

Section 1

Classification, pathology, and basic aspects

Chapter

1

Definition and classification of small vessel diseases

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Introduction

Cerebral small vessel disease (SVD) has become a popular and very widely used term today. As a reflection of this trend, the present book is entirely dedicated to this issue that has recently gained a central interest for clinicians, radiologists, pathologists, and many researchers in the fields of stroke, dementia, and aging.

In this chapter, I will briefly outline key definitions and concepts related to SVD, and also briefly report on new directions in the field. For a detailed discussion of the topic, readers can refer to a review [1] and a position paper recently published [2].

Definition of cerebral SVDs and nosologic issues

Before defining the pathologic processes affecting the small vessels of the brain, the definition itself of these vessels is needed. Generally speaking, a small vessel could be defined as any vascular structure that is not “large.” Obviously, this is quite simplistic, and a more precise definition should be provided. Of note, a survey performed some years ago reported that the agreement among neuropathologists on the definition of a small vessel was not high [3]. About half of the pathologists agreed on the definition of a small vessel being one that was less than 500 μm in diameter and located deeper than in the cortex. Other reported definitions with lower agreement were “vessels with a diameter less than 50 μm ” and “all the vessels within the brain parenchyma plus the vessels with a diameter less than 500 μm in the leptomeningeal space.” Also, use of the term as synonym of arteriole was mentioned [3]. Many investigators use the term “small

vessel” in almost exclusive reference to the arterial tree, likely because pathologic processes of the arterial component are better known than those of the other components (capillaries and small veins). Our current definition of small vessels refers to all the vascular structures (small arteries, arterioles, capillaries, venules, and small veins) that are located in the brain parenchyma or in the subarachnoid space. The general assumption behind this concept is that the diseases that affect the small vessels are at least in part different from those that affect the large vessels. This is obviously only partially true as some pathologic processes damage both large and small vessels. This is the case, for example, for diabetes and some inflammatory diseases (e.g., vasculitis). On the other hand, some other diseases, such as cerebral amyloid angiopathy, particularly affect the small vessels. The second assumption that leads to a distinction between pathologic processes of the small and large vessels is that the pathophysiology and the consequences on the brain parenchyma are different. Usually, the parenchymal consequences of SVD are less acute with the exception of lacunar infarcts, and tend to accumulate over time and may result in disability.

In addition to some inconsistencies in the definition of small vessels, another problem in the field of SVD is that current standard neuroimaging techniques used in practice do not allow the visualization of small vessels and, therefore, a direct understanding of their structural consequences. As a result, SVD is a term used today to describe the pathologic consequences of SVD on the brain parenchyma rather than the underlying diseases of the vessels. One of the consequent problems with this current view is that it tends to cause a uniform pathogenic interpretation of the brain lesions and, therefore, people to refer to

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“a disease” (see, e.g., Wardlaw et al. [4]). This approach can be somewhat misleading; for example, a small lacunar infarct can be caused by arteriolosclerosis due to aging and hypertension, but also to vasculitis or an infectious process that affects the small penetrating arteries and arterioles, and therefore is better referred to as a syndrome. Thus, just looking at the single neuroimaging lesion cannot be sufficient to make a comprehensive diagnosis.

One final concept to keep in mind when approaching SVD is that the parenchymal lesions can be of different nature, either ischemic or hemorrhagic. Hitherto, the view has been focused much more on the nonhemorrhagic brain lesions with scarce attention to the hemorrhagic ones. Our previous classification of brain lesions due to SVD recognized two types of ischemic (white matter lesions, lacunar infarcts) and two types of hemorrhagic (large hemorrhages, microbleeds) lesions [1]. Recently, the number of lesions attributable to SVD, and therefore classifiable as such, has expanded [2].

Etiologic classification of cerebral SVD

A possible etiologic classification of SVD is reported in Table 1.1 [1]. Some of the reported diseases are systemic, while others are particularly confined to the

brain. As stated elsewhere [1], the relative frequency of these diseases is different, and the first two types are by far more commonly encountered in clinical practice than the latter ones.

New developments in the field of the definition of SVD

Because at present SVD is mainly a neuroimaging-defined concept, it is expected that, parallel to the development of neuroimaging techniques, the definitions of SVD will continue to evolve and change accordingly. This has been indeed the case over the last few years. In 2011, a call for a collaborative effort focused on an appraisal of the different types of SVD and their definition was launched by the Centres of Excellence in Neurodegeneration (COEN) and the Canadian Institutes of Health Research (CIHR), and an ad-hoc International Working Group was established [5]. The Working Group met twice in 2012, and the collaborative efforts ended in the assemblage of a consensus paper that is now published [2]. The paper reports on a unified approach to the neuroimaging standards for research in SVD under the acronym STRIVE (STandards for ReportIng Vascular changes on nEuroimaging). The work done by the collaborative group is reflected in a series of major conclusions. The first one was that the number of SVD lesion subtypes was broadened to include six types of neuroimaging lesions: (1) recent small subcortical infarcts; (2) lacunes of presumed vascular origin; (3) white matter hyperintensity of presumed vascular origin; (4) perivascular spaces; (5) cerebral microbleeds; and (6) brain atrophy. Perhaps, the inclusion of this latter type lesion was the most advanced change, and was determined by recent data on the association between subcortical lesions and brain atrophy [6]. The second conclusion was the establishment of a common language about terms and definitions for SVD features visible on magnetic resonance imaging (MRI). A third was the suggestion of minimum standards for image acquisition and analysis. The fourth conclusion was an agreement on standards for scientific reporting of changes related to SVD on neuroimaging. In addition, emerging imaging methods for detection and quantification of preclinical manifestations of SVD were also reviewed. This methodological paper represents the basis for relevant future projects and research in the field of SVD.

