor of a common disease entity with different presentations in larger and smaller vessels rather than three different vessel disorders.

A pathogenetic link between AS and SVD on the one hand and CAA on the other is less obvious. However, apoE occurs in the SVD- and AS-related vessel wall lesions and in association with CAA-related A β deposits. Moreover, the apoE ϵ 4 allele is a risk factor for CAA [100, 115, 126],

SVD [154], and is discussed as a risk factor for AS [64, 75, 116]. The absence of apoE in apoE-knockout mice results in AS and hypercholesterolemia [156]. These points indicate that apoE is a common player in the pathogenesis of all three vessel disorder and may represent a pathogenetic link.

The role of apoE in vessel pathology of the aging brain

Apolipoprotein E appears to be a common player in the pathogenesis of AS, SVD, and CAA. It is a plasma protein produced by hepatocytes and macrophages [77] and it functions as a transporter for cholesterol and other lipids [77]. In the brain, apoE is produced by astrocytes [10, 77]. Under physiological conditions, an intact BBB prevents the influx of plasma apoE into the brain [22, 27]. Brain-apoE is drained along perivascular channels and vascular basement membranes [133]. It can bind cholesterol, lipids, and proteins such as A β [77, 123], which are cleared together with apoE [6, 106], suggesting that apoE may have a transporter function not only for cholesterol and lipids but also for proteins such as A β .

In AS- and SVD-affected vessels, plasma proteins including apoE leak into the vessel wall and accumulate in the respective lesion [1, 18, 91, 92, 139, 150] (Figs. 1, 2, 4). Plasma proteins also leak into the perivascular space of vessels affected by SVD indicating an alteration of the pre-capillary segment of the BBB [127, 139]. Thus, SVD presumably impairs perivascular clearance, including that of A β and apoE, by several mechanisms: (1) SVD-induced fibrosis of the vessel wall may decrease the capacity for drainage along the basement membranes [146], (2) the increasing stiffness of the SVD-affected arteries leads to a less effective outward transport of the perivascular fluid due to a cessation of the pulsations [146, 147], and (3) the SVD-induced leakage of plasma proteins including apoE into the vessel wall and the perivascular space competes for perivascular drainage with the extracellular fluid of the brain [127, 136, 137, 139] (Fig. 4). Therefore, SVD presumably contributes to the accumulation of A β in the brain leading to CAA and Alzheimer's disease-related A β plaque deposition. This hypothesis is supported by the association between SVD, CAA, and A β plaque deposition [13, 129] (Table 2) and by the increase of plasma A β _{1–40} in patients with SVD [35]. Since SVD and CAA are both localized in intracerebral small arteries and arterioles, which have a perivascular space, and since both disorders develop apoE-containing lesions [93, 139] and are associated with the apoE ϵ 4 allele as a genetic risk factor, it is tempting to assume that apoE represents a pathogenetic link between SVD and CAA. The hypothesis that apoE contributes to vessel wall destruction is further supported by the

