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6 Cerebral Small Vessel Disease

Seung-Hoon Lee

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Abstract

Cerebral small vessel disease refers to a variety of diseases caused by the degeneration of small arteries, arterioles, capillaries, and venules in the brain. It is a syndrome of pathological, radiological, and clinical abnormalities or dysfunction associated with damage to small arteries and arterioles. Hypertension and old age are the most important risk factors for this disease. Meanwhile, arteriosclerosis, whose representative finding has been known as lipohyalinosis, is the fundamental vascular pathologic feature when the risk factors are improperly controlled for at least several years. Arteriosclerosis may cause acute strokes such as lacunar infarction, cerebral microinfarct, and intracerebral hemorrhage, and can also cause subclinical radiologic lesions such as lacunes, microbleeds, and white matter hyperintensities. These lesions are significant in terms of prevention because they can predict future strokes, dementia, depression, and vascular parkinsonism. This chapter covers the underlying pathologic findings, clinical types, risk factors, and pathophysiologic theories of SVD.

S.-H. Lee (✉)
Department of Neurology, Clinical Division,
Seoul National University Hospital,
Seoul, Republic of Korea

Korean Cerebrovascular Research Institute,
Seoul, Republic of Korea
e-mail: sb0516@snu.ac.kr

Cerebral small vessels refer to small arteries, arterioles, capillaries, and venules in the brain. Arterial small vessels, except capillaries, are divided into two types: the first is the deep perforating arteries branching from the parent large arteries. These travel through the subarachnoid space in a perpendicular fashion, such as the lenticulostriate arteries. Second, is the small arteries (leptomeningeal perforators) that penetrate into the brain as the size decreases gradually from the superficial large arteries. Cerebral small vessel disease (SVD) is a syndrome of pathological, radiological, and clinical abnormalities or dysfunction caused by damage to these vessels. However, it is generally understood that SVD refers to old lacunes or white matter hyperintensities (WMHs) in the periventricular or subcortical areas, which are identified on brain magnetic resonance imaging (MRI). Here we can find some strange things. SVD refers to disease in the small "vessels," but WMHs are lesions on brain "tissue." For example, Takayasu's arteritis or coronary atherosclerosis are both abnormalities of blood vessels, not damage to tissues. In fact, even with the most advanced brain imaging, small vessels are not visible enough for clinical investigation, so we have little to see for direct evidence of the morphological abnormalities of actual small vessels. Even using 7T MRI, we can only just see the existence of lenticulostriate arteries, but not morphological status, such as vascular stenosis [1]. Accordingly, the term SVD is a misnomer,

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although the original nomenclature is not known. Personally, I consider the expression "microangiopathic cerebral lesions" to be much more accurate. For now, SVD is currently used to express the cerebral lesions caused by abnormalities of cerebral small vessels such as WMHs, lacunes, microbleeds, enlarged perivascular spaces (ePVS), microinfarcts, and brain atrophy that are found on brain computed tomography (CT) or MRI. In this situation, it is ironic that numerous articles or reviews on SVD do not include intracerebral hemorrhage (ICH), the most catastrophic result of cerebral microangiopathy.

SVD is often classified as symptomatic versus asymptomatic (or clinically silent) lesions. However, lacunes, microbleeds, and WMHs, largely known as asymptomatic lesions, are not completely asymptomatic. It may initially be asymptomatic, but can cause a variety of neurological dysfunction in advanced stages. Such neurological symptoms can be divided into those due to acute injury versus chronic, accumulated injury. Acute injuries comprise acute strokes, which include lacunar infarction (a type of ischemic stroke) and ICH (a type of hemorrhagic stroke). Both subtypes of acute stroke account for 20–40% of total strokes, although this can vary across the world [2]. Considering that proportions of other major subtypes, such as large-artery atherosclerosis and cardiac embolism, are similar to that of lacunar infarction, SVD accounts for the majority of strokes. The neurological symptoms of chronic, accumulated injury from SVD refer to higher cortical or subcortical dysfunction: (1) cognitive decline, including mild cognitive impairment and dementia; (2) emotional or psychological dysfunction, such as depression and psychosis; and (3) motor coordination problems, such as gait disturbance or vascular parkinsonism.

This chapter covers the underlying pathologic findings, clinical features, radiologic findings, risk factors, and pathophysiologic theories of SVD. SVD has been understood to occur passively by hypertensive end-organ damage. Recently, it was hypothesized that SVD can be actively acquired through endothelial injury, small vessel inflammation, blood–brain barrier (BBB) breakdown, and plasma protein extravasation [3]. This chapter will also discuss the possibilities and limitations of these new theories.

