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Brain Arteriolosclerosis

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Abstract

Brain arteriolosclerosis (B-ASC), characterized by pathologic arteriolar wall thickening, is a common finding at autopsy in aged persons and is associated with cognitive impairment. Hypertension and diabetes are widely recognized as risk factors for B-ASC. Recent research indicates other and more complex risk factors and pathogenetic mechanisms. Here we describe aspects of the unique architecture of brain arterioles, histomorphologic features of B-ASC, relevant neuroimaging findings, epidemiology and association with aging, established genetic

risk factors, and the co-occurrence of B-ASC with other neuropathologic conditions such as Alzheimer's disease and limbic-predominant age-related TDP-43 encephalopathy (LATE). There may also be complex physiologic interactions between metabolic syndrome (e.g. hypertension and inflammation) and brain arteriolar pathology. Although there is no universally applied diagnostic methodology, several classification schemes and neuroimaging techniques are used to diagnose and categorize cerebral small vessel disease pathologies that include B-ASC, microinfarcts, microbleeds, lacunar infarcts, and cerebral amyloid angiopathy (CAA). In clinical-pathologic studies that include consideration of comorbid diseases, B-ASC is independently associated with impairments in global cognition, episodic memory, working memory, and perceptual speed, and has been linked to autonomic dysfunction and motor symptoms including parkinsonism. We conclude by discussing critical knowledge gaps related to B-ASC and suggest that there are probably subcategories of B-ASC that differ in pathogenesis. Observed in over 80% of autopsied individuals beyond 80 years of age, B-ASC is a complex and under-studied contributor to neurologic disability.

Keywords

SVD; arteriosclerosis; cAVU; senescence; neuropathology; neuroimaging

Introduction

Brain arteriolosclerosis (B-ASC), a common subtype of cerebral small vessel disease (cSVD), is associated with substantial neurological morbidity [19, 30, 34, 84, 183, 194]. In the present review we discuss approaches to diagnosis and classification of cSVD pathologic changes including B-ASC. We review the literature on risk factors and biological mechanisms thought to underlie B-ASC, emphasizing the complex anatomy and physiology of arteriolar walls, and discuss relevant clinicopathological studies. We conclude by highlighting critical areas for further investigation.

Background and historical context

Combining the words “arteriole” and the Greek “*skl rós*”, arteriolosclerosis implies “hardening of the arterioles”. While histopathology provides the gold-standard criteria for determining the presence and severity of B-ASC, prior studies and reference sources have employed differing definitions of arteriolosclerosis. Some are presented in Table 1. A schematic representation of the histologic features of brain arterioles is presented in Fig. 1.

Historically, much of the early descriptions of arteriolosclerosis focused on renal pathology. Following Lobstein's use of the term “arteriosclerosis” [117], Gull and Sutton applied the term “arterio-capillary fibrosis” [70]. Moritz and Oldt later described how aging and hypertension are associated with renal “arteriolar sclerosis” [145], which evolved to “arteriolosclerosis” [51]. These terms were useful because the histopathologic changes observed in arteriolar vessel walls differ from findings typical of those in arteries. In arteries, lipid laden macrophages may infiltrate the vessel wall, forming a cholesterol-rich (and often calcified) matrix which is termed an atheroma, the pathologic substrate of atherosclerosis [94]. When small atheromas occur in arterioles or narrow arteries (so-called

microatheromas [14]), they are distinct from B-ASC. By contrast, B-ASC shows thickened and/or dysmorphic vessel wall changes, with increased arteriolar tortuosity, but no atheroma. B-ASC also lacks amyloid. At least two subtypes of arteriolosclerosis have been recognized: hyperplastic (i.e., vessel wall “onion-skinning”) and hyaline (i.e., glassy-looking acellular mural thickening). However, many arterioles have both histomorphologic patterns [52].

Although early studies of arteriolosclerosis were oriented toward the kidney, vascular pathology in the brain has recently generated intense interest among clinical and translational neuroscientists. The physiology and cellular elements of brain arterioles are unique [195, 211], and as yet incompletely understood. While arteriolosclerosis is commonly present in multiple organs [163], the pathobiology in brain arterioles may have features that are distinct from non-CNS arteriolosclerosis.

Neuropathologic workup: diagnostic and research approaches

B-ASC is typically identified in neuropathologic practice using routine hematoxylin and eosin (H&E) stains (Fig. 2). For diagnostic purposes, a semiquantitative severity scale is commonly used with categories typically corresponding to “none”, “mild”, “moderate”, and “severe” levels of pathologic change (Fig. 3). This type of B-ASC metric was used in Vascular Cognitive Impairment Neuropathology Guidelines (VCING) [183], in the National Alzheimer’s Coordinating Center Neuropathology (NACC NP) Data Set [26, 141], and elsewhere [100, 114, 154, 155].

The VCING system described and evaluated a protocol for diagnosing B-ASC neuropathologically (Fig. 2). The NACC data set includes comparable information related to cerebrovascular pathologies (Table 2). However, NACC NP cerebrovascular data have not been assessed for inter-rater reliability among neuropathologists. In the VCING study [183], sampling protocols were also recommended. The inter-rater reliability assessment of the B-ASC severity diagnoses (0–3 scale, Fig. 3) showed “moderate” agreement, whereas most other cSVD subtypes had “high” inter-rater reliability when diagnosed by 14 different neuropathologist raters. This is partly because the criteria for delineating each increment of B-ASC severity (e.g., mild vs. moderate) are highly subjective and investigators may weigh anatomic regions of interest differently. Based on the VCING study, B-ASC evaluation in the occipital cortex white matter provides a diagnostic marker with a combination of acceptable reliability and robust association with cognitive status (Fig. 2).

The aged brain may contain a broad spectrum of arteriolar pathologic changes [38, 81, 111, 159, 197, 210] (Fig. 4). Although the VCING system represents a validated neuropathologic method for diagnosing cSVD subtypes (Table 2), there were no recommendations for subclassifying B-ASC. The VCING article also acknowledged that there was some disagreement among the coauthors. A key stipulation of their B-ASC definition was that “[d]iagnosis requires absence of intramural inflammation, amyloid, or fibrinoid necrosis” [183]. Yet it has been noted that “there is clearly morphological overlap with [B-ASC and] the late stage of Fisher’s lipohyalinosis.” [94] Skrobot et al.’s specification that only blood vessels <150 µm in diameter can be affected by B-ASC is debatable, since larger vessels may be affected by the same pathogenetic mechanisms. Some researchers have examined B-ASC in larger vessels (> 300 µm diameter) [43]. As to the lower size limits, cerebral

vessels <20µm diameter may have a smooth muscle layer in their walls (Fig. 5c), and thus probably are arterioles. Tissue processing and staining may produce differing effects, and it is challenging to distinguish arterioles from venules in some circumstances. To date, no definition of arterioles based on lumen size is universally accepted.

To grade the severity of B-ASC quantitatively for research purposes (as opposed to the semi-quantitative method described above), several groups have used a “sclerotic index” (SI), which is based on measurements of arteriolar wall thickness and luminal narrowing ($SI = 1 - [\text{internal diameter}/\text{external diameter}]$) [76, 81, 111]. A similar approach calculated the ratio of the overall vessel radius to the thickness of the vessel medial layer [158, 197]. A third method assessed B-ASC based on the number of different brain areas affected (detected with H&E stains), rather than severity of the pathologic changes in any given region [199]. Importantly, there can be a wide spectrum of B-ASC pathologies in different areas of the same brain, not all necessarily highlighted best by using H&E stains.

As to other stains used in pathologic assessments of B-ASC features such as vessel wall disruption and collagenization, Verhoeff–Van Gieson elastic stain and Masson’s trichrome histochemical stains have been utilized [43, 197]. Immunohistochemical methods have also been used to evaluate B-ASC. Smooth muscle cells should be present in arterioles but not capillaries, whereas pericytes and endothelial cells are present in both arteriole and capillary vessel walls. Hence, α -smooth muscle actin (α -SMA) immunohistochemistry (Fig. 5b,c) was used to mark arterioles for a quantitative assessment of B-ASC in human frontal cortex [154]. The presence of B-ASC has also been inferred from parameters of blood-brain dysfunction, including using antibodies against fibrinogen and IgG, to detect extravasated plasma as evidence of blood-brain barrier leakage [32, 129, 142], which may be an indicator of B-ASC severity in specific circumstances.

Much remains unknown about B-ASC. Experts have previously remarked on the need for a more precise brain-specific terminology [51, 65, 120, 128, 152]. While previous definitions of B-ASC have enabled substantial scientific progress, future diagnostic methods focusing on specific mechanisms may better reflect the complexity of pathologic changes in aged brain arterioles.

Arteriole physiology and the cerebral arteriolar vascular unit

B-ASC affects the cerebral vasculature, which is a unique and complex network of blood vessels. Blood flowing into this network traverses the great cerebral vessels and then flows through pial arteries (usually 200–1,000 µm lumen diameter) located on the cerebral surface [27]. Branches from the pial arteries form penetrating arteries that pass into the brain parenchyma. These descending arteries feed parenchymal arterioles (usually ~20–200 µm lumen diameter) that further subdivide into smaller precapillary arterioles which connect with capillaries (~3–10 µm lumen diameter) [112, 127].

Arterioles serve important physiologic functions in the CNS. The brain is an energy demanding organ that couples synaptic function with fine-tuned vasoregulation. Arterioles are the primary site of vascular resistance, where the greatest changes in blood pressure and flow velocity occur [189]. Smooth muscle and pericyte constriction increases vascular

resistance in arterioles, modified by neural input, pH, CO₂, and oxygen, as well as paracrine, endocrine, and pharmacologic factors [105, 181].

Encircling the lumens of arterioles are a specialized combination of cells and structural elements (Fig. 1). There is no specific extant term for features of arteriolar walls. We will use a new term, cerebral arteriolar vascular unit (cAVU), which differs from the neurovascular unit (NVU) [46, 83, 95]; the latter term generally but not always [105] refers to capillaries. Some structures (e.g. endothelium) are present in the cAVU as well as in the NVU, and some functions overlap, such as preventing most large molecules from entering brain parenchyma. The terms for histologic layers of the arteriolar wall borrow from the terminology of arteries: intima, media, and adventitia (from the lumen to the periphery). Despite the similarities, the overall structure and functions of brain arterioles are unique. There also is diverse histology even among brain arterioles [112] that “blurs the traditional boundaries of a rigid layered classification.”[127]

Cellular components of the cAVU may include endothelial cells, pericytes, smooth muscle cells, inflammatory cells, fibroblast-like cells, and astrocyte end-feet processes (Fig. 1). The endothelium comprises one cell layer, allowing for exchange of chemicals through the cell membranes. Although commonly associated more with capillaries than arterioles [20], pericytes are found within the basement membrane in narrow arterioles and are vital for modulating cerebral blood flow [25, 220]. Pericytes also function in formation of blood vessels, maintenance of the blood-brain barrier (see below), and regulation of immune cell entry into the brain [139].

Of primary importance for cerebral vasoregulation are the arteriolar smooth muscle cells. These cells contract or relax to modify blood pressure and flow. Arteriolar vessel walls are generally described as having only 1–2 layers of smooth muscle cells [110, 127]. The precapillary sphincter is a microdomain in human cerebral cortex connecting small arterioles and capillaries, dynamically regulating blood flow via smooth muscle cell contraction [69]. Intriguingly, there is significant evolutionary molecular divergence (especially between rodents and humans) in vascular smooth muscle cells [113], underscoring the structural and functional uniqueness of human arterioles.