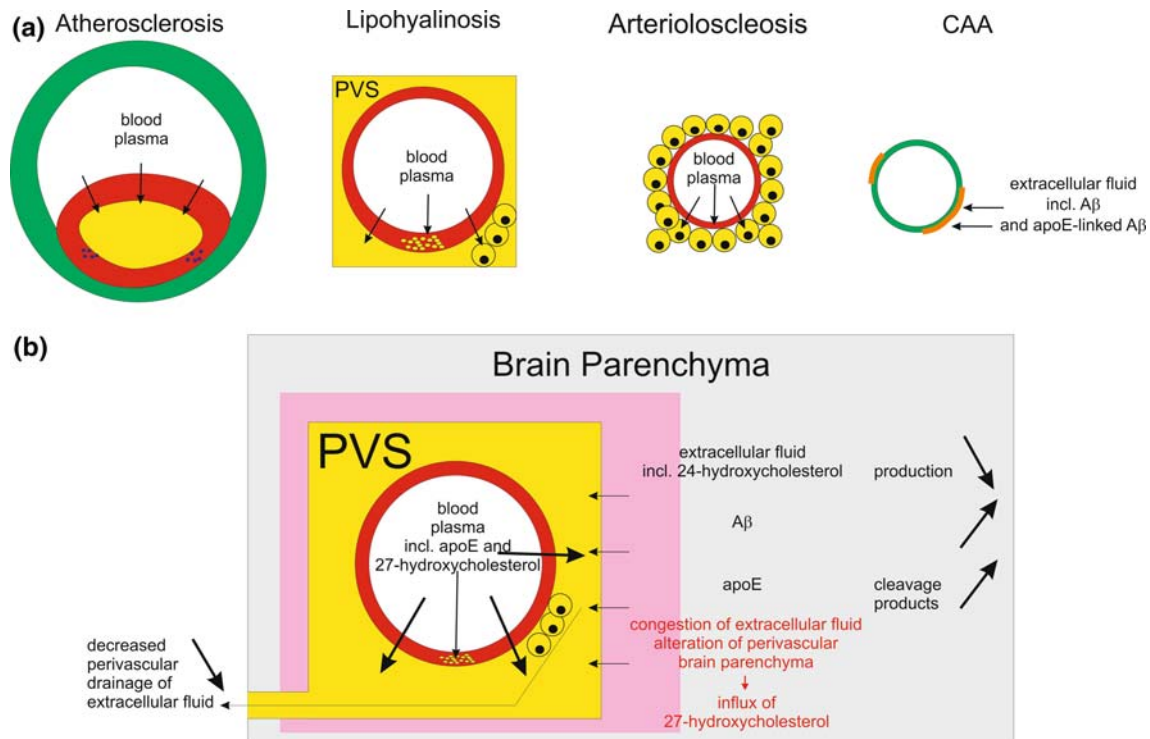


Fig. 4 Plasma protein leakage induced by vessel disorders and its relation to perivascular alterations of the brain parenchyma. **a** This schematic representation shows that plasma proteins occur (1) in the plaque cores of AS plaques, (2) in the vessel wall of lipohyalinotic vessels as well as in the perivascular space and in macrophages within the perivascular space, and (3) in the vessel wall of arteriolosclerotic vessels as well as in accompanying macrophages. CAA, on the other hand, is characterized by the deposition of proteins of the extracellular fluid of the brain, i.e. A β [15] and apoE [133]. **b** Impact of plasma protein leakage into the brain. Physiologically, extracellular fluid is drained into the perivascular space and along the vascular

basement membranes [16, 60, 155]. In the event of SVD, there is plasma protein leakage into the vessel wall and into the perivascular space [139] resulting in (1) a competition between leaking plasma and extracellular fluid from the brain for perivascular drainage and (2) the congestion of extracellular fluid leading to the accumulation and/or alternative processing of proteins of the extracellular fluid, and (3) the influx of the peripheral cholesterol metabolite 27-hydroxycholesterol into the brain [46, 127, 139]. The influx of 27-hydroxycholesterol into the brain is accompanied by decreased levels of brain derived 24-hydroxycholesterol indicating a reduction in the cerebral 24-hydroxycholesterol production [46]

association of the apoE ϵ 2 and ϵ 4 alleles with CAA-related hemorrhages [37, 88, 95, 97].

One argument against the hypothesis that SVD-related BBB alterations contribute to the development of CAA and parenchymal A β deposition is the lacking increase of apoE in the brain [139]. However, in the event that A β accumulates in the brain, e.g. in AD cases, apoE clearance switches from perivascular drainage to enzymatic cleavage as indicated by the predominance of C-terminal truncated apoE over full-length apoE [139]. Hence, the absence of an apoE increase in the brain of AD patients or of patients with perivascular drainage deficits does not argue against the hypothesis that altered perivascular drainage of extracellular fluid leads to a congestion of extracellular fluid and proteins in the brain. Moreover, the increase of 27-hydroxycholesterol levels in AD brains indicates an influx of plasma steroids through the BBB [46]. Another argument against a pathogenetic link between SVD and A β accumulation in the brain is that AD-related A β deposition

in aged individuals first occurs in the cortex [11, 104, 129, 134] whereas SVD affects mainly white matter, leptomeningeal and basal ganglia vessels [129]. However, the cortex is a distal area in relation to the areas with SVD-affected vessels, and A β is mainly produced by neurons located in this distal area [40, 94]. Thus, a proximal clearance block for peripheral extracellular fluid drainage containing neuron-derived A β will lead to a protein accumulation, e.g. of A β , in distal areas such as the cortex. This is exactly where parenchymal and vascular A β deposits occur first [11, 104, 129, 134]. Therefore, it is tempting to speculate that the distribution of A β deposits in aging and AD brains may represent the result of insufficient clearance of A β , rather than an anterograde neuronal expansion as previously discussed [134]. A strong argument in favor of this hypothesis is the fact that normal brain transplants into APP-transgenic mice, which produce a high number of A β plaques, also develop A β plaques in the absence of neuronal connections [89].