6.1 Underlying Pathologic Findings: Arteriolosclerosis

Pathologic findings of SVD have long been known as cerebral microangiopathies. Dr. Miller Fisher demonstrated microangiopathic findings by examining brains of patients with lacunar infarction and ICH using a serial section technique [4, 5]. With the advent of brain CT in the 1970s, the study of brain pathology almost completely ceased, and Fisher's body of work remains the most reliably cited literature on SVD pathology. He established pathological terms that are still in use, such as lipohyalinosis, microatheroma, etc., and proved that these lesions are caused by long-standing hypertension. In addition, as a neurologist, he classified the symptoms of patients with lacunar infarction and established a variety of lacunar syndromes. However, as the age of neuroimaging using CT and MRI has emerged, it is true that previous pathological knowledge has not been accurately retained, leading to some confusion. A survey of leading investigators in top class neuropathologic centers around the world showed a less than 50% agreement on the definition of small vessel [6]. To minimize confusion, one academic term to integrate these pathologic lesions has long been needed. There was an attempt to unite them under the term "arteriolosclerosis" by Dr. Leonardo Pantoni, but unfortunately no consensus was reached [7]. Indeed, this will be another misnomer. The term "arteriolosclerosis" refers to miniatherosclerosis in arterioles. However, according to the histologic classifications of arterial systems, microangiopathic findings responsible for SVD occur mainly in small arteries, rather than arterioles. The lenticulostriate arteries, which are typical of penetrating small arteries, have a diameter of 300–700 μm, whereas the arterioles typically range from 40 to 150 μm [8]. Furthermore, as mentioned later, arteriolosclerosis is an established histopathologic term indicating a concen-

tric microangiopathy in arterioles, so using this term only creates another confusion. Therefore, I suggest naming these lesions "arteriosclerosis" rather than arteriolosclerosis. In large arteries, we usually describe the vascular lesions responsible for ischemic stroke as atherosclerosis, so it would be easily differentiated from the term "arteriosclerosis." Collectively, arteriosclerosis in this chapter should be understood as a lesion that refers to all microangiopathic findings underlying SVD lesions, such as lipohyalinosis, microatheroma, microaneurysm, and fibrinoid necrosis (Fig. 6.1).

6.1.1 Lipohyalinosis

Dr. Fisher, while investigating the penetrating arteries that caused lacunar infarctions, observed foam cells in the subintimal layer and pink-staining fibrinoid material in the tunica media to thicken the vessel walls [4]. In some regions, these vessels were replaced by whorls, tangles, and wisps of connective tissue occluding the lumen (Fig. 6.2a) [9]. He named these vascular states segmental arterial disorganization, fibrinoid degeneration, or lipohyalinosis. Among them, lipohyalinosis generally described the pathologic features, and sometimes termed fibrohyalinosis or lipofibrohyalinosis. Lipohyalinosis describes the loss of smooth muscle cells in the tunica media, fibro-hyaline material accumulation, and foam cells, and leakage of plasma protein such as apolipoprotein E, alpha2-macroglobulin, and immunoglobulin G in asymmetric fashion in blood vessels of 40–300 μm (Fig. 6.2b–f) [10]. Contrary to lipohyalinosis, concentric stenosis of lumen due to concentric hyaline degeneration in smaller blood vessel levels, namely at the arteriole level (40–150 μm), is pathologically called "arteriolosclerosis." However, it should not be confused with arteriosclerosis, which denotes all microangiopathic changes to small vessels, as mentioned above.