Astrocytes serve multiple functions and have so-called end feet processes that cover the abluminal (peripheral) aspect of CNS vessels (Fig. 5a). They coordinate the delivery of oxygen and glucose and have inflammation/activation signaling pathways that are in some ways similar to those of leukocytes and microglia [157]. The astrocytic end-feet are enriched with potassium and water channels, which are essential for maintaining appropriate neuronal excitability [23, 24]. They play bidirectional roles in coupling smooth muscle contraction/relaxation to neuronal activity [106], while modulating neuronal activity to adapt to changes in cerebral blood flow and oxygenation [103].

In addition to the long-established components of the cAVU, other cell types have recently been studied. For example, the perivascular microglial “scavenger-type” cells (Figs. 5d,e) are among vascular-tropic inflammatory cells. These cells may be related to neurodegenerative disease pathogenesis and were recently shown to have rich phenotypic

variety [107, 208]. In some pathological circumstances, pericytes may adapt a microglia-like phenotype [162]. The arteriolar vessel wall adventitia consists of thin layers of fibroblasts, along with collagen and elastic fibers in healthy brains. By contrast, fibroblasts are not found in capillary walls [211].

The cAVU contains extracellular structures which help demarcate the concentric layers of the vessel wall. Endothelial cells rest on a basal membrane in the intima. An internal elastic lamina may be present in the adluminal (toward the lumen) portion of the media. The internal elastic lamina “is not always found at all levels of the arteriolar tree, but it is present in feed arterioles of ... cerebrum.” [127] Peripheral to the astrocytic end-feet, the perivascular space is an incompletely understood functional domain [1, 133, 215].

Precapillary arterioles lead into a highly branched capillary network. The cells and structural elements of the cAVU (arterioles) and capillary NVU are cooperative components of the blood-brain barrier [146, 165]. The blood-brain barrier regulates tightly what can move between the general circulation and the brain, protecting the brain from neurotoxins and pathogens [44]. B-ASC can induce blood-brain barrier leakage, causing plasma protein and other molecules to extravasate into the brain parenchyma [4, 66, 73]. However, multiple subtypes of cSVD can cause this type of injury.

Classifications of cerebral small vessel disease

Neuropathologic criteria-based classification systems provide a framework for evaluating the presence and severity of B-ASC, and a taxonomy to distinguish B-ASC from other cSVD subtypes. Researchers also use these classification systems to perform clinical-pathological correlation studies, to assess associations with genetics and environmental risk factors, to develop experimental models, to help estimate the disease prevalence in various populations, and to identify disease-driving mechanisms that might provide therapeutic targets.

There is no universally agreed-upon method for categorizing cSVD pathologic changes. Different classification methods include histomorphologic (the main method for distinguishing B-ASC from other cSVD), etiologic (e.g., genetic, diabetic, hypertensive), pathologic comorbidity (e.g., amyloid, vasculitis), and radiography-based criteria.

The VCING classification system incorporates neuropathologic criteria for diagnosing a broad range of cSVD (Table 2) [183], built on prior studies and recommendations [8, 45, 47, 49, 143, 172, 184]. Unlike the VCING system, the Newcastle categorization [93, 96] emphasizes common patterns of different pathologies and the corresponding clinical scenarios of those patterns. This approach acknowledges that the different subtypes of cerebrovascular pathology are often seen in combination with each other, with stereotypical clinical manifestations.

It is unlikely that the current versions of the VCING or Newcastle systems provide complete representations of the complexity of cSVD. However, some merging of these different approaches might be useful for identifying both the microscopic lesions and the combinatorial patterns that contribute to clinical diseases. In addition to these specific categorization systems, other cSVD categories include cerebral amyloid angiopathy (CAA),

inflammatory, and other subtypes; excellent reviews are available [66, 94, 120, 128, 213, 214].

Neuroimaging

No current neuroimaging modality allows 1-to-1 evaluation of the same phenomena that are observed using neuropathologic methods, and while no neuroimaging method captures the full spectrum of changes seen neuropathologically, the converse is also true. However, these approaches can complement one another in the study of cSVD. Autopsy studies are inherently cross-sectional and limited by sampling and staining methods. By contrast, neuroimaging allows for assessment of whole-brain metrics, multiple analyses of the same brain regions of interest, association with real-time, within-scanner behavioral performance, and longitudinal monitoring of the onset and progression of cerebrovascular changes.

It is important to distinguish between diseases of vessel walls (e.g. B-ASC, CAA) and the secondary parenchymal changes that are often detected with neuroimaging. Specific vessel wall pathologies cannot always be correlated exactly with measures of parenchymal injury. Further, the parenchymal changes that are sometimes described as cSVD can also be caused by extracranial disease processes such as renal disease, microemboli, and other disorders.

Structural magnetic resonance imaging (MRI) is the most widely used and standardized method for cSVD diagnoses and research applications, owing both to its high spatial resolution and its ability to detect a spectrum of cerebrovascular abnormalities without the need for application of extensive post-acquisition image analyses. There is currently no universally accepted method for categorizing cerebral cSVD using MRI but proposed standards are evolving rapidly. Another challenge is that the terminology differs between the neuropathologic and neuroimaging literatures.

White matter hyperintensities (WMH) on T2-weighted MRI are an established, often-studied marker of cerebral cSVD. WMH are readily visible on standard T2-weighted MRI, and their visibility is further enhanced through fluid-attenuation (i.e. MRI FLAIR imaging). Often seen bilaterally in aged persons' brains, particularly in periventricular or peripheral regions of subcortical white matter (Fig. 6a), WMH have been associated with cognitive impairment, reduced local blood flow, gliosis, and demyelination [12, 57, 115, 153]. B-ASC has been cited as the "main, but not the only" underlying cause of WMH [7, 210].

WMH is believed to indicate tissue injury, but the specificity, sensitivity, and predictive value of WMH have been debated. Indeed, specific cut-offs and locations for their measurement are not widely agreed upon. Although there are barriers for comparing imaging findings with pathologic changes [64], the study of WMH on brain imaging studies helps motivate further neuropathological investigation [217].

Other markers of cerebral cSVD on MRI include lacunes (Fig. 6b), enlarged perivascular spaces (EPVs; perivascular spaces are also known as Virchow-Robin spaces, Fig. 6c), and cerebral microbleeds (Fig. 6d). Each of these cSVD markers is frequently observed in the basal ganglia and other regions associated with penetrating and tortuous vessels. These may be directly relevant to B-ASC in some contexts. However, these MRI-based markers differ

in size, are associated with different vascular events, and are thus best appreciated with different MRI sequences.

Lacunae are ~3–15 mm diameter infarcts visible on T1 or T2 images [216]. Lacunae must be distinguished from EPVs, which tend to be smaller (1–3mm) fluid-filled spaces, rather than infarcts, surrounding perforating arterioles and venules; EPVs are best appreciated on T2 images [216]. Cerebral microbleeds are small signal voids (usually < 5mm) on susceptibility-weighted imaging (SWI), or T2* gradient echo sequences [222]. They may signal the accumulation of hemosiderin (iron) associated with blood and old microhemorrhages, but may also be a surrogate for ischemic cSVD rather than necessarily a hemorrhagic diathesis [88]. Notably, some imaging sequences like SWI are associated with blooming effects which artifactually enhance microbleed size on MRI [104, 130].

Although there are limitations to MRI resolution, newer studies are extending the limit of detection to resolve features related to B-ASC *in vivo*. Fig. 7 shows results from a novel high-resolution MRI technique [122] which enables the study of vessels of several hundred micrometers in diameter. With this method, which can be accomplished at 3T or ultra-high magnetic field (7T), the vessel wall tortuosity can be readily observed and the decreased vessel number with aging quantified in three dimensions, as well as over time.

A number of other new neuroimaging methods focus more on functional than structural phenomena. For example, one recently developed technique involves cerebral perfusion imaging using pseudo-continuous arterial spin labeling (pCASL), which measures local blood flow without the use of a contrast agent such as gadolinium [209]. This approach permits quantification of blood flow to different brain regions. Unlike the structural techniques described above, many of the newer functional studies require specialized resources that are not readily available at most centers. Despite this limitation, neuroimaging methods have profoundly augmented the study of how cSVD develops over time.

Anatomic distribution

The anatomic distribution of B-ASC is important to consider because vascular pathology may have focal clinical manifestations. One group of investigators report [199] that non-amyloid cSVD appear to affect “first arteries of the basal ganglia and then expands into the peripheral white matter and leptomeningeal arteries, as well as into thalamic and cerebellar white matter vessels” [200], in a stereotypic spatio-temporal pattern. Not all prior studies have found that B-ASC follows a predictable anatomic sequence, however [111]. Anatomic associations with risk factor data, for instance basal ganglia B-ASC related to hypertension, are better established [99, 146]. Neuroimaging studies, by contrast, have emphasized the periventricular and deep white matter changes [59] (Fig. 6).

Other brain regions are also affected by B-ASC in aged persons, with possible clinical manifestations. The amygdala appears vulnerable to B-ASC. The amygdala has an idiosyncratic blood supply [82, 149], with a tendency to show extensive B-ASC in elderly brain, along with venous collagenosis, especially near the inferior horn of the lateral ventricle [94]. In addition to its importance in emotion and behavior, the amygdala serves roles in autonomic nervous system regulation; autonomic dysfunction has been

linked to B-ASC [76]. It seems likely that amygdala microangiopathy has other functional consequences, but the correlates of B-ASC in this region have not been extensively studied. We note that the amygdala is also the brain area apparently first affected by TDP-43 proteinopathy in limbic-predominant age-related TDP-43 encephalopathy (LATE) [90, 147], and perivascular TDP-43 proteinopathy can be prominent near small vessels, as discussed below.

Epidemiology and risk factors

The main risk factors generally discussed in association with ASC are hypertension and diabetes [94]. Other comorbidities reported to increase risk of B-ASC include obesity, renal failure, and sleep pattern perturbations [84, 114]. Environmental factors, including air pollution and chemical toxins, may promote B-ASC, and may worsen hypertension and other risk factors, according to both epidemiologic and animal studies [61, 102]. However, in advanced age, risk factors widely associated with B-ASC correlate less robustly with B-ASC pathology than in younger subjects, according to multiple studies, as described below.

Hypertension is a strong risk factor for mortality and morbidity worldwide [67, 136, 221]. Arteriosclerosis is considered a downstream complication of hypertension, because in hypertensives there is narrowing of the vessel lumens in both arteries and arterioles [99]. Radiographic evidence of hypertension-induced brain injury includes WMHs, small and large infarcts, enlarged perivascular spaces, and cerebral aneurysms [55, 160]. The recent SPRINT-MIND trial found that intensive lowering of blood pressure was associated with a relative decrease of WMH size, and reduced incidence of cognitive impairment [67, 68].

Type II diabetes mellitus (T2DM) is also associated with increased risk for B-ASC, probably via increased exposure of the cAVU to hyperglycemia, inflammatory cytokines, and other factors [28]. Neuropathologic studies establish associations between T2DM and B-ASC as well as with small and large infarcts [3, 153, 172, 188]. Correspondingly, neuroradiography has also showed T2DM-linked increased risk for WMHs, brain infarcts, and blood flow disturbance [57, 196].

Metabolic syndrome (MetS) is a term to describe a common combination of abnormalities in the same individual, including hypertension, T2DM, obesity, and dyslipidemia [109]. Approximately a third of American adults have MetS in some form [177]. MetS has negative impacts on brain function [48, 97], but the mechanism underlying this association requires further study. A number of additional phenomena cluster with MetS, including hyperhomocysteinemia and a generalized pro-inflammatory state [42]. These phenomena may have synergistic deleterious effects on arterioles; for example, hypertension, hyperglycemia, hyperhomocysteinemia, and dyslipidemia may each harm components of the cAVU and promote B-ASC [93, 137, 187].