Thus, SVD-related alterations of the BBB may contribute to the development of CAA and possibly of parenchymal A β deposition. In general, the results reviewed here for the fate of A β and apoE after SVD-related BBB alteration point to two different effects of protein retention in the brain (1) accumulation, as documented for A β , and (2) degradation as presumed for apoE. Therefore, it is likely to posit that accumulation or degradation of other proteins also takes place and may be related with other SVD-associated brain lesions.

Vascular brain lesions and their relationship to AS, SVD, and CAA

Brain infarction, hemorrhage, and WMLs are the major brain lesions related to AS, SVD, and CAA. The location and size of the lesions vary according to the underlying vessel disorders and the potential risk factors. Here, we will briefly describe the vascular brain lesions and their association with AS, SVD, and CAA.

Brain infarction

Brain infarction is a circumscribed brain tissue necrosis resulting from insufficient blood supply [73, 102]. Infarcts are subdivided by nature into ischemic (anemic) or hemorrhagic infarcts. Alternatively, the descriptive classification distinguishes large infarcts (those involving the supply territories of major cerebral arteries and veins), lacunar infarcts (i.e. small vessel infarcts), and microinfarcts.

First, we will describe the relationship between ischemic and hemorrhagic infarcts to AS, SVD, and CAA regardless of the size of the infarct. *Ischemic infarcts* occur when focal brain perfusion falls below critical levels and no relevant collateral or remaining blood flow is available. This type of infarct is seen after thrombosis of large- to medium-sized arteries with atherosclerotic plaque rupture with or without subsequent embolism or after occlusion of SVD- or CAA-affected vessels [14, 73, 141]. Cardiac embolism also causes ischemic brain infarction [29, 33, 73]. *Hemorrhagic infarcts* are characterized by blood influx into the infarct territory. Different mechanisms can be responsible for hemorrhagic infarcts: (1) embolism due to AS or cardiac thrombosis [29, 81] with insufficient blood influx into the infarcted tissue (the mechanism is not clear, partial lysis of the embolus with resting blood flow, which is insufficient to save the tissue, is considered), (2) reperfusion of an anemic infarct (e.g. following lysis therapy or resuscitation), (3) collateral blood influx (insufficient to save the tissue but enough to bleed), (4) infarction in areas in which the remaining vessels are fragile due to a vessel

disease such as SVD or CAA [41], and (5) venous obstruction with subsequent congestion and extravasation of blood into the infarct area. Thus, AS, SVD, and CAA are related to infarcts, regardless of their nature. The underlying vessel disorder is, therefore, not predictive of the ischemic (anemic) or hemorrhagic nature of an infarct.

On the other hand, the underlying vessel disorders have influence on the infarct size. *Large infarcts* are bigger than 15–20 mm³. They are frequently ischemic (70–80%) and due to thrombotic or embolic artery occlusion [73]. AS plaque rupture with subsequent thrombosis and/or embolism usually occurs in the extracranial parts of the vertebral and the internal and common carotid arteries [73, 81]. Large infarcts due cardiac embolism are less frequent [73, 81]. About 10% of all large infarcts are watershed infarcts. It is a distinct type of infarct located between two vessel territories that results from insufficient blood supply during hypotensive episodes [52, 57, 157]. SVD and CAA usually do not lead to large infarcts [73]. Therefore, large infarcts are mainly linked to AS and its complications. *Lacunar infarcts* are cavitating infarcts, measuring up to 5–15 mm³ in volume or 5–10 mm in diameter [30, 44, 73, 102]. They are largely confined to the cerebral white matter and subcortical structures, most commonly found in the putamen, caudate nucleus, thalamus, pons, internal capsule and the cerebral white matter. Lacunar infarcts are associated with SVD [17, 74] but not with CAA. Pathogenetically, hypertension, diabetes, previous brain infarcts, an increase of high-density lipoproteins and triglycerides in the blood [36] were considered risk factors, but a recent review reported that this risk is not greater than that for large infarcts [49]. However, SVD-affected vessels showing lipohyalinosis or small vessel atherosclerosis are often found in the center of lacunar infarcts [30, 31, 111] presumably indicating that SVD is a major cause of lacunar infarcts. The risk factors described for lacunar infarcts are similar with those of AS and SVD. AS-related or cardiac embolism can also cause lacunar infarcts [33]. As opposed to large and lacunar infarcts, *microinfarcts* are usually not visible at gross examination. They are smaller than 5 mm in diameter. Multiple microinfarcts in the cortex and the white matter rather than a single one likely impact cognition [48]. Microinfarcts result either from AS-related embolism, SVD, or CAA [14, 33, 53, 61, 99]. Due to the location of the underlying vessel disorder, cortical microinfarcts are often associated with CAA whereas subcortical infarcts are mainly linked to SVD [7, 14, 53, 99, 118, 129, 132, 143].