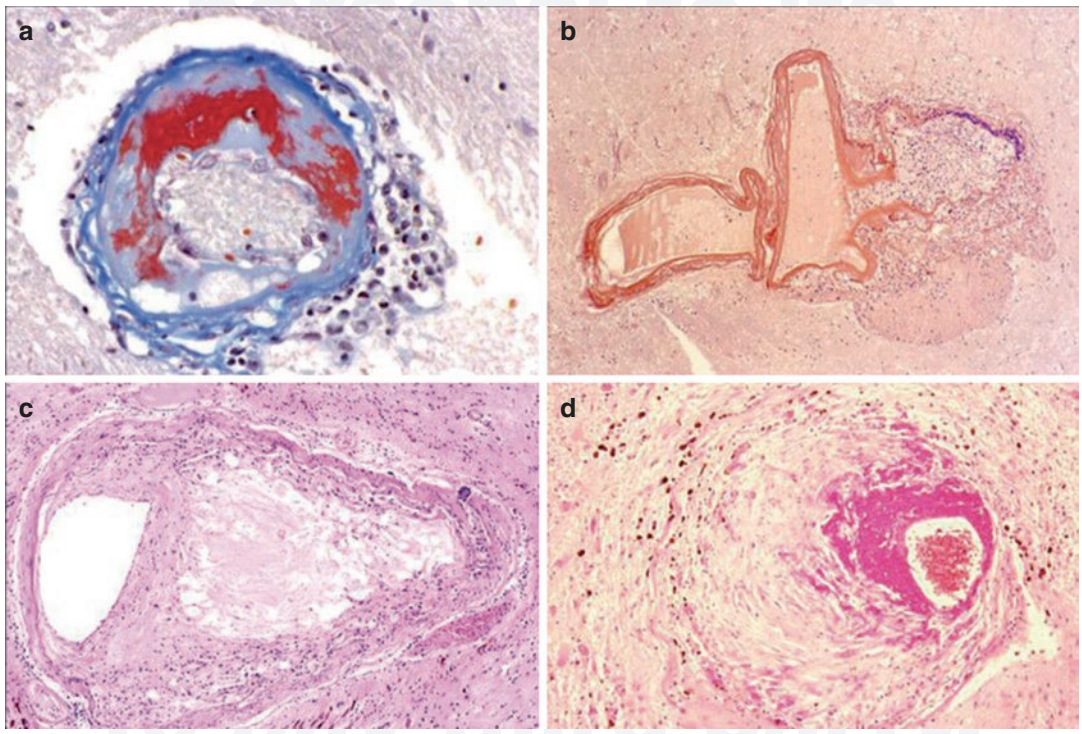

Fig. 6.1 Pathology of the cerebral small vessel disease. (**a**) Lipohyalinosis, (**b**) microaneurysm, (**c**) microatheroma, (**d**) fibrinoid necrosis. Adapted with permission from Lancet Neurology, Copyright Elsevier [7]

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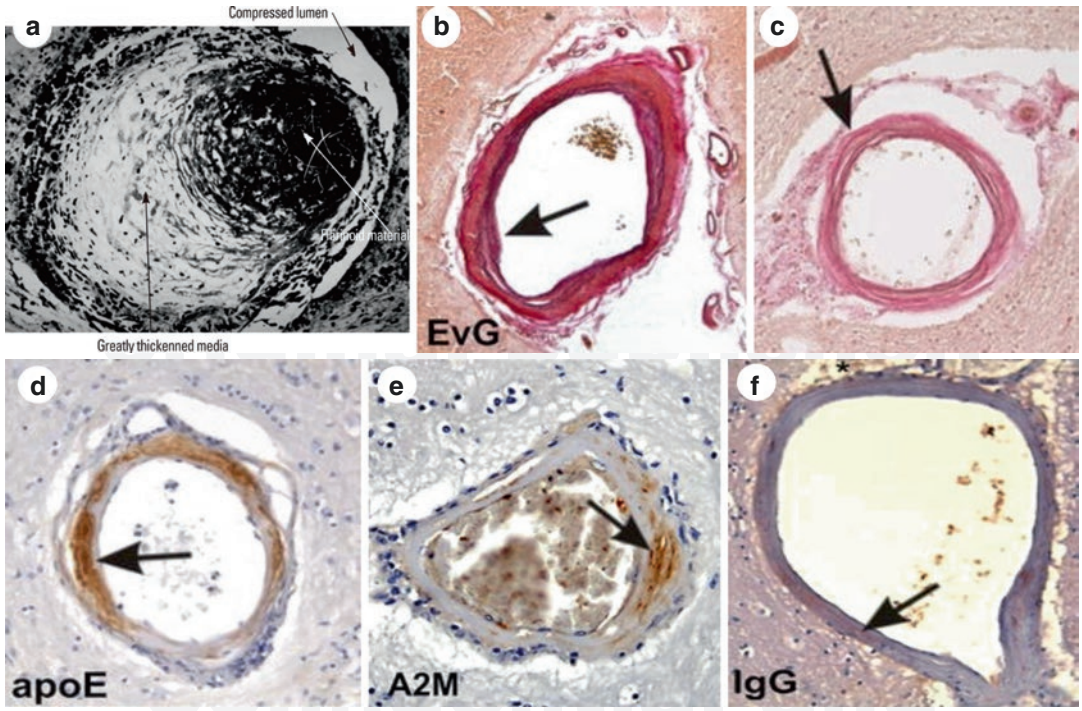

Fig. 6.2 Pathologic features of lipohyalinosis. (**a**) Whorls, tangles, and wisps of connective tissue, adapted with permission from Journal of Stroke, Copyright Korean Stroke Society. (**b**) Splitting of the internal elastic lamina, (**c**) fibrosis and fibrinoid necrosis, (**d**) plasma proteins apolipoprotein E, (**e**) alpha2-macroglobulin, and (**f**) immunoglobulin G shown within the affected vessel. Adapted with permission from Acta Neuropathologica, Copyright Springer Nature [10]