Table 1.1 Etiologic classification of cerebral SVDs

Type 1. Arteriolosclerosis (or age and vascular risk factors-related SVD)

Type 2. Cerebral amyloid angiopathy (sporadic and hereditary)

Type 3. Inherited or genetic SVD (distinct from cerebral amyloid angiopathy; e.g., CADASIL, CARASIL, Fabry's disease, SVD due to *COL4A1* mutations, etc.)

Type 4. Inflammatory and immunomediated SVD (systemic and cerebral vasculitis, central nervous system vasculitis secondary to infections)

Type 5. Venous collagenosis

Type 6. Other SVD (e.g., post-radiation angiopathy and nonamyloid microvessel degeneration in Alzheimer's disease)

Modified from Pantoni [1].

CADASIL, cerebral autosomal dominant arteriopathy with subcortical ischemic strokes and leukoencephalopathy; CARASIL, cerebral autosomal recessive arteriopathy with subcortical ischemic strokes and leukoencephalopathy; SVD, small vessel disease.

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Chapter

2

Pathology of cerebral small vessel disease

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Introduction

The term small vessel disease (SVD) refers to brain parenchymal injury associated with distal leptomeningeal and intracerebral vessel pathology. From a viewpoint that knowledge of vascular pathology is mandatory for understanding the pathophysiology of brain parenchymal injury and establishing preventive and therapeutic strategies, the principal vessel histopathology of the most common forms of SVD is reviewed. The authors describe pathologic aspects of vascular changes in the brain associated with hypertension and other vascular risk factors (henceforth referred to as hypertensive vasculopathy) and those of sporadic cerebral amyloid angiopathy (CAA). Hereditary forms of SVD are not specifically discussed in this review, including familial CAA and cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). The different underlying mechanisms of SVD development are briefly discussed.

Materials and methods

This review is based on postmortem pathologic materials and surgical specimens in the National Cerebral and Cardiovascular Center, Osaka, Japan, from 1977 onward, and data reported in the literature. Pathologic examination was performed as described previously [1, 2]. Immunohistochemical staining for β -amyloid ($A\beta$) was performed with a monoclonal antibody against human $\beta/A4$ protein (DAKO) at a concentration of 1 : 100.

Hypertensive vasculopathy

Hypertensive vasculopathy takes place as follows, separately or in various combinations.

Fibrinoid necrosis appears in small arteries and arterioles in the brain, kidneys, and other organs, predominantly in patients with poorly controlled, severe hypertension. It often appears in cases with intracerebral hemorrhage. Fibrinoid material deposits segmentally and commonly occupies a portion of the vessel. The vessel wall has deposits of an eosinophilic, amorphous, or finely granular material, called fibrinoid, which appears red with Masson trichrome and blue with phosphotungstic acid hematoxylin (PTAH). Fibrinoid consists of exudated plasma protein (fibrin and fibrinogen) and necrotic smooth muscle cells (SMCs) on electron microscopic and immunohistochemical examination. Rod- or polygonal-shaped masses with high electron density are the most characteristic finding. The fibrinoid structures have two types of periodic striation of 11 and 22 nm. Mural or occlusive thrombus formation, aneurysmal dilatation, or leakage of blood components through the disintegrated wall often appears consequently [3–5]. With time, this acute vascular change loses the red tint with Masson trichrome and takes on a glassy acellular hyalinous appearance (Figure 2.1).

Microaneurysm was originally described by Charcôt and Bouchard in 1868 and is currently referred to as a Charcôt–Bouchard aneurysm. C. Miller Fisher [6, 7] described microaneurysms in hypertensive patients with small strokes or massive brain hemorrhage. Microaneurysms (also referred to as miliary saccular aneurysms) (300–1100 μm in diameter) involve intracerebral arteries (40–160 μm in diameter) and often arise at bifurcations. The wall of the aneurysm lacks even a trace of muscle or elastic tissue, and sometimes shows fibrinoid necrosis. Thrombi usually line the inner surface of the wall. The aneurysm is often surrounded by red blood cells or hemosiderin-laden