In summary, AS is capable of causing infarcts of all size, whereas SVD is only related to lacunar infarcts and microinfarcts and CAA is mainly restricted to microinfarcts. These relationships can be easily explained by the vessel types affected by the respective vessel disorders and do not seem to reflect a more specific pathomechanism.

Hemorrhages

Cerebral hemorrhages are blood extravasations into the brain parenchyma larger than 10 mm in diameter and are differentiated from microbleeds. Together with other disorders, such as saccular aneurysms of the circle of Willis, vascular malformations, or coagulation disorders, AS, SVD, and CAA can lead to hemorrhage. In particular, AS results in hemorrhage after rupture of an atherosclerotic aneurysm [56], although this is a rare cause of intracerebral hemorrhage. More often, SVD leads to intracerebral hemorrhage, especially when it is associated with arterial hypertension. These hemorrhages preferentially occur after rupture of the lenticulostriate artery [125, 153]. Lobar hemorrhages with destruction of cortical tissue are frequently associated with severe CAA [50, 79, 141, 143]. Microaneurysms can be formed in SVD- and CAA-affected vessels (Fig. 3c) and are prone to rupture [87, 141, 142]. *Microbleeds* are blood extravasations into the perivascular and/or Virchow-Robin space without further tissue displacement and/or small intracerebral hemorrhages. They usually measure less than 10 mm in diameter [44] and are found in ~6% of the population with an increasing tendency during aging, especially in the presence of CAA [38, 63, 138]. Hemosiderin-laden macrophages within the perivascular space indicate prior microbleeds [149]. Hypertension-related microbleeds are preferentially located in the basal ganglia, thalamus, and the pons in association with SVD-affected vessels [54]. Thus, SVD and CAA are the major causes of cerebral hemorrhage and microbleeds in the aged human brain, whereas AS complications rarely lead to cerebral bleedings.

White matter lesions

White matter lesions, synonymous with leukoaraioses when found in imaging examinations, are present in up to 65% of the subjects over 65 years of age. They are more prevalent in patients with cerebrovascular disease or with cardiovascular risk [58, 96]. Clinically, WMLs are often asymptomatic [12, 25], but they can also impair cognition [26, 105]. Leukoencephalopathy, Binswanger's disease (synonymous with subcortical arteriosclerotic encephalopathy), periventricular arteriosclerotic leukoencephalopathy, and leukomalacia are clinical correlatives of WMLs [26, 48, 138]. Risk factors for the development of WMLs are advanced age, female sex [114], increased plasma homocysteine [47], increased ICAM levels [80], and arterial hypertension [24]. Some of these risk factors such as hypertension and increased plasma homocysteine levels also act as risk factors for AS and SVD. WMLs usually display, in variable degrees, white matter rarefaction (i.e., demyelination and axon loss), mild reactive astrocytosis,

edema, and macrophage reaction [28, 39, 48, 124]. These changes are frequently observed in the frontal, parietal, temporal, and occipital deep white matter, especially in the centrum semiovale, and as a rule, spare the subcortical U-fibers, which are located close to the border between the cortex and the white matter [59, 98, 101, 113]. It is not clear whether periventricular WMLs have the same nature as those in the deep white matter [28]. White matter infarcts, hemorrhages and enlarged perivascular spaces do not fall into the category of WMLs [48]. SVD-affected vessels are often seen together with perivascular WMLs [140]. AS and CAA, on the other hand, are not directly associated with WMLs because these vessel diseases are usually not seen in white matter vessels. Pathogenetically, SVD-related chronic hypoperfusion of the white matter and BBB alterations are presumed to lead to the degeneration of axons and myelin sheets, i.e. to WMLs [59, 98, 101, 136, 137, 140].