As one of the major underlying pathological characteristics of hypertensive microangiopathy or SVD, lipohyalinosis is the most common causative lesion of lacunar infarction and the most common background lesion of WMHs. Because of a strong association with lacunar infarction, there is a preconception that it may only be related to occlusion-type SVDs. However, lipohyalinosis is one of the most causative microangiopathies responsible for bleeding-type SVDs, such as microbleeds and ICH [11, 12]. In other words, it is important to understand that lipohyalinosis not only blocks small vessels, but also ruptures them.

6.1.2 Microatheroma

In penetrating arteries with relatively large diameters (200–800 μm), there may be some pathologic features with endothelial proliferation, splitting of internal elastic lamina and small plaque-like protrusion with accumulation of plasma proteins and macrophages, known as microatheroma (Fig 6.1c). This usually develops at the beginning of perforating arteries. When the microatheroma occurs at the junction where the brain branches from the large artery that travels across the subarachnoid space, it is also called a junctional atheroma (Fig. 6.3) [9]. Then, atherosclerosis in the branching site of a large artery may obstruct the blood flow of perforating arteries, often called “branch atheromatous disease.” In this case, it is reasonable to classify strokes with large-artery atherosclerosis, even if the sizes of the stroke lesions meet the definition of lacunar infarction. It is reasonable to classify SVD and its lacunar infarction only if the microatheroma is confined within the small vessel, so a complete differentiation between branch athero-

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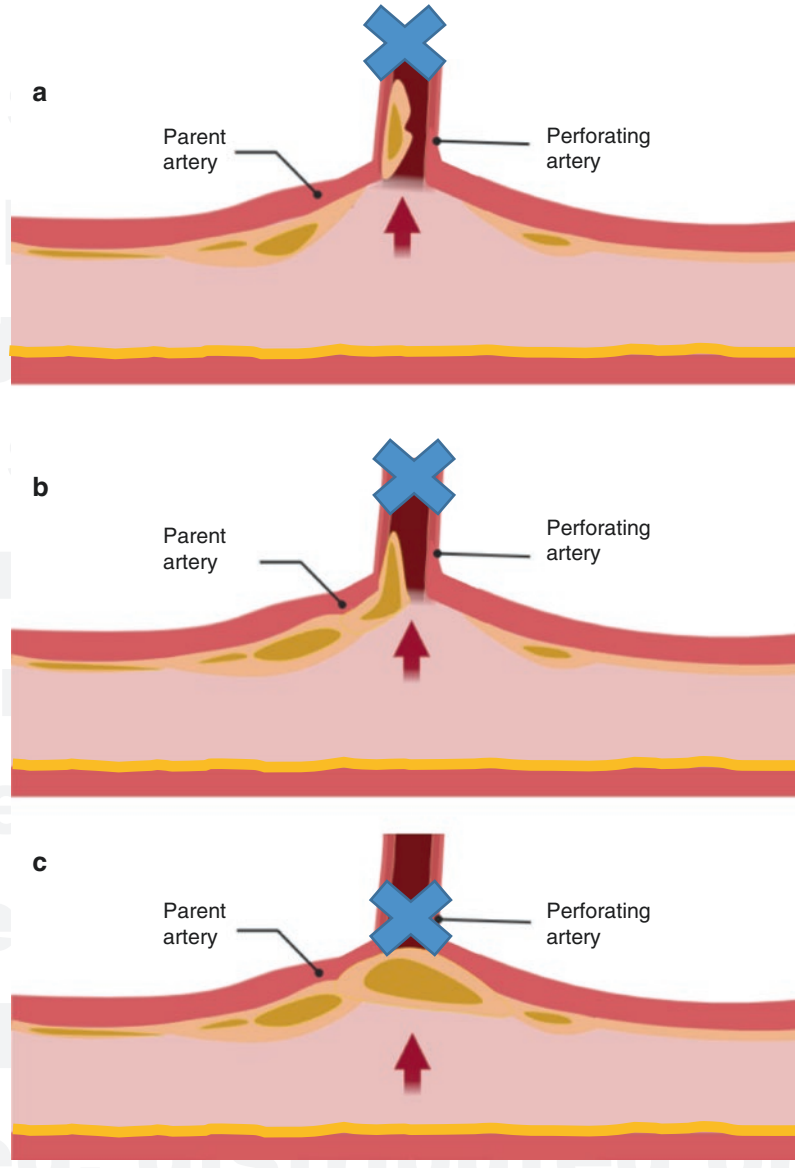

Fig. 6.3 Schematic illustrations of arterial pathology. (**a**) microatheroma blocked at the orifice of a branch; (**b**) junctional atheroma growing from the parent artery to the branch; (**c**) occlusion of perforating artery by atheroma of the parent artery

matous disease and lacunar infarction related to microatheroma or junctional atheroma would not be possible in a real clinical practice setting. Recently, however, it is increasingly possible to distinguish them with a high-performance 1.5T MR angiography or a 3T high-resolution MRI.