Trends have been reported for an association of MetS-related conditions (hypertension and T2DM) with more severe B-ASC [18, 84]. Yet these associations were not as strong in persons beyond age 80 years. Arvanitakis et al. [18] and Ighodaro et al. [84] both reported that the association between hypertension and B-ASC was attenuated in advanced age. In another study of aged research participants, neither hypertension nor T2DM was

statistically significantly associated with B-ASC [194]. These data indicate that a substantial proportion of elderly persons' B-ASC may be attributable to causes other than traditional MetS or cardiovascular risk factors. However, these studies and their conclusions need to be considered carefully because of potential confounders such as medicated diseases (a person may have a history of hypertension but have it under control medically), death/survivor bias, racial disparities, differing risk factors in midlife and late life, and comorbid conditions [18, 87, 118].

Table 3 shows analyses of recent data from the NACC NP v10 Data Set. Data were limited to autopsies reported after June 2014 through the March 2020 data freeze, and these volunteers were recruited and evaluated at 32 different U.S. research centers. As reported earlier with a different set of NACC subjects [84], a clinical history of hypertension was associated with increased odds for moderate or severe B-ASC pathology, but the trend was only statistically significant in persons dying before age 80 years. Notably, myocardial infarction was strongly associated with hypertension, T2DM, and hypercholesterolemia (Table 3).

These data indicate collectively that traditional cardiovascular risk factors are less predictive of B-ASC severity in advanced age than they are predictive of cardiac pathology in the same persons. While the associations between B-ASC and hypertension or T2DM were less strong than might be expected, there are other notable comorbidities robustly associated with B-ASC in aged individuals (Table 3), including cerebrovascular disease and neurodegenerative pathologies [84]. Perhaps the most salient risk factor for B-ASC is aging itself.

Genetics and aging

B-ASC appears to be influenced strongly by genetics and senescence. One clue comes from persons of age <20 years with “progeria” (accelerated senescence phenotype), driven by specific gene mutations, who tend to have substantial B-ASC [78, 174, 185]. B-ASC is also seen with aging in wild-type animal species [72, 180]. Different genetic risk factors affect people within distinct ranges of the aging spectrum, and there has been extensive focus on how aging and genetics influence the vasculature – combining with stress, caloric intake, glycemia/insulinemia, immune factors, and other processes that modulate an individual's lifespan [95, 140, 198, 207].

Chronologic age is linked consistently to increased prevalence of B-ASC in autopsy series. Smith and colleagues showed that cSVD was evident in ~3% of individuals in their 40s, but ~19% of 70-year-olds [186]. B-ASC increases even more dramatically among persons beyond age 80 years [50, 151, 199]. Fig. 8 depicts how B-ASC pathologic changes evolve in aging. Prior studies agree that over 80% of individuals beyond age 80 had identifiable B-ASC [50, 84, 89]. Further studies are needed in diverse population-based cohorts.

B-ASC in aged individuals is common, and genetics also appears to have a strong influence. Table 4 presents genetic risk factors of B-ASC identified to date. Recent articles by Marini et al. [125] and Vinters et al. [213] provided overviews of prior studies on the genetic influence on B-ASC associated phenotypes.

Rare monogenic forms of cSVD, with Mendelian modes of inheritance, shed light on the genes and biological pathways with potential strong impacts. The most common monogenic cSVD is cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), attributed to *NOTCH3* gene mutations [91, 138]. A pathologic hallmark of CADASIL is the presence of granular osmiophilic material adjacent to smooth muscle cells in the walls of arterioles (on electron microscopy), loss of smooth muscle in the tunica media, and adventitial fibrosis [15]. Other aspects of arteriolar pathology in CADASIL were well described by Miao et al. [135].

Mutations in genes that encode collagen or other vessel-related proteins can also lead to B-ASC. *COL4A1* and *COL4A2* encode type IV human collagen, which is a key protein in endothelial basement membranes. High-penetrance *COL4A1* mutations lead to a variety of rare monogenic brain infarction phenotypes which include severe B-ASC, and more common *COL4A1* single nucleotide polymorphisms (SNPs) are also associated with brain cSVD [41, 134]. *TREX1* mutations are another interesting cause of degenerative microvascular lesions in the eye, brain, and elsewhere, implicating inflammatory dysfunction at the basement membrane of arterioles and other small vessels [171, 176]. Other genes associated with monogenic B-ASC phenotype include *HTRA1* and *FOXC1/FOXF2* [108, 125, 213].

In contrast to the rare monogenically inherited conditions, the common, chronic diseases of aging (which presumably include B-ASC) can be influenced by a large number of lowpenetrance risk alleles. Human genetic variants that include chromosomal loci at 16q24, 2q33, 14q22, and 12q24 have been linked to B-ASC-type phenotypes [125]. Specific SNPs were linked via genome-wide association studies (GWAS) to risk for WMH or other radiographic cSVD phenotypes [5, 6, 16, 21, 41, 54, 126, 164, 202, 203]. However, not all of the phenotype-driving genes have been elucidated to date.

Chou and colleagues [39] investigated the association of candidate SNPs with cerebrovascular pathologies including B-ASC. Variants located within or near the following genes were suggestively associated with B-ASC: the diabetes risk genes *JAZF*, *TSPAN8*, *LGR5*, and *KCNJ11*; the LDL risk gene *PCSK9*; and, the atrial fibrillation risk gene *ZFHX3* [39]. The ε4 isoform of Apolipoprotein E (*APOE*), the major late-onset AD risk allele, has also been associated with B-ASC severity [223].

Another gene candidate for B-ASC is *ABCC9*, which encodes SUR2. SUR2 proteins function as K⁺ channel regulators and can affect the stress response, metabolism, and regulation of blood flow and the cAVU [152]. *ABCC9/SUR2* is a pericyte marker in mouse brain [211] but is also expressed in vascular smooth muscle cells in humans [152]. *ABCC9* mutations in humans are a cause of Cantu syndrome, with a phenotype that often includes tortuous CNS blood vessels [152]. A common *ABCC9* genetic polymorphism has been associated with B-ASC severity but only among persons over 80 years of age at death [84], a finding in need of replication. Overall, more work is required on gene variants that are associated with the B-ASC phenotype.

Pathologic mechanisms

We have described “upstream” risk factors that may drive B-ASC. The “downstream” pathologic mechanisms promoted by B-ASC are also important to consider. Harmful mechanisms linked with B-ASC include impaired blood flow [71], mechanical stiffening [148], functional synaptic uncoupling [144], blood-brain barrier leakage [32], synergies with neurodegenerative disease mechanisms [119], impaired angiogenesis [205], vessel wall mineralization [194], failure of “glymphatics” [1, 55, 133, 215], impaired access to growth factors or growth factor receptors [74], release of reactive and oxidizing agents [11, 156], harmful neuroinflammation [4, 175], micro-hemorrhages [191], micro-thrombi [201], vasospasm [62], seizure kindling [86], perturbations of calcium and other electrolytes [167], and various cell type-specific cytopathic changes [73, 168, 206]. Although it is not clear which of these mechanisms are “downstream” of B-ASC, two common diseases with possible synergistic effects with B-ASC are MetS (see above) and LATE.

Whereas it is commonly thought that MetS promotes B-ASC, there is a credible hypothesis that B-ASC works in the other direction, contributing to hypertension and other aspects of MetS [28]. Blood pressure is partly regulated by the brain via hypothalamic and brainstem autonomic signaling [121]. The CNS lacks energy reserves, so maintaining cerebral perfusion is a critical biologic priority. When human cerebral perfusion is impaired, the brain can release paracrine and endocrine factors that augment blood flow and increase systemic blood pressure [218], in a pattern comparable to that of renovascular hypertension [79]. According to this hypothesis, B-ASC and hypertension might promote each other in a deleterious cycle: hypertension leads to blood vessel abnormalities, including more B-ASC, which in turn worsens hypertension, culminating in ischemic brain damage [17, 166]. There may also be additional, analogous feed-forward central regulation (via hormones, adipokines, cytokines, etc.) of hyperglycemia, hyperlipidemia, and inflammatory factors which may maintain cerebral energy supply in advanced age, at the expense of harming the cAVU.

There is also growing evidence that B-ASC is associated with a common neurodegenerative condition referred to as LATE [150]. Among the conditions that may mimic AD clinically, LATE generally affects persons of advanced age (>80 years), with memory loss that can evolve to a dementia syndrome, and is often comorbid with AD (in which case the dementia phenotype is more severe than either AD or LATE alone) [150]. In multiple independent data sets, LATE is more common in persons with moderate-to-severe B-ASC than in those with no or low B-ASC [26, 101, 154, 155]. The papers that reported an association with LATE and B-ASC tended not to find an association between AD and B-ASC. In a recent study by Bourassa et al. [29], brain arteriolar mural cell markers (α -SMA for smooth muscle cells, PDGFR β and CD13 for pericytes) in parietal cortex were substantially decreased in brains with comorbid TDP-43 proteinopathy. It was previously noted that TDP-43 proteinopathic deposits may be present in the perivascular astrocytic end-feet in frontotemporal lobar degeneration with TDP-43 (FTLD-TDP) as well as in LATE [116, 152]. As shown in Fig. 9, TDP-43 deposits may be detected outside both arterioles and capillaries, particularly the latter. TDP-43 proteinopathy is associated with increased HS pathology [13], which is also linked to cerebral ischemia [152, 212]. These observations

raise questions about how LATE and B-ASC interact mechanistically. Microangiopathy, including B-ASC, may contribute to TDP-43 proteinopathy, or vice versa, or there may be a synergistic feed-forward process in which each exacerbates the other. A critical question remains as to which more directly affects neurological function.

Clinical-pathological correlation

Multiple studies have supported the hypothesis that the severity of B-ASC is strongly associated with impaired cognition. However, testing this hypothesis is complicated by potential confounders [93, 120, 128]. Many factors can contribute to cognitive impairment, for an individual or a population [100, 123]. Therefore, optimal clinical-pathological correlation studies should employ analytical models that factor in the effects of different neurodegenerative diseases, CAA, lacunar infarcts, microhemorrhages, and microinfarcts, among other co-pathologies.

Some studies have evaluated the clinical impact of B-ASC-associated pathologic findings, rather than B-ASC itself. White matter disruption and astrocytosis attributed to vascular disease were associated with cognitive impairment [53, 131]. Methods that combined B-ASC with other cSVD subtypes also found associations with dementia [184]. Since B-ASC may be partially responsible for microinfarcts and lacunes (B-ASC is indeed strongly associated with those comorbid pathologies, as shown in Table 3), it is a valid approach to focus on those ischemia-related pathologic endpoints [53, 131]. Note that a separate literature exists on the association between WMH and neurological function [9, 214]. Further, B-ASC is a common comorbidity in AD and other neurodegenerative diseases [76, 154]. Although these considerations are germane to B-ASC, the main focus here is on whether autopsy-diagnosed B-ASC pathology is associated with antemortem clinical status.

Clinical-pathologic studies related to B-ASC are listed in Table 5. Most of the relevant prior studies assessed the association between B-ASC and global cognitive status. For example, the VCING study [183] evaluated a sample of 113 autopsies to assess the “likelihood that cerebrovascular disease contributed to a cognitive impairment” of mild or severe degree (dementia). A robust association was found between B-ASC and cognitive impairment [183]. Ighodaro et al. [84] evaluated the NACC dataset (n=2,390) using regression models that adjusted for AD, Lewy body disease, and other cerebrovascular pathologies. In that study, the association between B-ASC severity was tested with final MMSE and CDR Sum of Boxes scores, finding a significant association for both metrics [84]. Two clinical-pathologic series from Brazil also showed positive association between B-ASC and decreased cognitive status [193, 194]. An interesting finding by Suemoto et al. (2019) was that siderocalcinosis in the arterial/arteriolar vessel walls (Fig. 4d) was associated with dementia in participants <80 years of age at death [194].