Pathogenetic relations between vessel disorders and brain lesions

According to the issues discussed above, SVD can lead to infarction, hemorrhage, and WMLs. In turn, infarction and hemorrhage can be caused by AS, SVD, and CAA. Thus, the type of brain lesion cannot be related to a specific vessel disorder and vice versa. All vessel disorders result in narrowing of the lumen of the affected blood vessels and can lead to vessel occlusion with subsequent infarction. Likewise, AS, SVD, and CAA damage the vessel wall. Rupture with subsequent hemorrhage can take place.

In addition to these non-specific mechanisms, WMLs and lacunar infarcts are mainly related to SVD. Despite vessel occlusion leading to lacunar infarcts, chronic hypoxia and SVD-related congestion of extracellular fluid may contribute to the development of WMLs and lacunar infarcts. This hypothesis is supported, first, by studies showing that chronic hypoxia presumably causes WMLs and lacunar infarcts given that oligodendrocytes are the most vulnerable cell type under these conditions and that their degeneration contributes to the development of WMLs and lacunar infarcts [48, 82, 83, 101, 122, 152]. Thereby, chronic hypoxia may result from SVD-related concentric fibrosis of the arterial walls and consecutive hypoperfusion [30, 31, 111, 112, 140]. Second, SVD leads to a leakage of plasma proteins, such as IgG, A2M and apoE, into the enlarged perivascular spaces [139]. Recently, BBB alterations in patients with leukoaraiosis (i.e. WMLs) and lacunar stroke have been described [136, 145]. Accordingly, these observations point to a SVD-related alteration of the pre-capillary BBB segment involved in the pathogenesis of WMLs and lacunar infarcts

and, thereby, extend the present knowledge of SVD-related BBB alterations and its association with vascular lesions in addition to AD-related changes [127, 139]. Moreover, it is well-known that plasma proteins leak into the brain parenchyma of hypertensive or hypotensive animals [91, 137] and patients with vascular dementia [1]. Endothelial changes have been found in animal models for hypo- as well as hypertension [91, 92, 137] indicating that endothelial cell alterations due to high arterial pressure or due to chronic hypoxia in hypotensive states are capable of promoting alterations of the pre-capillary BBB segment. In the light of all these considerations, it is tempting to speculate that chronic plasma protein leakage into the brain and retention of extracellular fluid due to altered perivascular clearance for the above-mentioned reasons contributes to the development of WMLs and/or lacunar infarcts (Fig. 4b) in addition to chronic hypoxia. Such a mechanism causing alterations of tissue is well-known in liver and lung congestion. Here, chronic hypoxia and a decreased venous drainage of extracellular fluid and blood lead to a perivascular parenchymal necrosis with subsequent fibrosis [90].

In short, hemorrhage and infarction result from non-specific vessel wall changes seen in AS, SVD, and CAA whereas WMLs and lacunar infarcts appear to be specifically linked to SVD-related BBB leakage and chronic hypoxia.

Conclusions

Despite the etiology of the vessel disorders, infarction and hemorrhage appear to result non-specifically from vessel wall changes of the respective vessel disorders. WMLs and lacunar infarcts can be addressed quite specifically to SVD [140]. The alteration of the pre-capillary segment of the BBB, thereby, allows leakage of plasma proteins into the vessel wall and into the perivascular space. These plasma proteins may compete with the extracellular fluid of the brain for perivascular drainage leading to retention of extracellular fluid, including A β in the brain. Such a retention of A β may also contribute to the development of CAA and Alzheimer's disease. ApoE is physiologically involved in the perivascular clearance of the extracellular fluid from brain. It is found in AS, SVD, and CAA lesions, and may represent a link between these disorders. Taken together, SVD-related alterations of the pre-capillary segment of the BBB seem to play an important role in vascular pathology, i.e. WMLs, lacunar infarcts, and CAA.

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