6.1.3 Microaneurysm

In 1868, Charcot and Bouchard found miliary saccular aneurysms connected to hemorrhages by autopsy of ICH brains and claimed that these lesions were a direct cause of ICH [13]. Because of this, these are also called "Charcot-Bouchard type microaneurysms." Then, in 1972, Dr. Fisher published a detailed analysis of the pathological findings of this type of lesion [11]. It differs in size from intracranial saccular aneurysms of large arteries within the subarachnoid space but is very similar in shape. Its diameter is approximately 300–1100 μm and protrudes approximately 40–160 μm from the blood vessel. It communicates with a parent arterial lumen through a nar-

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row well-formed mouth and is not created by irregular tears or wall dissections. However, this lesion probably consists of an extremely thin layer of collagenous adventitial tissue, without a trace of muscle or elastic tissue except for the 100-μm stretch of wall adjacent to the parent artery. There is no definite endothelial lining. Hemosiderin-filled macrophages are often scattered in the region. If so, is this lesion a direct cause of ICH? In 1967, Cole and Yates found circumstantial evidence for the relationship between hypertensive hemorrhage and microaneurysms: microaneurysms existed in 46 of the hypertensives versus seven of the normotensives and had a common topographic distribution with the hematomas [14]. However, Dr. Fisher did not find evidence supporting aneurysms as the cause of the hemorrhages, asserting that the same type of hypertensive vascular disease (lipohyalinosis) under some circumstances evokes ischemia and under others tends toward bleeding [11]. Challa et al. (1992) used microradiography of sections stained histochemically for alkaline phosphatase and failed to find any aneurysm in 35 hypertensive brains, four with ICH, or in 20 normotensive brains [12]. Moreover, they showed that miliary microaneurysms were extremely rare in their routine examination of 2800 autopsies examined over one decade. Compared to lipohyalinosis, microaneurysms are uncommon findings. In addition, lipohyalinosis is a lesion capable of rupture as well as occlusion, and there are some mixed features, such as lipohyalinotic miliary aneurysm. Thus, it is reasonable to conclude that lipohyalinosis, a common cause of lacunar infarction, is the most causative lesion of ICH rather than microaneurysm.

6.1.4 Fibrinoid Necrosis

Fibrinoid necrosis is produced by the insudation of plasma proteins into the arterial wall, which includes fibrin or fibrinogen. The affected area is deeply eosinophilic and structureless (Fig 6.1a) or very finely granular, and may be segmented, as in lipohyalinosis. Extensive studies have shown that abrupt, marked elevations of blood pressure alone can cause fibrinoid change in a matter of minutes. Therefore, many lesions from fibrinoid necrosis are observed early in an acute hypertensive crisis or in hypertensive microangiopathy. There is much controversy about a direct association between fibrinoid necrosis with lacunar infarction or ICH.

6.1.5 Is Arteriosclerosis Found Only in the Brain?

In fact, all arteriosclerosis lesions are not characteristic lesions specific to the brain. They are common forms of hypertensive vessel changes and are observed in the kidney, heart, or retina. Why then are these pathological findings best known in the brain? The clinical manifestations of SVD, such as lacunar infarction, ICH, or dementia are common in the brain, so have been studied extensively. In the heart, these lesions may cause progressive dilated cardiomyopathy, and in the kidney, chronic kidney disease with low glomerular filtration rate. However, pathological correlations for non-brain clinical diseases have not been studied much in the past and there is still a lack of education on pathological background. SVD in the brain has been autopsied since the 1850s for people who died of ICH, and Fisher's historic achievements are far better known. The idea that SVD only occurs in the brain is therefore a misconception.

6.2 Clinical Manifestations of Small Vessel Disease

Regarding cerebral SVD, there has been a preconceived notion that the clinical impact of SVD is relatively small because lacunar infarctions are a subtype causing the least neurological deficit among strokes. However, as mentioned earlier, SVD is often overlooked as the most fatal cause of ICH. This is because most reviews dealing with SVD have focused on explanations of subclinical lesions, such as WMHs, lacunes, and microbleeds. In this chapter, we describe the clinical manifestations of SVD in two categories: (1)

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lesions identified by acute stroke symptoms—lacunar infarction and ICH, and (2) lesions found on brain imaging without acute stroke symptoms—lacunes, WMHs, microbleeds, ePVS, and microinfarcts.