Several relevant studies from the Rush University Religious Orders Study and Memory and Aging Project cohorts further demonstrated that B-ASC is associated with cognitive impairment. In a study of 1,143 individuals, B-ASC was associated with global cognitive status, episodic memory, working memory, and perceptual speed (all $p < 0.05$), with a trend ($p = 0.052$) for visuospatial abilities [19]. Women in this cohort were more likely than men to have severe B-ASC [161], as was the case in the NACC data set [84]. In a separate

study, researchers estimated that the attributable risk for AD-type dementia due to B-ASC was 5.2% [30]. Analogous attributable risks in the same sample were 10.8% for all Lewy body diseases, 8.9% for macroscopic infarcts, and 8.1% for CAA [30]. Therefore, in this community-based cohort, the estimated proportion of AD-type dementia risk due to B-ASC was on par with other neuropathologic changes that are known to have a very large public health impact.

Although the overall contribution of B-ASC to cognitive impairment in a cohort can be estimated, it is much more difficult to estimate the degree of cognitive impairment resulting specifically from B-ASC in a given individual, particularly without an autopsy. This has been a challenging problem in the dementia research field. Some of the cognitive impairment attributed to AD-type dementia in clinical studies was almost surely due to B-ASC instead. This phenomenon has noteworthy implications. For example, in studies lacking autopsy confirmation, T2DM was associated repeatedly with increased risk for the clinical diagnosis of Probable AD [37, 170]. However, in studies where autopsy evaluation was part of the study design, the severity of AD pathologic change was not associated with T2DM; rather, the severity of cSVD pathologic change (including B-ASC) was increased in T2DM cases and was associated with antemortem cognitive impairments [3, 153, 172, 188]. Similar phenomena may underlie the observation that AD-type dementia risk is disproportionately high among African-American adults—neuropathologic studies indicate that the relevant disease-driving factor is cSVD pathologies including B-ASC, instead of the amyloid plaques and neurofibrillary tangles of AD [22, 179]. However, there are challenges in studying dementia in African Americans due to historic medical mistreatment, which has led to low willingness to participate in studies that involve brain autopsy [85]. More work is required in this area.

B-ASC has also been associated with motor [34, 35, 77] and autonomic [76] impairments. For example, Buchman and colleagues analyzed motor assessments in 850 participants with postmortem cSVD workup [35]. When the global motor scores of individuals with and without arteriolosclerosis were compared, the average global motor score was lower in individuals with more severe B-ASC. In a separate study, Buchman and colleagues evaluated autopsy data from 165 elderly adults [34] and found that “spinal arteriolosclerosis is common and may contribute to the severity of spinal white matter pallor and parkinsonism in older adults.” [34] In this cohort, spinal ASC explained substantial variability in parkinsonism as defined by the Unified Parkinson’s Disease Rating Scale [34, 63]. These non-cognitive findings underscore the widespread effects of B-ASC and the complex inter-relationship between vascular disease and clinical phenotypes.

Possible future directions: differentiating B-ASC subtypes

Diagnostic classification may evolve to recognize clinically meaningful subtypes of B-ASC. It is possible that some, but not other, mechanisms that cause what we currently refer to as B-ASC may be targetable by specific therapeutic or disease-prevention strategies in the future. We highlight four broad categories of phenomena that could form the bases of classifiable B-ASC subtypes: (1) the influence of different cellular subcomponents of the cAVU; (2) interactions with comorbid CNS vascular and/or neurodegenerative diseases; (3)

B-ASC caused by systemic diseases including endocrine, inflammatory, and coagulopathic conditions; and, (4) the biology of human aging.

There may be contributions to vasculopathy from multiple different cellular and extracellular elements. Potential cell-specific influences of astrocytes [192], pericytes [95], endothelial cells [73], smooth muscle cells [58, 80], microglia [75], non-cellular and shared micro-domains [2, 182] have been hypothesized [173]. In the future, it may become possible to categorize B-ASC according to the cell type or micro-domain that is primarily responsible for dysfunction in a given vascular segment. We have suggested a new term that may help in focusing efforts to understand the pathobiology of B-ASC, namely the cAVU, comprising the components within the arteriolar portions of the cerebral vasculature.

In addition to the B-ASC related dysfunction attributable to specific cAVU domains, another important area which merits further attention is understanding how B-ASC contributes to, or is affected by, comorbid brain conditions including neurodegenerative “misfoldingopathies” and various cerebrovascular diseases. As shown in Table 3, the associations between B-ASC and comorbid brain conditions are strong in advanced age. Extensive research and prior review articles have focused on the associations between cSVD and AD [31, 93, 137, 187]. Moreover, B-ASC was substantially more severe in both the white matter and neocortex in many different dementias compared to age-matched controls [76]. It has also been shown that in patients with one type of cSVD, other subtypes of cSVD are often present (e.g., CAA and microinfarcts, along with B-ASC) [31].

B-ASC is also affected by systemic medical conditions. There are many ways that non-CNS organ systems may influence the physiology of brain arterioles. The complex influences of MetS are discussed above. Many other systemic perturbations including auto-immunity, coagulopathy, cardiopulmonary disease, and renal dysfunction are common in aged persons and may affect cells of the cAVU. Drugs and surgical (including anesthetic) interventions used to treat the various aging-related diseases may also influence brain vascular health in ways that are not now fully known.

Finally, biological senescence itself may be a critical factor affecting arteriolar walls in aging brains. The literature on the interactions between biological aging and the vasculature, although extensive [95, 140, 198, 207], is incomplete with respect to B-ASC. Related areas of research have included age-related protein modifications (e.g., carbamylation, citrullination, and deamidation) [60], effects of oxidative stress [190], insulin signaling abnormalities [178, 224], mitochondrial dysfunction [10, 36], and dysregulated inflammation and autophagy [132]. Arguably, to study each of these topics in isolation is a reductionist approach to an organismwide senescence program with a genetic component, which includes progression of B-ASC at the final stage of the human aging spectrum. Investigating these pathways more comprehensively, and further addressing the biologic complexity of B-ASC, may help researchers to tailor strategies designed to preserve neurologic function in aging.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations (gene and protein names not listed):

AD	Alzheimer’s disease
B-ASC	brain arteriolosclerosis
CAA	cerebral amyloid angiopathy
CADASIL	cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
cAVU	cerebral arteriolar vascular unit
cSVD	cerebral small vessel disease
EPV	enlarged perivascular space
FLAIR	fluid-attenuated inversion recovery
FTLD-TDP	frontotemporal lobar degeneration with TDP-43 proteinopathy
H&E	hematoxylin and eosin
HS	hippocampal sclerosis
LATE	limbic-predominant age-related TDP-43 encephalopathy

MetS	metabolic syndrome
NACC NP	National Alzheimer's Coordinating Center Neuropathology
NVU	neurovascular unit
pCASL	pseudo-continuous arterial spin labeling
SI	sclerotic index
SNP	single nucleotide polymorphism
SWI	susceptibility weighted imaging
T2DM	type II diabetes mellitus
VCING	vascular cognitive impairment neuropathology guidelines
WMH	white matter hyperintensity

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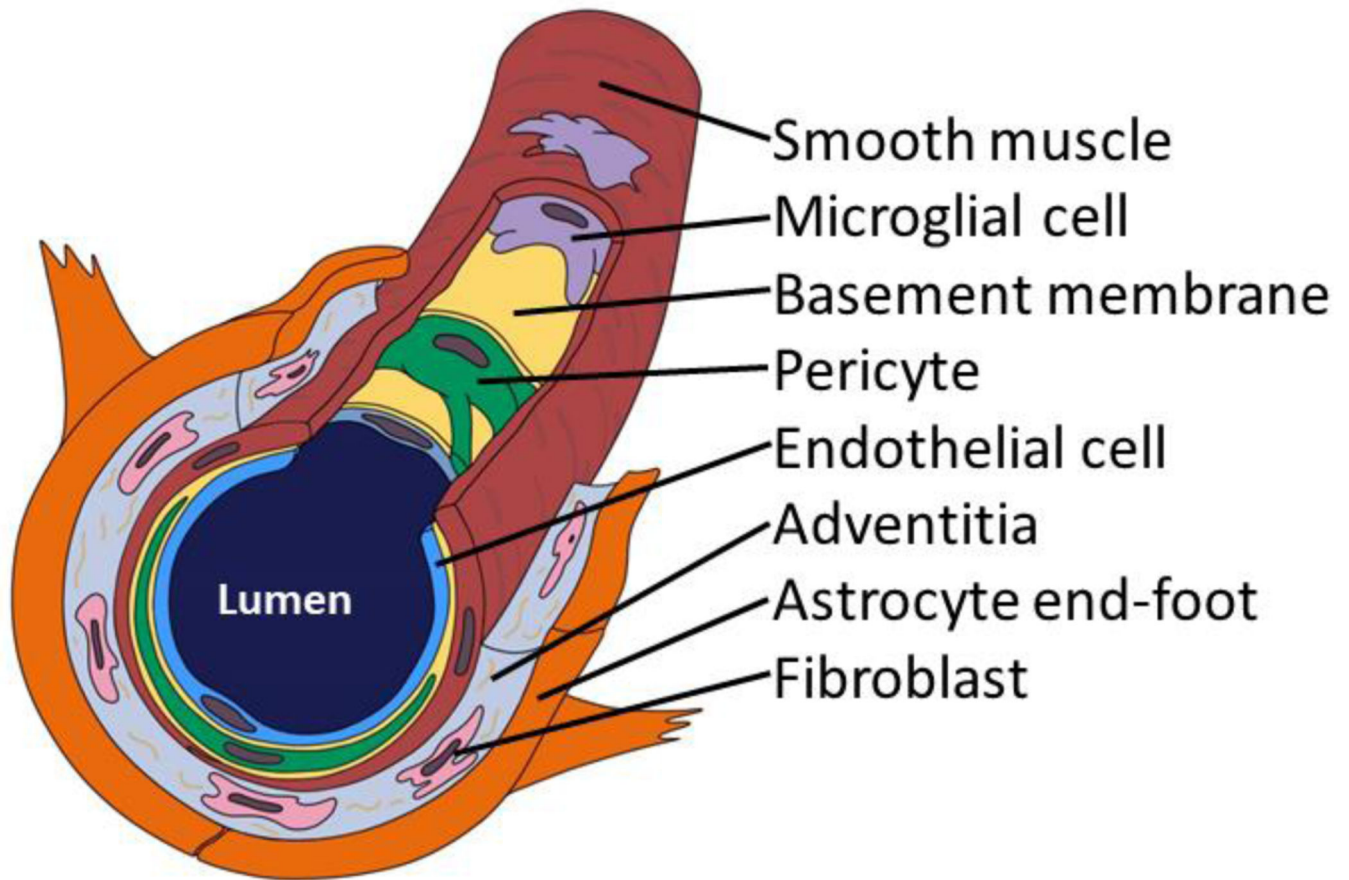


Fig. 1. A brain arteriole and constituents of the cerebral arteriolar vascular unit (cAVU). Brain arterioles are not all alike, but this schematic depiction may orient readers to some cAVU components. Shown here is a relatively thin-walled arteriole--no internal elastic lamina or adventitial nerve fibers are depicted. Inflammatory cells including macrophages and microglia are commonly found in and around the arteriolar wall. Acellular strands of elastin and collagen are interwoven with fibroblast-like cells in the adventitia.