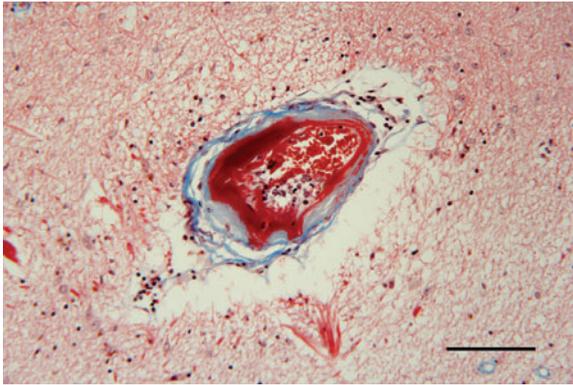


Figure 2.1 A lenticulostrate artery with an area stained red (fibrinoid necrosis and thrombus) and areas stained light blue (hyalinosis). Masson trichrome (MT). Bar = 100 μ m.

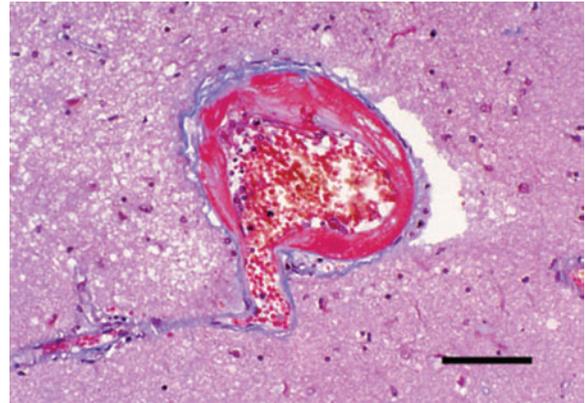


Figure 2.2 A microaneurysm with mural thrombus arising from a lenticulostrate artery. Masson trichrome (MT). Bar = 100 μ m.

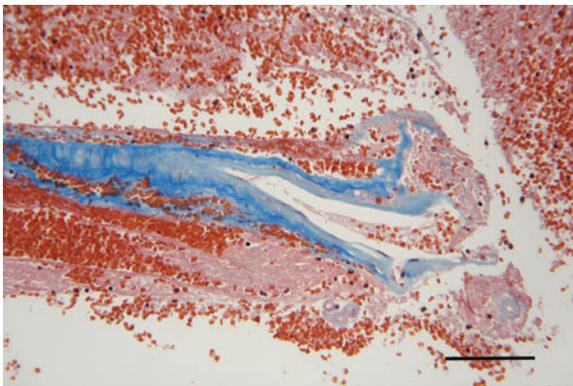


Figure 2.3 A ruptured small artery with arteriosclerosis at the hilus of the cerebellar nuclei in a massive cerebellar hemorrhage. Masson trichrome (MT). Bar = 100 μ m.

macrophages, indicating both recent and old extravasation. Microaneurysms are usually found in the areas where hemorrhage is common (Figure 2.2). Bleeding globes (also referred as pseudoaneurysms) consist of masses of red blood cells and platelets (0.3–1.0 cm in diameter) that are enveloped in concentric rings of fibrin emanating from a break in the artery (100–200 μ m in diameter). The bleeding globes are found in the presence of massive hemorrhages.

It remains under debate whether rupture of a microaneurysm secondary to fibrinoid necrosis of the vessel wall or weakening of the arterial wall by arteriosclerosis is primarily responsible for intracerebral hemorrhages (Figure 2.3). Takebayashi and Kaneko [8] collected lenticulostrate arteries at surgical evacuation of intracerebral hemorrhage and at

autopsy, and examined them by electron microscopy to verify the mechanism of arterial rupture. Severe arteriosclerosis with medial degeneration at or near bifurcations of the artery was observed in 46 of 48 ruptured arteries, whereas rupture from a microaneurysm was observed in only two specimens. Wakai et al. [9, 10] examined complete serial sections of bleeding globes found at the wall of hematomas, following surgical evacuation of massive lobar or cerebellar hemorrhages. They confirmed that bleeding globes encompass rupture of microaneurysms in cases with and without hypertension, and in a case with CAA.

Hyalinosis appears as a light eosinophilic amorphous wall in intracerebral small arteries of hypertensive patients. This term is used because the area stains lighter with hematoxylin and eosin than areas containing fibrinoid and light blue with Masson trichrome. Hyalinosis can be differentiated from fibrinoid by its distinguishing stain to Masson trichrome and PTAH. Electron microscopic examination shows that hyalinization involves degenerated collagen and SMCs and unspecified amorphous structures [4, 5]. Hyalinization does not cause intracerebral hemorrhage, but it is regarded as a common finding in hypertensive subjects. Fibrinoid necrosis may precede hyalinosis, because hyalinosis is a prevalent finding compared to fibrinoid necrosis (Figures 2.1, 2.4). Short-lived fibrinoid necrosis may alter to a stable hyalinosis. No study, however, has proven this process [5].

Fibrohyalinosis is the term applied to the perforating arteries with thickened hyalinized wall that contain areas of fibrosis.