6.2.1 Lesions Identified by Acute Stroke Symptoms

6.2.1.1 Lacunar Infarction

Lacunar infarction is a subtype of stroke, based on TOAST classification, caused by small vessel occlusion (Fig 6.4a). Dr. Fisher analyzed lacunar infarctions using serial sections of human brains and found that most lacunar infarctions are due to obstruction of penetrating artery with a diameter less than 225 μm [4]. Cerebral infarctions in blood vessels larger than 300 μm was uncommon. Most of these blockages occur when fibrous connective tissue, resulting from lipohyalinosis-related denaturation, mechanically block the small arteries. As in large-artery atherosclerosis-related stroke, thrombosis originating from vessel lesions is rare in lacunar infarction. In lacunar infarctions occurring in small vessels of 300 μm or more, the probability of clot is increased by approximately 50%, and microatheroma is largely associated with such cases. Indeed, clear identification of lacunar infarction is difficult in some situations. Traditionally, it meant cerebral infarction due to occlusion of a penetrating small artery, but strokes due to large-artery atherosclerosis as a form of branch atheromatous disease are frequently classified as lacunar infarction because we do not conduct pathological examinations in actual clinical practice [15].

Only 50% of acute lacunar infarctions are observed on CT, but almost all can be seen on a diffusion-weighted sequence of MRI [16]. According to a recent clinical consensus, cerebral infarctions less than 2 cm on diffusion-weighted imaging are defined as lacunar infarctions [17]. With a single occluded small artery, deep brain

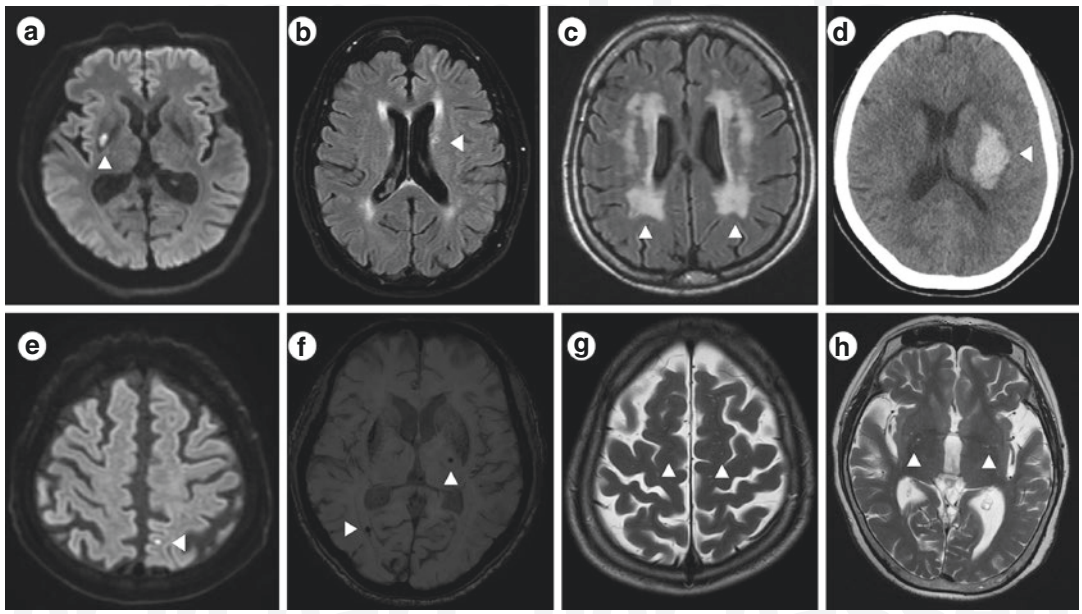

Fig. 6.4 Neuroimaging features of cerebral small vessel disease. White arrow heads show general types of the cerebral small vessel-related lesion. (**a**) Lacunar infarction in the right basal ganglia on DWI-sequence MRI, (**b**) lacune in the left corona radiata on FLAIR-sequence MRI, (**c**) white matter hyperintensities on FLAIR-sequence MRI, (**d**) intracerebral hemorrhage on CT, (**e**) Cortical microinfarct in left frontal lobe on DWI-sequence MRI, (**f**) Microbleeds in left internal capsule and right occipital lobe on SWI-sequence MRI, (**g**) enlarged periventricular spaces in bilateral frontal lobe, and (**h**) bilateral basal ganglia on T2-weighted MRI. DWI: diffusion-weighted imaging, MRI: magnetic resonance imaging, FLAIR: fluid-attenuated inversion recovery, CT: computed tomography, SWI: susceptibility weighted imaging