VCING methods and selected results (Skrobot et al, 2016)

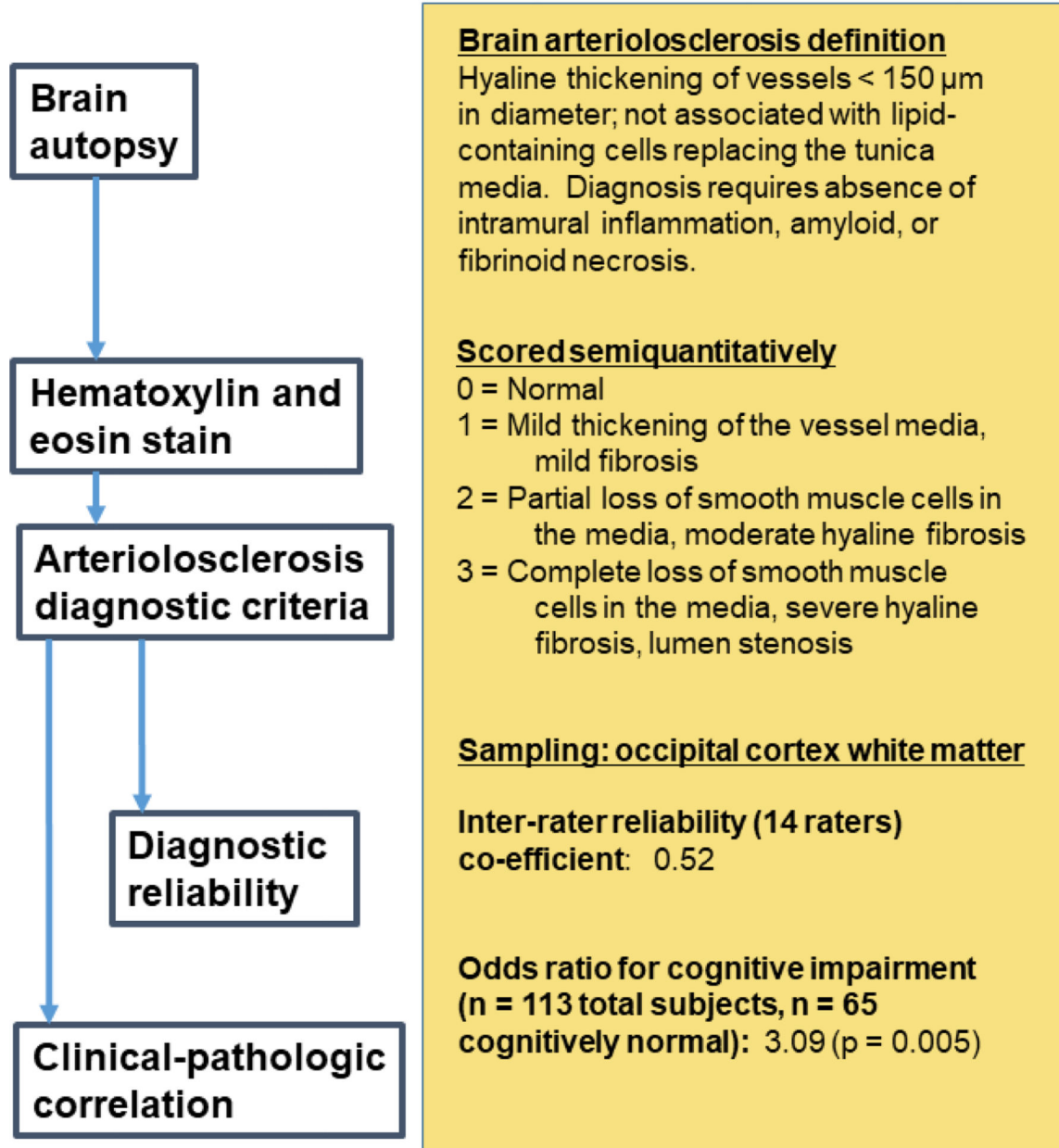


Fig. 2. Autopsy diagnosis of B-ASC involves staining with hematoxylin and eosin (H&E). The VCING collaborative group provided a consensus among experts describing criteria for defining B-ASC and for generating parameters that reflect different severity of the pathology. These diagnostic criteria are presented on the right side of the figure. In this study [183], which included evaluation of n=113 brains and sampling from many different brain areas, stained slides of the occipital cortex white matter produced moderately strong inter-rater reliability among different neuropathologists, and a robust association with cognitive

impairment, i.e., B-ASC pathology was more often present in cases with dementia than those with normal cognitive status.

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Brain arteriolosclerosis severity

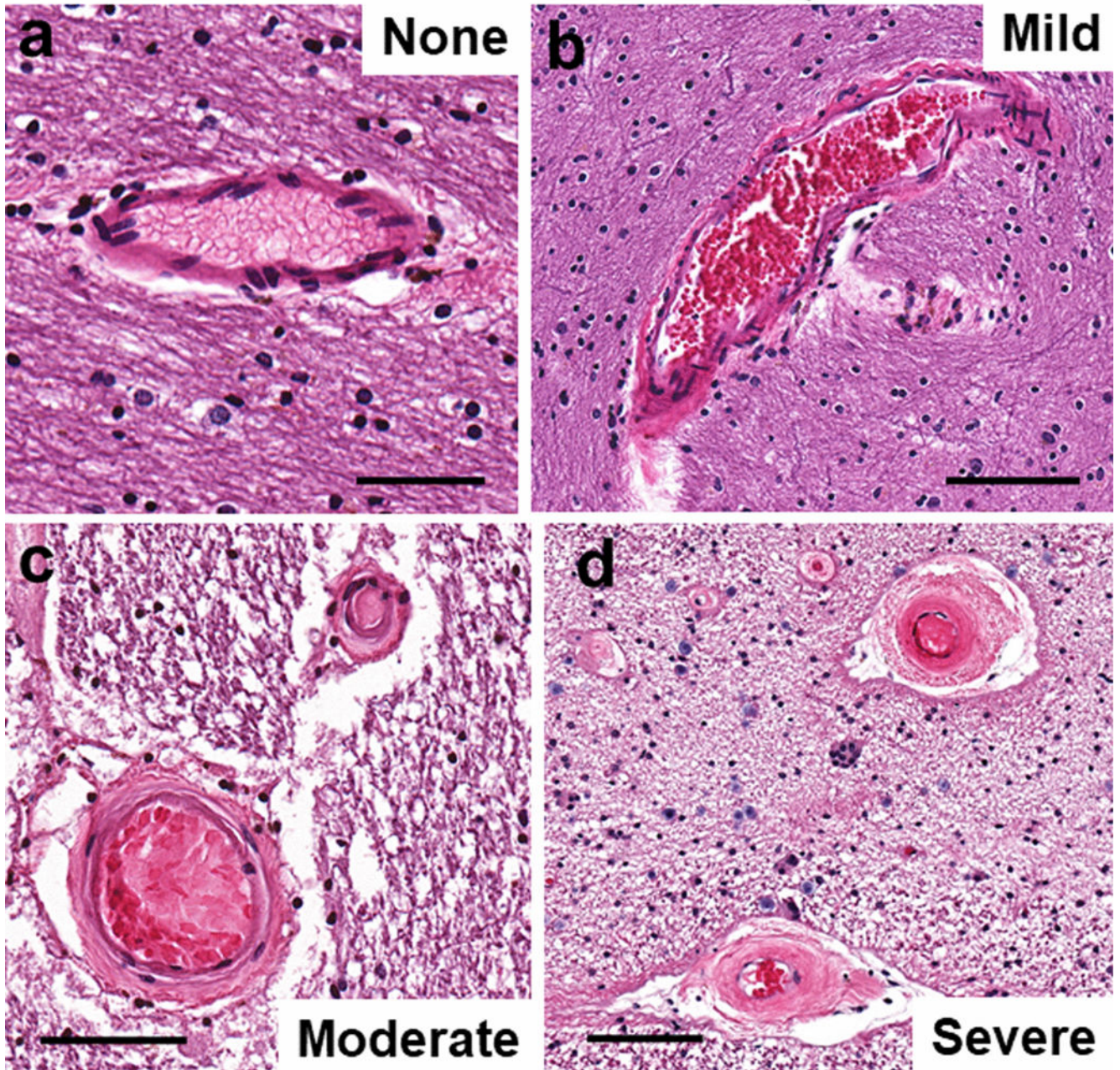


Fig. 3. One approach to grading arteriolosclerosis (B-ASC) pathologic severity is on a semiquantitative scale of “none”, “mild”, “moderate”, or “severe” B-ASC. A score of 0 corresponds to no/very minimal changes (a); a score of 1 indicates mild changes (b); a score of 2 is moderately severe B-ASC (c); and a score of 3 indicates severe B-ASC (d). Note that in (d), the arterioles are partly occluded by severe hyperplastic (“onion-skin”-type) arteriolosclerotic changes. Scale bars = (a): 80 μ m; (b): 200 μ m; (c): 100 μ m; and, (d): 100 μ m. All of these 4 panels show vascular profiles from occipital cortex white matter of human subjects.

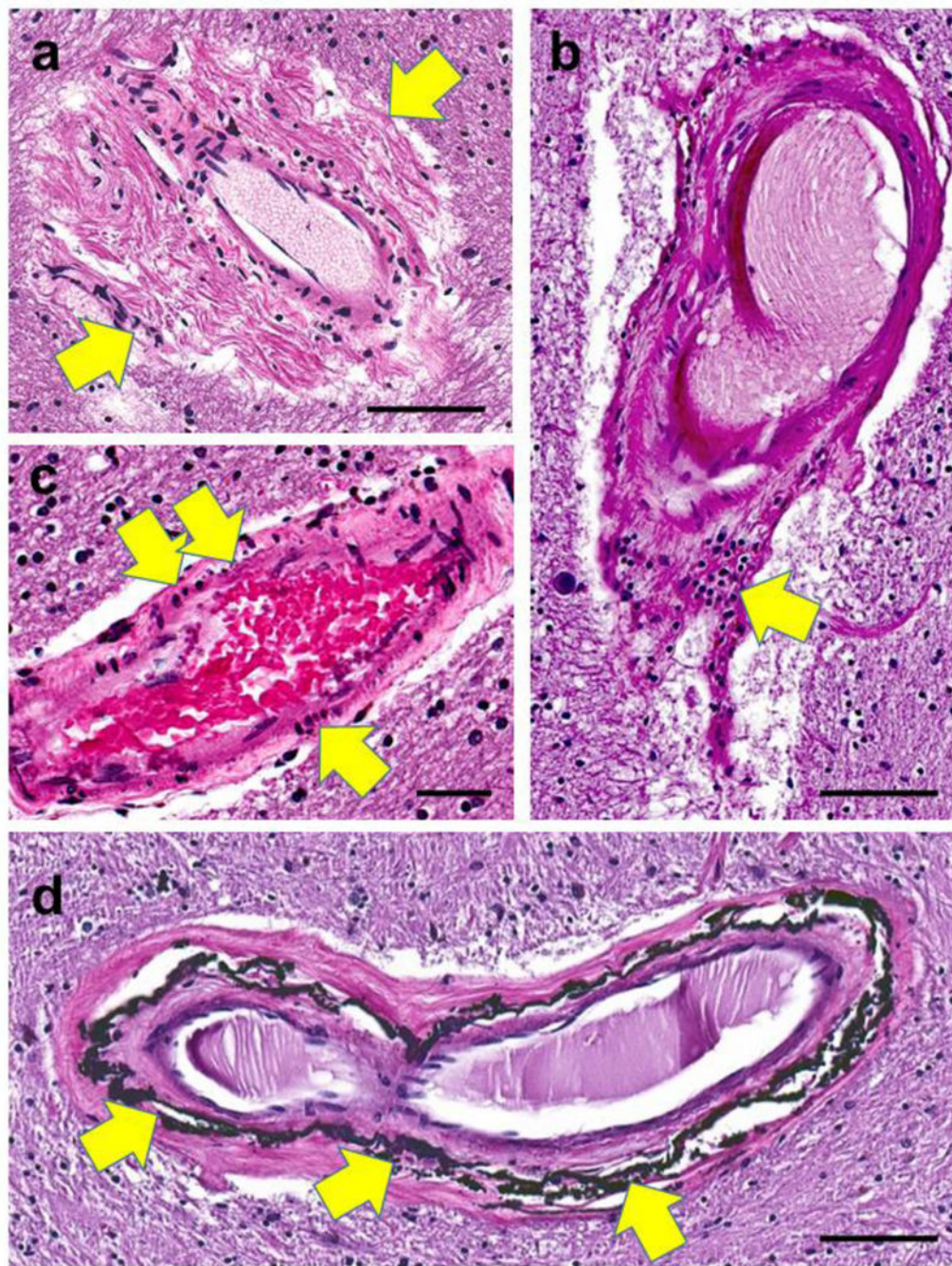


Fig. 4. Arteriolar walls can show different histomorphologies with aging.