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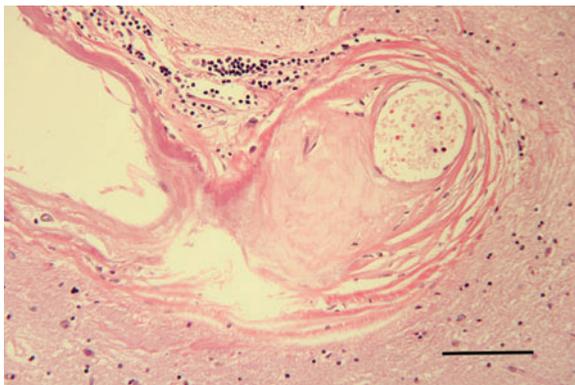


Figure 2.4 A lenticulostriate artery narrowed with hyaline material (segmental arterial disorganization). Hematoxylin and eosin (H&E). Bar = 100 μ m.

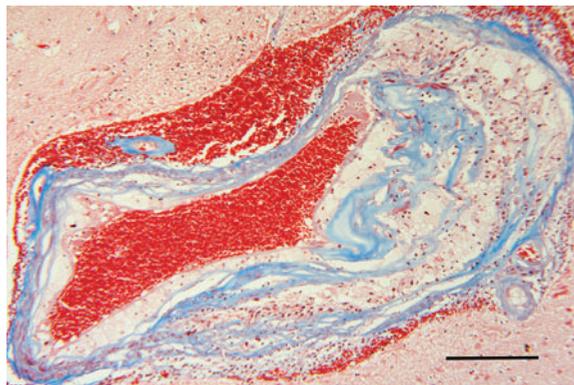


Figure 2.5 Microatheroma of a lenticulostriate artery close to the base of the brain. This artery appears vulnerable to thrombosis. Masson trichrome (MT). Bar = 100 μ m.

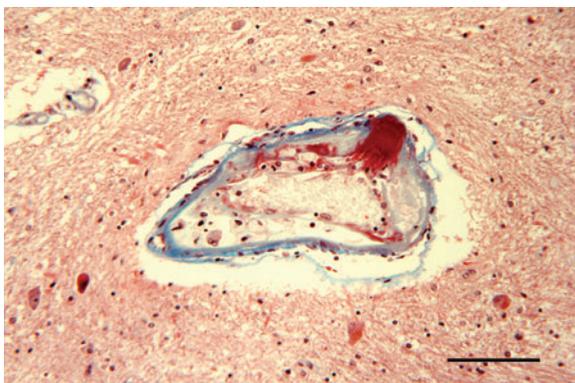


Figure 2.6 Lipohyalinosis of a lenticulostriate artery close to the base of the brain. Note areas stained light blue (hyalinosis), an area stained red (fibrinoid necrosis), and macrophage infiltration of the arterial wall. Masson trichrome (MT). Bar = 100 μ m.

Microatheroma encompasses atherosclerotic changes consisting of subintimal proliferation of fibroblasts and lipid-laden macrophages, and deposition of cholesterol crystals in the penetrating arteries close to the surface of the brain. This is occasionally seen in patients with chronic hypertension. Though microatheroma that looks vulnerable to thrombosis [11] is occasionally encountered (Figure 2.5), we have not experienced a microatheroma responsible for recent occlusion.

Lipohyalinosis is a term introduced by Fisher [6] to describe a destructive vascular process with deposition of hyaline and fat-laden macrophages in the wall of the penetrating arteries. Fisher described lipohyalinosis as preferentially appearing in the regions that frequently show hypertensive hemorrhages and lacunar infarcts. Our own observations indicate that

lipohyalinosis appears at the penetrating arteries in the basal ganglia and thalamus as well as the cerebral cortex close to the brain surface, in contrast to fibrinoid necrosis and hyalinosis situated deep in the brain. A lipohyalinotic artery wall may be admixed with fibrinoid and/or fibrosis (Figure 2.6). In the areas where lipohyalinosis is detected, we also find microatheroma. We regard lipohyalinosis as a pathologic feature combined with both hypertensive arteriolar and atherosclerotic arterial changes. We have not encountered a lipohyalinotic artery responsible for a recent occlusive event.

Atherosclerosis is occasionally observed in the leptomeningeal portion of the penetrating arteries at the base of the brain and in the distal convexity leptomeningeal arteries in cases with chronic hypertension. “Capsular infarct” associated with atherosclerosis was designated by Fisher [12] for infarcts larger than lacunes that mainly involve the internal capsule. The segment of a single lenticulostriate artery immediately distal to the orifice of the middle cerebral artery up to the middle of the basal ganglia is involved, and the vessels are 300–800 μ m in diameter. The underlying arterial changes are composed of atheromatous plaques with severe stenosis, some of which are associated with superimposed thrombi. The arterial lesions within the brain parenchyma can be referred to as microatheroma. An intracerebral artery involved in Fisher’s capsular infarct [12] was exceptionally occluded by a hemorrhagic lipohyalinotic lesion.