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structures with poor collateral supply can be involved, such as the corona radiata, basal ganglia, internal capsules, thalamus, and pons. Its shape is round, ovoid, or tubular. Larger or tubular lesions are more likely to be caused by more proximal artery diseases, such as microatheroma [18]. However, in actual clinical practice, it is almost impossible to distinguish the causes of infarctions only by size and shape. It is not uncommon for emboli from the heart, parent arteries, or hypercoagulability to cause lacunar-like infarctions. However, a primate model study showed that less than 6% of emboli from internal carotid arteries move to lenticulostriate arteries, and most of them move on to cortical branches [19]. Despite this, in some cases of suspected embolism, lacunar syndrome or lacunar infarction requires more attention to identify the causes.

Because the lesion sizes are small, patients usually have one or two neurological deficits. Three or more deficits are extremely rare, and acute cognitive decline is not a symptom in most cases. Dr. Fisher has summarized several lacunar syndromes through clinico-pathologic studies (Table 6.1). Lacunar syndromes are useful to express the patients' status in a word, but is less useful in a contemporary context where advanced stroke imaging with MRI is available. As mentioned above, lacunar syndromes are often caused by large-artery atherothrombosis or cardioembolism, even in small-size hemorrhages.

In terms of the natural course of lacunar infarction, the acute lesion may become one of three chronic lesions: (1) small cavity (lacune) (Fig. 6.4b), (2) WMH lesion without cavity (if the stroke is mild at first) (Fig. 6.4c), and (3) no visible lesion [20]. The general prognosis of lacunar infarctions is excellent because the patient's symptoms are relatively mild and do not involve the cerebral cortex. In many cases, even without treatment, the disease will automatically improve without the need to visit emergency centers. However, it is important to remember that if the initial treatment is not appropriate, it is not uncommon for the neurological deficits to worsen during the acute stage (i.e., early neurological deterioration). Further, a better strategy for secondary prevention should be implemented during admission.

6.2.1.2 ICH

ICH is a type of hemorrhagic stroke, together with subarachnoid hemorrhage (SAH). The incidence of hemorrhagic stroke is approximately 15–40 people per 100,000 [21]. It accounts for approximately 15% of strokes (ischemic stroke, 85%), where ICH comprises approximately 10–15% and SAH approximately 5% of cases [22]. The incidence of ICH varies widely between ethnic groups and is known to be highest in Asian countries such as Korea, China, and Japan [21]. The Global Burden of Disease 2010 Study, which comprehensively analyzed various studies published from 1990 to 2010, indicated a 47% increase in ICH patients worldwide; compared to an 8% reduction in incidence and 38% reduction in mortality in high-income countries, the ICH incidence increased by 22% in middle- and low-income countries [23].

Table 6.1 Lacunar syndromes

Syndrome	Lesion localization	Vessels involved
Pure motor stroke	Posterior limb of internal capsule Corona radiata Ventral pons Cerebral peduncle	Lenticulostriate perforators, anterior choroidal artery, perforators from basilar artery, or perforators from posterior cerebral artery
Pure sensory stroke	Ventroposterolateral (VPL) nucleus of thalamus	Perforators from thalamogeniculate artery
Sensorimotor stroke	Thalamocapsular area: Posterior limb of internal capsule and VPL nucleus of thalamus	Lenticulostriate perforators, anterior choroidal artery, or perforators from thalamogeniculate artery
Dysarthria-clumsy hand syndrome	Same as pure motor stroke	Same as pure motor stroke
Ataxic hemiparesis	Same as pure motor stroke	Same as pure motor stroke

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ICH refers to a disease in which hemorrhage occurs spontaneously in the cerebral intraparenchymal area without trauma (Fig. 6.4d). Hypertension, cerebral amyloid angiopathy (CAA), arteriovenous malformation, arteriovenous fistula, cavernous hemangioma, moyamoya disease, brain tumor, cerebral venous thrombosis, and coagulopathies are important risk factors for ICH. Because of the influence of hypertension, hypertensive ICH has been used as a general term for communication, particularly for differentiation from ICHs caused by CAA. More accurately, ICH is a clinical manifestation of advanced SVD (a rupture of small vessels with arteriosclerosis) rather than hypertension itself. Among the microangiopathic features, lipohyalinosis is the most common and important causative lesion, as mentioned earlier. ICH is most common in the basal ganglia and thalamus because blood pressure is higher in deep brain structures than in the cerebral cortex. As for lobar ICH, a variety of causes including metastatic tumors or arteriovenous malformations can be involved, but it is certain that the most common cause is hypertension-related arteriosclerosis. Most clinical neurological deficits characteristic of ICH are identified as high density lesions on CT, so brain MRI is not necessary for initial ICH treatment. However, MRI is much more useful than CT for identifying associated vascular diseases, the burden of SVD, and the presence of microbleeds. Please refer to the textbook series "Stroke Revisited Volume 2: Hemorrhagic Stroke" for more details on ICH.