In panel (a), periarteriolar (adventitial) fibrosis is extensive and non-concentric (arrows). Panel (b) shows a collection of lymphocytes (arrow) in portions of the vessel wall. In panel (c), vessel wall changes include pyknotic-appearing smooth muscle cells (arrows). Siderocalcinosis, distinct from B-ASC, has been associated with dementia [194] and is usually seen preferentially in the globus pallidus (arrows in d). Synonyms for this include medial vascular calcification, calcific medial arteriosclerosis, and Monckeberg's medial sclerosis. Scale bars = (a, b, and d): 100 μ m; (c): 60 μ m.

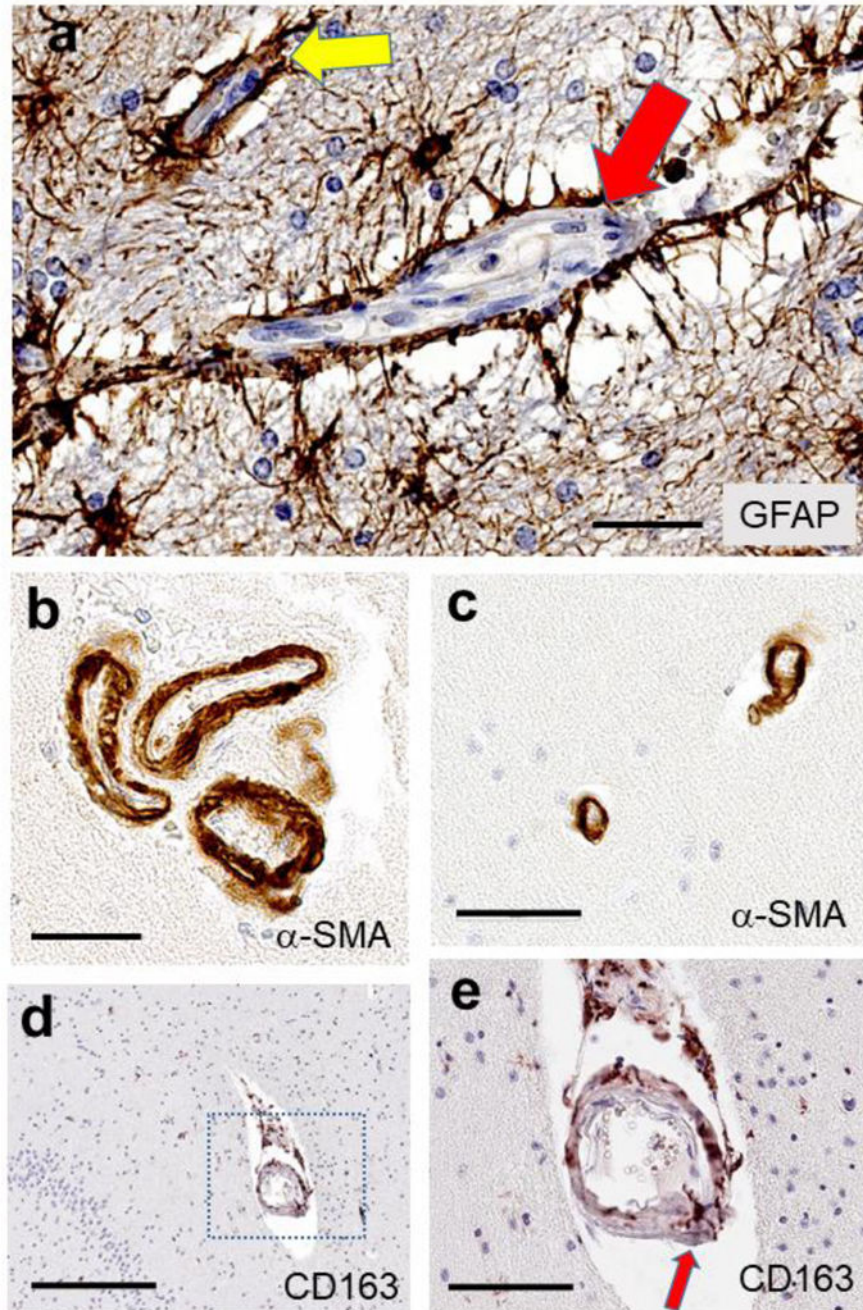


Fig. 5. Photomicrographs to highlight features of the cAVU with immunohistochemistry. Astrocytes and astrocytic end feet processes (a) are shown immunostained for GFAP, surrounding a capillary (yellow arrow) and a larger arteriole (red arrow). Smooth muscle cells, immunolabeled for α -SMA (panels b, c) in arterioles cut in cross-section, may highlight that multiple arterioles can exist in a single Virchow-Robin space (b), and the vascular profiles may be rather narrow, $<20\ \mu\text{m}$ lumen diameter (c). Some cellular constituents have only recently been appreciated, such as the “scavenger microglia” that express CD163 antigen and are arranged in and around small blood vessels, such as this

hippocampal arteriole (**d**, **e**). In panel (**e**), a magnified view of the panel (**d**) inset, a CD163 immunoreactive cell spans the full thickness of the arteriolar wall (red arrow). Scale bars = (**a**): 60 μm ; (**b**): 50 μm ; (**c**): 60 μm ; (**d**): 300 μm ; and, (**e**): 90 μm .

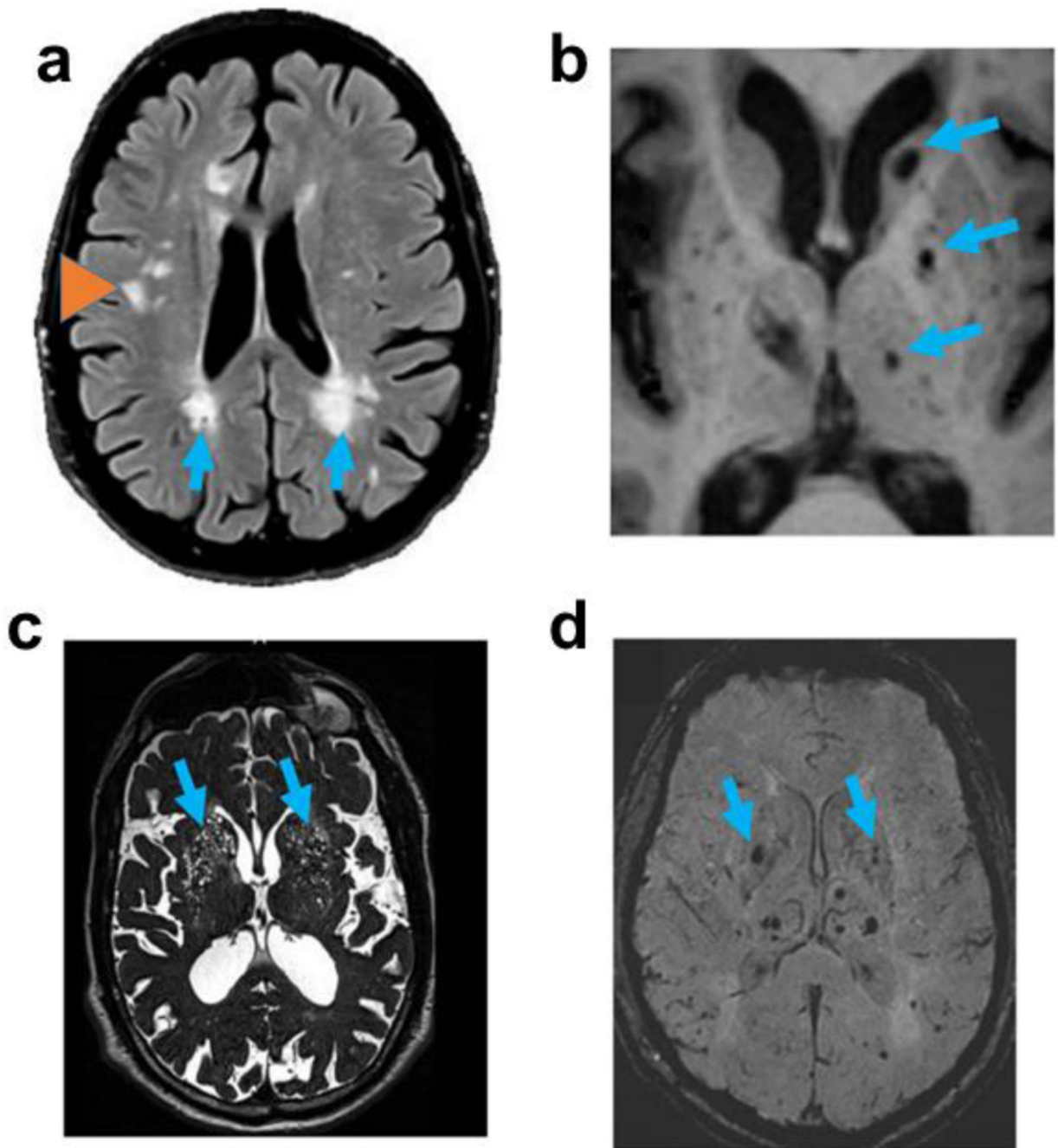


Fig. 6. Magnetic resonance imaging (MRI) modalities are commonly used in the study of cerebral small vessel disease.

FLAIR imaging (**a**) showing regions of periventricular white matter hyperintensities (WMHs; arrows) and deep WMHs (orange arrowhead); T1-weighted imaging (**b**) showing lacunes (arrows); T2-weighted imaging (**c**) showing expanded perivascular spaces (arrows); and, susceptibility-weighted imaging (**d**) showing presumed microbleeds (arrows).