“Intracranial branch atheromatous disease” was designated by Caplan [13] for pontine infarcts caused by atherosclerotic occlusive lesions at the mouth of a single artery branching from the basilar artery [14]

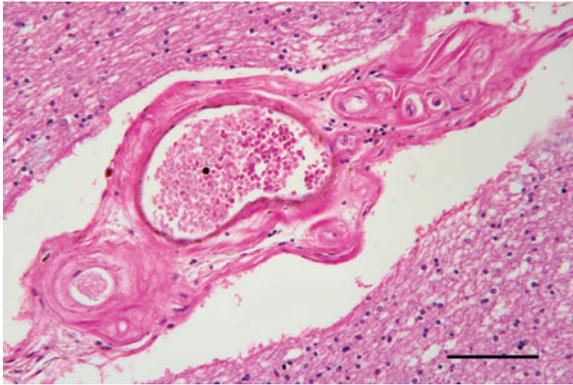


Figure 2.7 Vascular bundle formation in a dilated perivascular space in the parietal deep white matter in an 83-year-old man with nonamyloid subcortical vascular dementia. Hematoxylin and eosin (H&E). Bar = 100 μ m.

and other infarcts associated with the same mechanism in the major cerebral arteries. This infarct characteristically abuts the basal surface, while lacunes are ordinarily caused by vascular lesions deep within the parenchyma [15]. Therefore, this type of infarct is not included among the SVD.

Segmental arterial disorganization is a nonspecific term introduced by Fisher [6, 16] to describe a variety of focal vascular changes, mostly old, that have the common feature of loss of arterial architecture that leads to stenosis or occlusion of the lumen. Connective tissue often entirely replaces the vessel eventually (Figure 2.4).

Microangioarchitectural changes of the cerebral arteries have been analyzed by using high resolution microradiography of brain specimens treated with intra-arterial injection of barium, scanning electron microscopy of corrosion casts of the arteries, and alkaline phosphatase-stained thick celloidin sections. Arteriolar tortuosity in the cortical branches, as well as in the medullary arteries of the white matter, is more common in the elderly [17, 18]. Paraffin sections occasionally show large periarterial spaces in the white matter containing tortuous or intertwining arteries in the elderly (Figure 2.7) [17]. These appear to be a contributing factor to impaired cerebral perfusion, especially in the white matter, but the relationship between the arterial changes and tissue damage is not clear [17, 18].

Arterial lesions related to lacunar infarcts were meticulously studied by Fisher [15]. Fisher defined lacunar infarcts as ischemic infarcts of restricted size, less than 15 mm at their greatest diameter, in the

deeper parts of the brain. They are commonly observed in the chronic healing stage, forming irregular cavities principally in the basal ganglia, thalamus, and basis pontis. They predominantly occur in patients with hypertension and/or diabetes mellitus. Fisher [16] in 1969 investigated the arterial lesions causing lacunar infarcts from four patients with histories of hypertension and small strokes. In 45 of 50 consecutive lacunar infarcts, the artery supplying the territory of the infarct was occluded. Most of the vascular lesions showed segmental arterial disorganization occluding a single artery. Fisher [6] found two lacunar infarcts in the subcortical white matter due to thrombotic occlusion of the asymmetric fusiform miliary aneurysm of penetrating arteries running in the cerebral cortex, but he did not make a systematic study of lacunar infarcts in the subcortical white matter [15].

Challa et al. [19] in 1990 used the alkaline phosphatase technique of microvascular staining and high resolution microradiography to make three-dimensional observations in a study of 31 lacunar infarcts from 15 hypertensive subjects. Their study supported Fisher's conclusion that SVD was the cause of lacunar infarcts, but with one major difference. Variable narrowing due to intimal hyperplasia or atherosclerosis was demonstrated in the vast majority of the lacunar infarcts in the basal ganglia and thalamus. These lacunar infarcts were from patients who predominantly had well-controlled hypertension with current antihypertensive regimens that were not available before the 1960s, while 36 of the 50 lacunar infarcts studied by Fisher were from a single patient, who probably had more severe hypertensive SVD. Challa et al. [19] also observed a high incidence of lacunar infarcts in the deep white matter. The susceptibility of deep white matter to lacunar infarcts could derive from the characteristic angioarchitecture, including the long, penetrating medullary arteries, which show segmental or extensive narrowing of the lumen.