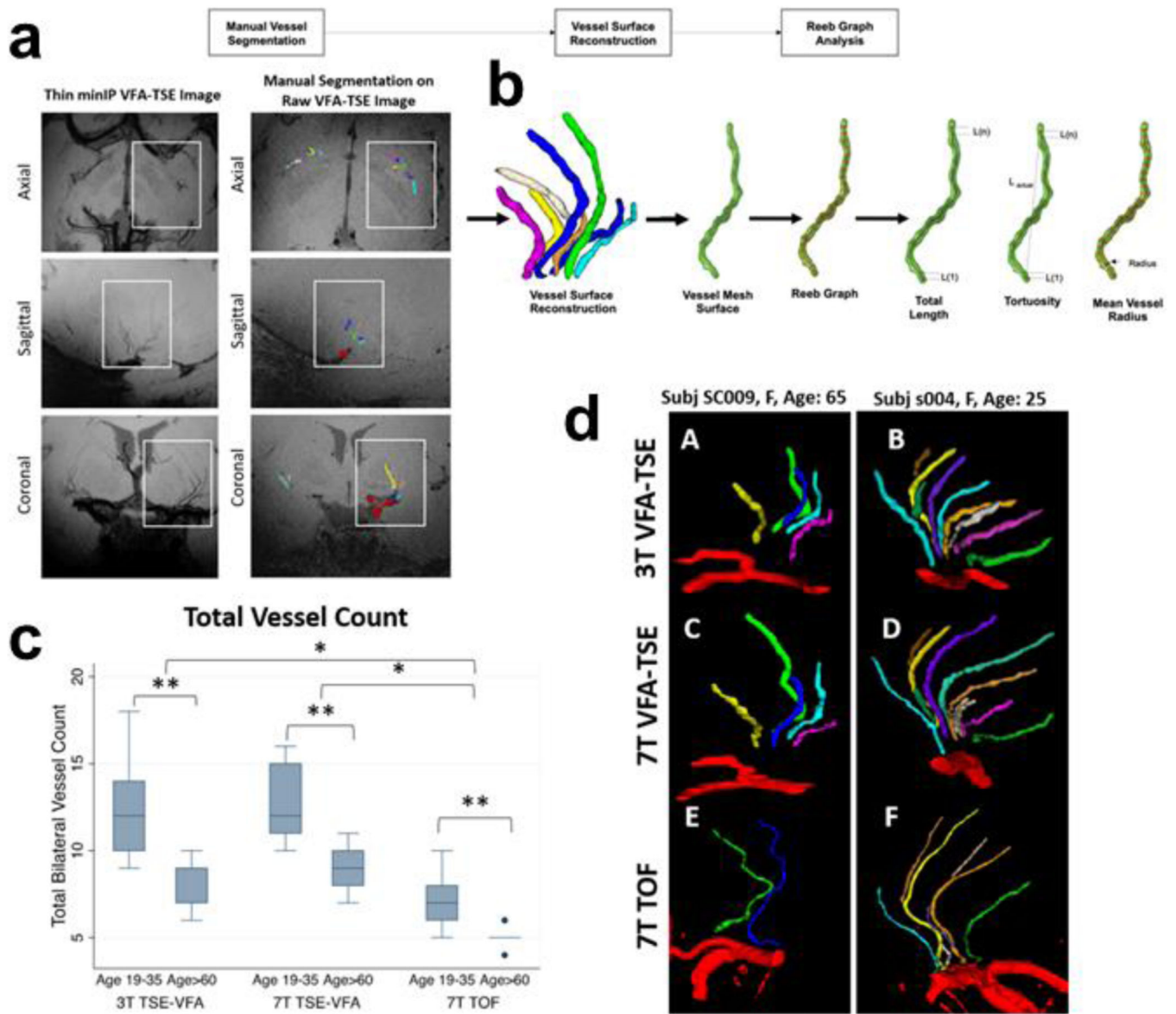


Fig. 7. High resolution MRI for the characterization of basal ganglia lenticulostriate arteries using 3T and 7T magnets.

This relatively high-resolution *in vivo* imaging [122] enables visualization of slender arteries/arterioles. In aging, there is increased tortuosity and decreased number of blood vessels resolved. In the raw images (a), blood is rendered black. Workflow is illustrated in panel (b), beginning with manual vessel segmentation on the raw turbo spin echo variable refocusing flip angles (TSE-VFA) image. The vessel volumes are reconstructed, and a mesh surface is created in preparation for shape analysis. Quantitative measures of vessel length, tortuosity and radius can be calculated. The box plot (c) shows that more vessels were detected in young participants than in older participants and more vessels were detected using 7T VFA-TSE compared to the more conventional 7T time-of-flight magnetic resonance angiography (7T TOF-MRA) [122]. An example comparing an older and younger

adult (**d**) illustrates the smaller number of vessels detected in an older participant (A,C,E) than a younger participant (B, D, F).

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Brain arteriolosclerosis (B-ASC) severity stratified by age range: NACC Neuropathology v10 data set

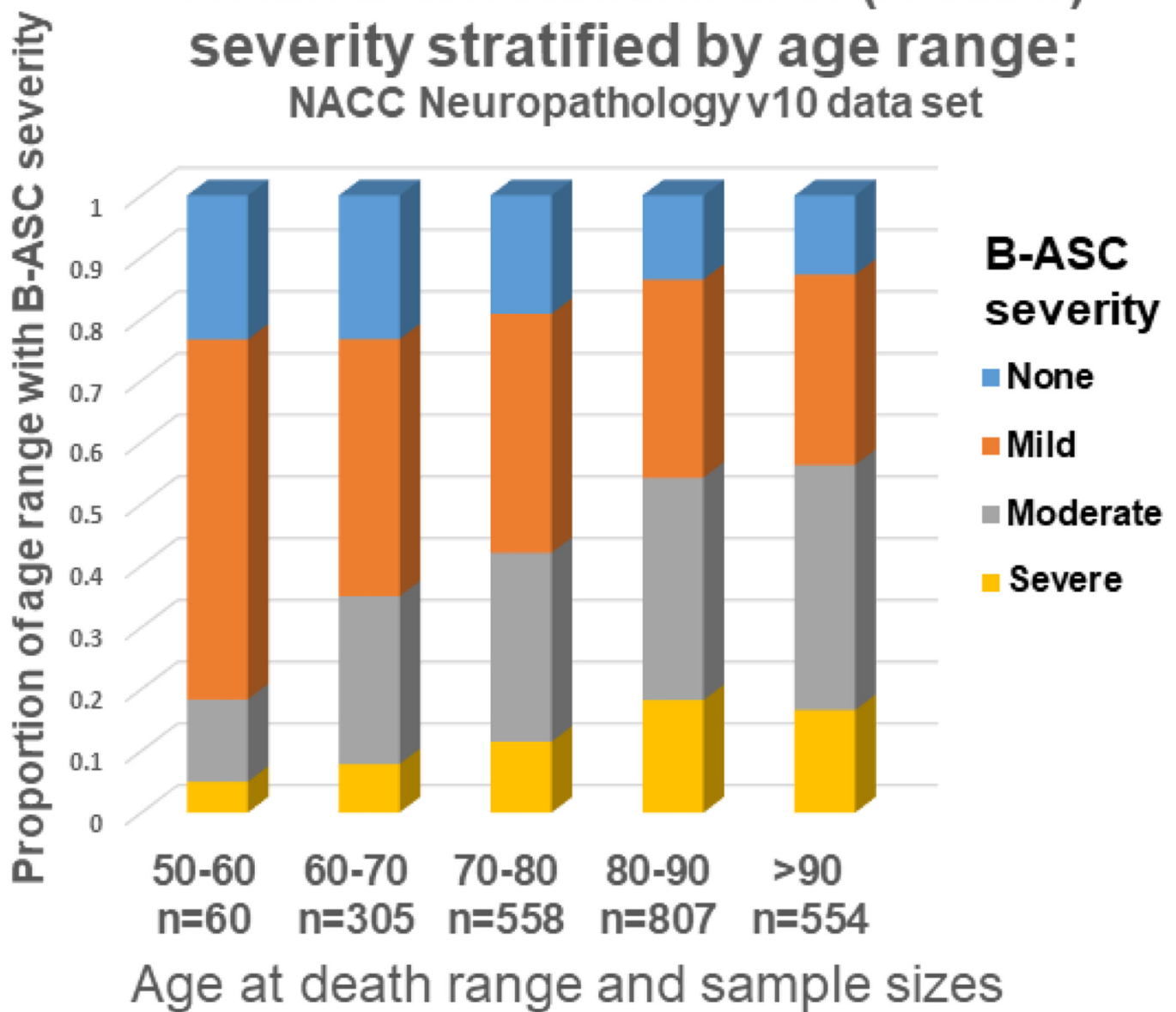


Fig. 8. Brain arteriolosclerosis (B-ASC) pathology by age at death, from the NACC Neuropathology version 10 data set (n=2,284).

B-ASC pathology increases with advanced age. Note that <20% of subjects had moderate or severe B-ASC pathology before age 60, whereas in subjects over 80, >50% had moderate or severe B-ASC pathology, and >80% had some degree of B-ASC.

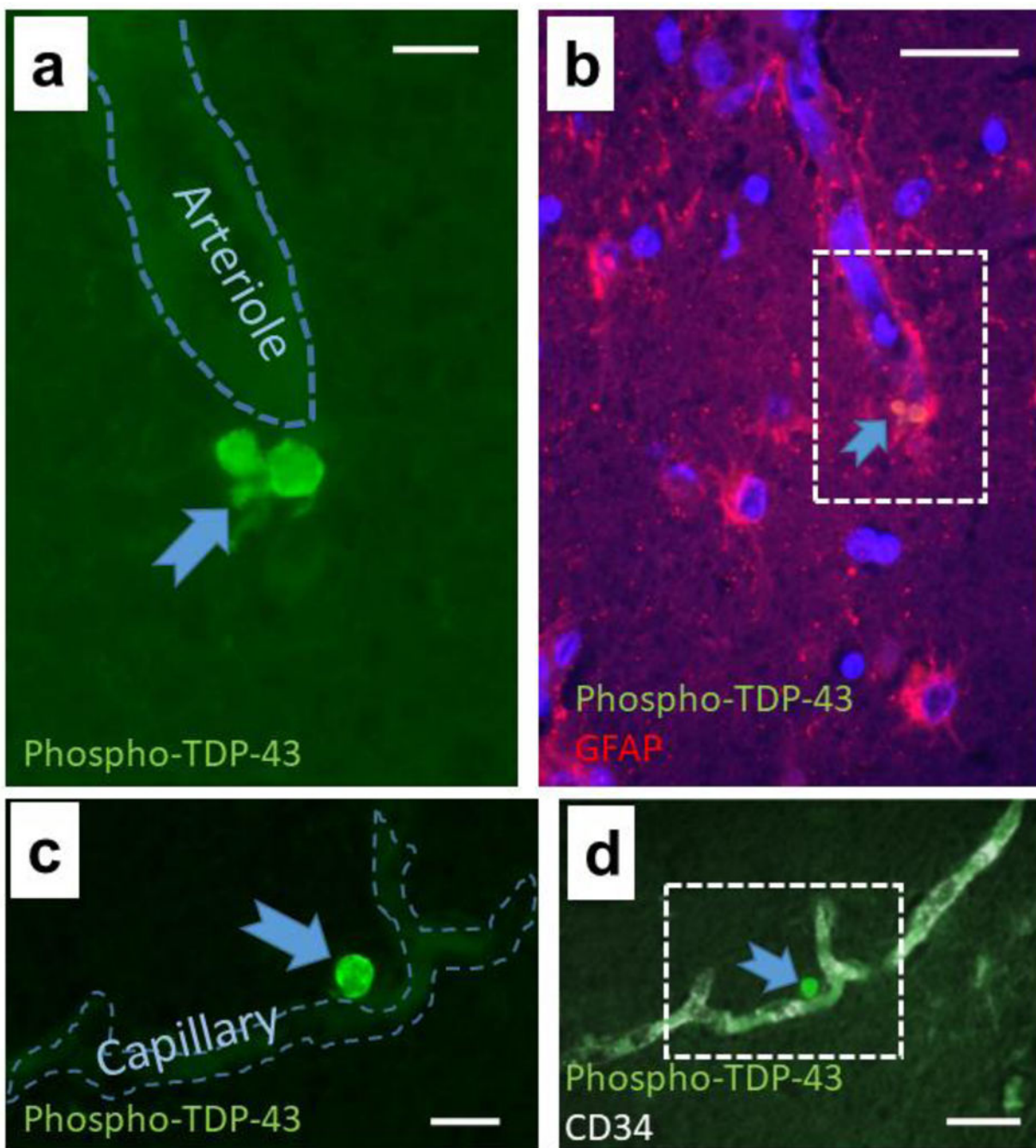


Fig. 9. Phospho-TDP-43 immunoreactive proteinopathy can be seen immediately adjacent to small blood vessels in brains with limbic-predominant age-related TDP-43 encephalopathy (LATE).

The micrograph shows perivascular TDP-43 proteinopathy near an arteriole (**a**, **b**) and a capillary (**c**, **d**) in hippocampi of 2 subjects with autopsy-proven LATE. In panel (**a**), the green filter shows the TDP-43 proteinopathy adjacent to an arteriole. Panel (**b**) shows lower magnification and the red filter shows GFAP immunoreactivity, revealing the colocalization with GFAP and TDP-43 (arrow). Panel (**c**) shows a phospho-TDP-43 deposit adjacent to a capillary as indicated by CD34 immunofluorescence at lower magnification

(d). The presence of TDP-43 proteinopathy in astrocyte end-feet in FTLD-TDP was shown previously by Lin et al. [116]. LATE neuropathologic change is associated with relatively severe B-ASC [101, 154]. Thus, there may be parallel or synergistic disease-driving mechanisms related to the pathologies that usually are categorized separately as cerebrovascular or neurodegenerative. Scale bars = **(a)**: 15 μm ; **(b)**: 40 μm ; **(c)**: 20 μm ; and, **(d)**: 40 μm .

Table 1.

Definitions of Arteriolosclerosis

Source	Arteriolosclerosis definition
Skrobot et. al., 2016	Hyaline thickening of walls of vessels <150 µm in diameter, not associated with lipid-containing cells replacing the tunica media. Diagnosis requires an absence of intramural inflammation, amyloid or fibrinoid necrosis.
Buchman et. al., 2013	Arteriolosclerosis describes the histologic changes commonly found in the deep penetrating small vessels of the brain in aging, including intimal deterioration, smooth muscle degeneration, and fibrohyalinotic thickening of arterioles with consequent narrowing of the vascular lumen.
Grinberg and Thal, 2010	Concentric hyaline thickening of small arteries (40 – 150 µm in diameter) leading to a concentric stenosis of the vessel lumen.
Taber's Medical Dictionary, June 2020	A disease of the arterial vessels marked by thickening and loss of elasticity in the arterial walls. It is known colloquially as "hardening of the arteries."
Merriam-Webster Medical Dictionary, June 2020	Thickening of the intima of arterioles (as of the kidney in hypertension) by hyaline and fatty deposits that reduce the lumen and obstruct blood flow

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Table 2.

Small vessel pathologies as noted in Vascular Cognitive Impairment Neuropathology Guidelines (VCING) system and National Alzheimer's Disease Coordinating Center (NACC) Version 10 Neuropathology data set

Cerebrovascular Pathology	VCING scoring system[183]	NACC v10 scoring system[26, 141]
Arteriolosclerosis	0–3 scale *	0–3 scale
Microinfarcts	0/1	Numbers and locations
Lacunar infarcts	0–3 scale	Numbers and locations
Large infarcts	0/1	Number, size, & location of old large infarcts, also acute and subacute large infarcts
Microhemorrhage	0/1	Numbers and locations
Larger hemorrhage	0/1	Gross, subdural or epidural, and epidural hemorrhages noted separately
Cerebral amyloid angiopathy (CAA)	Meningeal, cortical, or capillary scored separately	0–3 overall scale
Myelin loss	0–3 scale	“White matter rarefaction”, 0–3 scale
Other	Fibrinoid necrosis (0/1), microaneurysms (0/1), Perivascular space dilation (0–3 scale), Perivascular hemosiderin leakage (0–3 scale)	Any type of aneurysm (0/1), Laminar necrosis (0/1), vascular malformation (0/1), blood vessel mineralization (0/1)
Atheroma/atherosclerosis in the Circle of Willis	0–3 scale	0–3 scale

* See Figs. 2, 3

Table 3.

Clinical and pathological correlations in NACC Neuropathology v10 Dataset, stratified by age of death

	Brain arteriolosclerosis (B-ASC)							Overall p-value	Association with history of myocardial infarction [#] (p-value)
	<80 years at death			≥80 years at death					
	B-ASC: None or mild, n(%)	B-ASC: Moderate or severe n(%)	p-value*	B-ASC: None or mild n(%)	B-ASC: Moderate or severe n(%)	p-value*			
Cardiovascular risk factor by clinical history**									
Diabetes	No	303 (88.9)	188 (85.8)	0.35	300 (86.5)	340 (85.4)	0.77	0.31	<0.0001
	Yes	38 (11.1)	31 (14.2)		47 (13.5)	58 (14.6)			
Hypertension	No	276 (60.5)	158 (51.6)	0.018	183 (36.2)	182 (32.2)	0.19	0.0002	<0.0001
	Yes	180 (39.5)	148 (48.4)		322 (63.8)	383 (67.8)			
Hypercholesterolemia	No	149 (44.5)	86 (39.6)	0.30	126 (36.7)	135 (34.1)	0.50	0.11	<0.0001
	Yes	186 (55.5)	131 (60.4)		217 (63.3)	261 (65.9)			
Body mass index (BMI) ≥ 30	No	215 (81.1)	138 (73)	0.053	273 (84.3)	284 (84.5)	1.0	0.32	0.75
	Yes	50(18.9)	51 (27)		51 (15.7)	52 (15.5)			
Cerebrovascular pathology**									
Cerebral microinfarct(s), >0	No	470 (86.9)	285 (83.3)	0.17	480 (79.2)	408 (61.4)	<0.0001	<0.0001	0.082
	Yes	71 (13.1)	57 (16.7)		126 (20.8)	257 (38.6)			
Cerebral microbleed(s), >0	No	499 (97.1)	314(93.5)	0.018	579 (97.1)	618 (93.6)	0.0051	0.00015	0.66
	Yes	15 (2.9)	22 (6.5)		17 (2.9)	42 (6.4)			
Cerebral large or lacunar mfarct(s), >0	No	495 (91.5)	299 (87.2)	0.050	536 (88.7)	497 (74.6)	<0.0001	<0.0001	0.50
	Yes	46 (8.5)	44(12.8)		68 (11.3)	169 (25.4)			
White matter rarefaction (moderate/severe)	No	405 (84.2)	168 (53.5)	<0.0001	527 (92.8)	348 (56.4)	<0.0001	<0.0001	0.41
	Yes	76(15.8)	146 (46.5)		41(7.2)	269 (43.6)			
CAA (moderate/severe)	No	369 (68.3)	177 (51)	<0.0001	464 (76.6)	390 (58.7)	<0.0001	<0.0001	0.19
	Yes	171 (31.7)	170 (49)		142 (23.4)	274 (41.3)			
Neurodegenerative disease pathology**									
LATE-NC, Stage ≥2	No	283 (74.5)	191 (71.8)	0.51	268 (75.9)	291 (64.2)	0.00045	0.00077	0.97
	Yes	97 (25.5)	75 (28.2)		85 (24.1)	162 (35.8)			
Hippocampal sclerosis, Any	No	480 (88.2)	286 (81.9)	0.012	526 (86.8)	509 (76.3)	<0.0001	<0.0001	0.54
	Yes	64(11.8)	63 (18.1)		80 (13.2)	158 (23.7)			
Alzheimer's disease, Intermediate/Severe	No	121 (22.2)	64(18.3)	0.19	182 (30)	133 (19.9)	<0.0001	0.00015	0.43
	Yes	423 (77.8)	285 (81.7)		424 (70)	534 (80.1)			
Lewy body disease, Any	No	289(53.1)	176 (50.4)	0.47	414(68.3)	395 (59.2)	0.00093	0.022	0.73
	Yes	255 (46.9)	173 (49.6)		192 (31.7)	272 (40.8)			

* Chi-square test, 2-tailed

** Cardiovascular risk factors are by self-report at last exam; pathological features are autopsy results

Myocardial infarction indicates either remote or recent by clinical history

Table 4.

Human genes associated with brain arteriolosclerosis and other inherited small vessel disease

Gene	Chr.*	Known Function of gene product	Associated subtype of small vessel disease	Refs*
<i>Mendelian/monogenic</i>				
<i>NOTCH3</i> **	19p13	Transcription regulator in vascular smooth muscle cells	WMH*, ischemic stroke, ICH*, CADASIL	[91, 138]
<i>COL4A1/A2</i> **	13q34	Collagen IV, endothelial basement membrane protein	WMH, ischemic stroke, ICH	[92, 169]
<i>HTRA1</i> **	10q26	Serine protease involved in repression of TGF- β	WMH, ischemic stroke, CARASIL	[138, 169]
<i>TREX1</i>	3p21	3'-exonuclease involved in DNA repair	WMH, ischemic stroke	[171, 176]
<i>Contributory/polygenic</i>				
<i>FOXC1/FOXF2</i>	6p25	DNA regulation in eye, brain, heart, and kidney development.	WMH, ischemic stroke	[56]
<i>ZCCHC14</i>	16q24	Transcription factor and metal ion-binding protein	WMH, stroke	[202]
<i>WDR12/CAIL</i>	2q33	Protein domain-specific binding	WMH, stroke	[124]
<i>PMF</i>	1q22	Transcription factor involved in mitosis	WMH, ICH	[204, 219]
<i>APOE</i>	19q13	Apolipoprotein involved in lipid transport and metabolism	B-ASC*, WMH, ischemic stroke	[98, 223]
<i>ABCC9</i>	12p12	K+ channel regulators in blood vessels	B-ASC in persons >80y.o. at death	[84]
<i>JAZF</i>	7p15	Transcription factor involved in transcription repression	B-ASC	[40]
<i>TSPAN8</i>	12q21	Cell-membrane protein involved in cell growth regulation	B-ASC	[40]
<i>LGR5</i>	12q21	Receptor in Wnt signaling pathway	B-ASC	[40]
<i>KCNJ11</i>	11p15	K+ channel regulated by ABCC8andABCC9	B-ASC	[40]
<i>PCSK9</i>	1p32	Protease involved in cholesterol metabolism regulation.	B-ASC	[40]
<i>ZFH3</i>	16q22	Transcription factor associated with atrial fibrillation	B-ASC	[40]

* Abbreviations: Chr.: Chromosomal location; Refs: References; WMH: white matter hyperintensities; ICH: intracerebral hemorrhage seen via radiography; B-ASC: Brain arteriolosclerosis; CADASIL: cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CARASIL: Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy

** For *NOTCH3*, *COL4A1/A2*, and *HTRA1*, gene variants also may be contributory in polygenic disease

Table 5.

Clinical-pathological correlations for CNS arteriolosclerosis

Source	Cohorts and sample sizes	Avg age at death	Main findings
Skobrot et al, 2017[183]	Oxford Brain bank and Newcastle Brain Tissue Resource, n=113	83.4yrs	Cognitive impairment (either mild cognitive impairment or dementia) was associated with more severe B-ASC
Arvanitakis et al, 2017[19]	Rush University (Chicago, USA) cohorts, n=1,143	88.8yrs	Odds of clinically suspected Alzheimer's type dementia were higher with more severe B-ASC
Boyle et al, 2018[30]	Rush University cohorts (Chicago, USA), n=1161	89.6yrs	B-ASC accounted for 5.2% of risk for clinical Alzheimer's type dementia diagnosis
Buchman et al, 2011[33]	Rush University cohorts (Chicago, USA), n=418	88.5yrs	B-ASC was associated with parkinsonism gait disturbance, same trend for global parkinsonism and tremor
Buchman et al, 2017[34]	Rush University cohorts (Chicago, USA), n=163	91.2yrs	Spinal arteriolosclerosis was prevalent (24% modsevere) and is associated with parkinsonism
Suemoto et al, 2019[194]	Biobank for Aging Studies (BAS) of the University of Sao Paulo, Brazil n=677 <80y.o.; n=412 >80y.o.	<80y.o.: 67.0yrs; >80y.o.: 85.7yrs	Hyaline B-ASC was associated with cognitive impairment in younger and older groups (effect size trended larger in younger group); siderocalcinosis was associated with cognitive impairment in younger group only
Suemoto et al, 2014[193]	The São Paulo Autopsy Service, Brazil, n=1,092	74yrs	Hyaline B-ASC severity was associated with cognitive status
Ighodaro et al, 2017[84]	NACC data set, n=1008 <80y.o.; n=1,382 >80y.o.	<80y.o.: 78.0yrs; >80y.o.: 88.0yrs	Moderate and severe B-ASC were associated with global cognition measured by final CDR-SB and MMSE scores. Hypertension was associated with B-ASC in younger but not older group.