Cerebral medullary artery lesions in serial sections were investigated by Tanoi et al. [20] to identify arterial changes characteristic of Binswanger's encephalopathy (BE). They analyzed leptomeningeal and intracerebral arteries of BE autopsy specimens by reconstructing serial sections of individual arteries from the penetrating site at the cortical surface to the distal portion in the deep white matter. The results were compared with those from hypertensive

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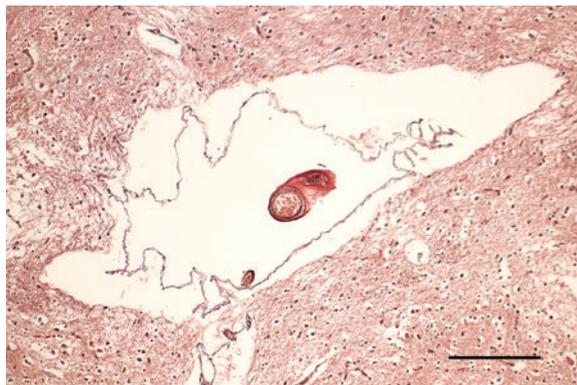


Figure 2.8 A dilated perivascular space in the basal ganglia. A membranous structure exists between the patent small artery and the brain parenchyma. No gliosis in the surrounding brain parenchyma. Watanabe's reticulum fiber silver stain. Bar = 200 μ m.

intracerebral hemorrhage (HH) and normotensive (NT) specimens. There was nonspecific but significantly more widespread intimal fibrosis with or without atheroma, as well as segmental loss of the SMCs, which was sometimes associated with intimal plasma exudation or microaneurysm. Intimal fibrosis of the leptomeningeal arteries was significantly more widespread in BE than HH and NT. The media of the leptomeningeal and intracerebral arteries was significantly thicker in BE than in HH. In NT specimens the intracerebral arteries tended to be thinner in medial thickness than the leptomeningeal arteries. They regarded dysfunction of blood flow regulation, secondary to increased intimal fibrosis, and loss of medial SMCs to be the essential mechanism for diffuse myelin loss of the subcortical white matter in BE.

Dilatation of perivascular spaces, which commonly appear in the basal ganglia, are lined by a simple membranous structure but are not surrounded by gliosis (Figure 2.8), while cavities associated with lacunar infarcts are surrounded by gliosis [21]. Pollock et al. [21] analyzed the difference in structures of perivascular spaces in the basal ganglia and cerebral cortex. They found that those in the basal ganglia dilate to form dilated perivascular spaces and, rarely, accumulate A β in Alzheimer's disease (AD); however, in the cortex lacunar infarcts are rare but amyloid angiopathy is common. The arteries in the basal ganglia are surrounded by two distinct coats of leptomeninges separated by a perivascular space, which is continuous with the perivascular space around arteries in the subarachnoid space. The inner layer of leptomeninges closely invests the adventitia of the

vessel wall, and the outer layer is continuous with the pia mater on the surface of brain. In the cerebral cortex, there is only a single periarterial layer of leptomeninges. Veins in the basal ganglia have no outer layer of leptomeninges and the perivascular space is continuous with the subpial space. Differences in structure of perivascular spaces around arteries may reflect relative efficacies in the drainage of interstitial fluid from different sites in the brain. The structure of the perivascular spaces may contribute to the relative high frequency of dilated perivascular spaces in the basal ganglia, and the low frequency of amyloid angiopathy at this site in AD. Regarding the pathogenesis of the dilatation of the perivascular spaces, Pollock et al. [21] suggested abnormality of the arterial permeability, allowing fluid to leak out and overload the perivascular space to form dilated perivascular spaces, and fibrosis and obstruction of perivascular spaces along the length of arteries increasing the impedance of fluid drainage pathways, among others.

Cerebral amyloid angiopathy (CAA)

CAA denotes progressive amyloid deposition in the vessels of the central nervous system (CNS). Sporadic CAA commonly seen in the elderly and AD patients shows A β peptide deposition within the intracortical and distal leptomeningeal blood vessel walls, and secondary vascular changes [22–25].

The incidence and severity of CAA increase with age and in association with AD pathology. CAA appears first in the intracortical and distal leptomeningeal vessels of the neocortex. The posterior portion of the cerebrum is involved more frequently and heavily than the anterior portion. The allocortex and cerebellum are involved next. The medial aspects of the temporal lobes, hippocampus, basal ganglia, and thalamus are rarely involved, and the brainstem is usually not involved. CAA is not associated with hypertension, arteriosclerosis, or amyloidosis of other organs [22–26].

A β accumulates in the wall of arterioles, small arteries, and medium-sized arteries, and rarely occurs in the veins and capillaries in the cerebral cortex and leptomeninges. CAA appears to be widespread, but in a patchy or segmental fashion. The large branches of the circle of Willis are not involved. In advanced CAA, staining with hematoxylin and eosin reveals acellular thickening in small artery walls. Under

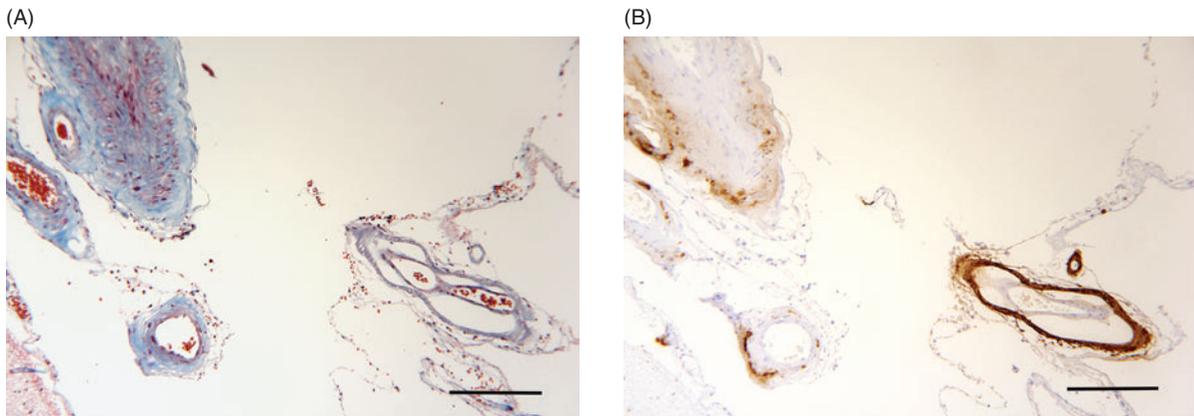


Figure 2.9 Leptomeningeal arteries of the parietal lobe show β -amyloid ($A\beta$) positions in the abluminal media and adventitia, and double-barrel formation. (A) Masson trichrome (MT); (B) immunostain. Bar = 200 μ m. (A) is an adjacent section to (B) immunostained with an antibody against $\beta/A4$.

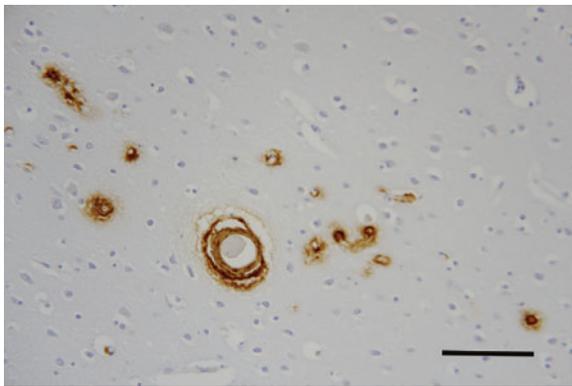


Figure 2.10 β -Amyloid depositions and dyschoric changes of capillaries and larger vessels in the parietal lobe. Immunostain. Bar = 100 μ m.

polarized light, thin sections of vessels stained with Congo red show apple-green birefringence in the walls. Vessels affected by $A\beta$ and senile plaques stain positive with anti- $A\beta$ antibody. The deposition of $A\beta$ begins from the abluminal side of the media as well as in the adventitia (Figure 2.9A,B). The medial smooth muscle layer is infiltrated and substituted with $A\beta$, which reaches to the intima. Vascular endothelial cells are preserved [22–25].

A hypothesis on the pathogenesis of CAA by Weller and his co-workers [27] has advocated that $A\beta$ is deposited in periarterial interstitial fluid drainage pathways of the brain in AD and that this contributes significantly to CAA. Weller et al. [27] examined the evidence for this hypothesis. There is firm evidence in humans for drainage of interstitial fluid from

the brain to cervical lymph nodes along periarterial spaces. Biochemical study of brains without AD revealed a pool of soluble $A\beta$ in the cortex. Histology and immunocytochemistry of brains with AD showed that $A\beta$ accumulates five times more frequently around arteries than around veins, with selective involvement of smaller arteries. Initial deposits of $A\beta$ occur at the periphery of arteries. These observations support the hypothesis.

The vessels involved with $A\beta$ show secondary changes, such as fibrinoid necrosis, loss of medial SMCs, microaneurysm, thrombus formation, fibrohyalinous wall thickening, luminal stenosis, amyloid depositions in the surrounding neuropil (referred to as dyschoric changes), inflammatory cell infiltration at the vessel wall and around the vessel, and perivascular blood pigment deposition. The vessels affected by CAA show thickening or thinning of the tunica media, and stenosis or dilation of the arterial lumen. Dissociation of vessel wall layers, particularly in the leptomeningeal small arteries, referred to as double barreling, could be produced as an artifact during tissue processing due to the different physical properties of tissue components (Figure 2.9A,B) [22–25].

The $A\beta$ depositions lining capillary walls are referred to as capillary CAA (capCAA). The surrounding neuropil frequently shows $A\beta$ depositions (Figure 2.10). Capillary CAA may show additional $A\beta$ depositions in noncapillary blood vessels, whereas in large vessel CAA $A\beta$ depositions are restricted to the cortical and leptomeningeal arteries, arterioles, and rarely veins, with the exception of capillaries [24]. Richard et al. [28] suggested that capCAA is

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pathologically and possibly pathogenetically distinct from larger vessel CAA.

A grading system for CAA proposed by Vonsattel et al. [29] is widely used in routine pathology. Mild indicates amyloid deposition in the tunica media without significant SMC disruption; moderate means replacement of the tunica media by amyloid causing thickening of media, with no evidence of blood leakage; and severe means extensive amyloid deposition with focal wall fragmentation and evidence of blood leakage.

Intracerebral hemorrhages associated with CAA are characterized by lobar hemorrhage. Incidence rises among the elderly, and intracerebral hemorrhages are not necessarily associated with hypertension. Therefore, a specific term, spontaneous intracerebral

hemorrhage, is applied to this. Primary subarachnoid hemorrhage due to CAA is rare in spite of involvement of the superficial lobar vessels. Cerebellar hemorrhages also occur. Recurrence of lobar hemorrhages at multiple locations is common. Lobar hemorrhage is assumed to occur secondary to rupture of weakened blood vessel walls laden with A β or to microaneurysms (Figures 2.11–2.13) [22]. Vonsattel et al. [29] noted that a severe degree of CAA and the presence of fibrinoid necrosis, with or without microaneurysms, are consistently related to intracerebral hemorrhage. A serial section study by Wakai et al. [10] found ruptured microaneurysms associated with CAA. There is evidence that CAA is the risk factor for intracerebral hemorrhage associated

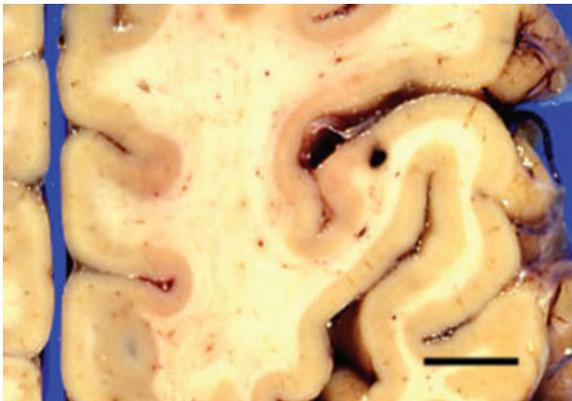


Figure 2.11 A horizontal section of the brain with a dark spot in the corticomedullary junction of the parietal lobe. This was a histologically aneurysmal enlargement of a β -amyloid laden artery occluded by a thrombus. Bar = 10 μ m.

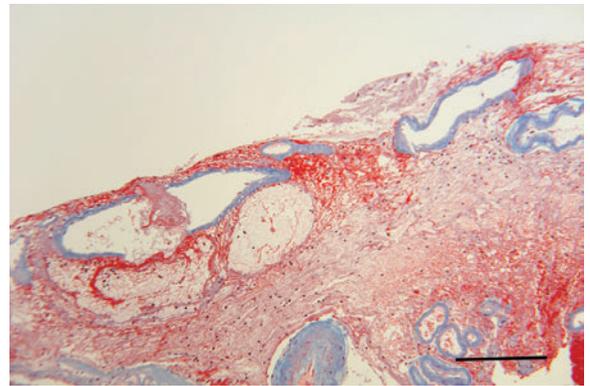


Figure 2.13 Small arteries in a surgically evacuated clot from a patient suffering from a parietal lobar hemorrhage. Arterial walls were heavily laden with β -amyloid in the immunostaining. Cracks in the arterial walls are seen. Masson trichrome (MT). Bar = 200 μ m.

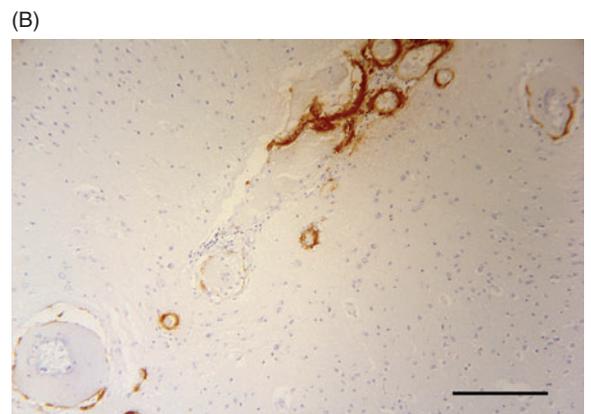
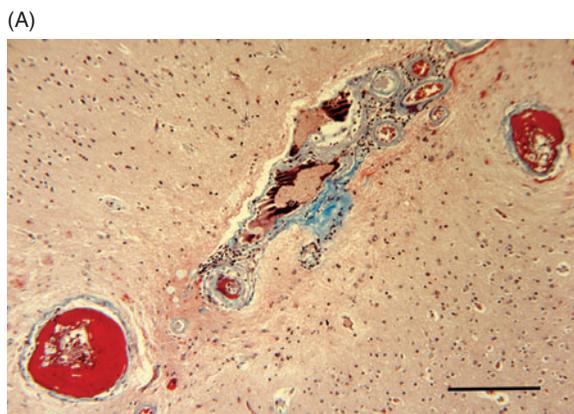


Figure 2.12 β -Amyloid depositions in intracortical and leptomeningeal vessels and microaneurysms in the parietal lobe. Microaneurysms are occluded with thrombi. (A) Masson trichrome (MT); (B) immunostain. Bar = 200 μ m.