6.2.1.3 Cerebral Microinfarct (Fig. 6.4e)

Before the introduction of diffusion-weighted images, cerebral microinfarcts were not detectable, even when patients had relevant neurological dysfunction. However, thanks to the development of diffusion-weighted images and high-resolution MRI techniques, we can diagnose microinfarcts even when no neurological symptoms appear. Microinfarcts are usually found in the cortical or subcortical area and are defined as 1–5 mm in size [24]. A systematic review of neuropathological studies reported that cerebral microinfarct was found in 62% of patients with vascular dementia, 43% of Alzheimer's patients, and 24% of normal elderly patients without dementia aged 75 years or older [25]. In fact, when these lesions are identified, embolic infarction is usually suspected, but it can be caused by SVD or even by hemodynamic insult. When the SVD is related to microinfarcts, it may result from CAA-induced degeneration of leptomeningeal arteries [24]. However, the clinical effects and causes of cerebral microinfarct need to be further elucidated.

6.2.2 Lesions Found on Brain Imaging Without Acute Stroke Symptoms

6.2.2.1 Lacunes

Lacune is a neuropathologic term that is used in various situations and thus causes confusion. Dr. Fisher mentioned: "historically, the original SVD feature was the lacune (hole), which was derived from French for a small fluid-filled cavity that was thought to mark the healed stage of a small deep infarct" [4]. Since then, lacune has been the term for small cavitary lesions containing cerebrospinal fluid (CSF), regardless of relevant neurologic deficits. Lacunar infarction and lacune have been used interchangeably, so in recent years, a definite consensus has been established on the definition of these states. Lacunar infarction refers to a small acute infarction due to occlusion of a penetrating artery with a relevant neurological deficit, whereas lacune refers to a cavity lesion found by chance in brain imaging, regardless of neurological symptoms. Therefore, old, chronic, asymptomatic or subclinical lacune were also used alternatively. Although lacune is generally known to be a chronic change resulting from lacunar infarction, a residual lesion from a small hemorrhage can be possible [26]. Poirer et al. (1983) proposed to divide lacunes into three types using neuropathological studies: type I lacune, secondary to lacunar infarction (ischemic lacune); type II lacune, secondary to small hemorrhage (hemorrhagic lacune); type III lacune, ePVS [27]. This classification is not widely accepted, though it was a meaningful attempt to some extent in that type II lacune might suggest

microbleeds, which would be discovered on gradient-echo (GRE) MRI in the near future.

A typical lacune is found mainly in deep gray structures (e.g., basal ganglia and thalamus), subcortical white matter, and the pons. It is usually between 3 and 15 mm in diameter [17]. In most cases where it is less than 3 mm, the lesions are ePVS, and in cases larger than 15 mm, it is likely to be a territorial infarction by other mechanisms, such as large-artery atherosclerosis or embolism, rather than lacunes. The imaging criteria for lacunar infarction are a high-signal intensity lesion less than 2 cm on a diffusion-weighted sequence, whereas a lacune is a cavitary lesion less than 1.5 cm on T2-weighted or fluid-attenuated inversion recovery (FLAIR) sequences. This is because lacunar infarction may initially appear larger due to cytotoxic edema, but shrinks over time as it becomes chronic. Clear imaging criteria to distinguish them from ePVS are also required. Both lacunes and ePVS have CSF-filled small cavitary lesions (high signal on T2, low signal on FLAIR or T1) in common, but lacunes are larger (3–15 mm) and are more likely to have a high-signal intensity gliotic rim on FLAIR images. In addition, lacunes are found in distal portions of the parent artery, compared to ePVS. The prevalence of lacunes in adults varies considerably from report to report, but populations with vascular risk factors or a stroke history are likely to have more lacunes than normal elderly adults. There is a 28–94% chance of developing lacunes after lacunar infarctions [28, 29]. In other cases, the lesions become invisible or become WMHs.

6.2.2.2 WMHs

WMHs refer to symmetric, bilateral degeneration of cerebral white matter, especially the centrum semiovale or periventricular area. Although commonly found in cerebral white matter, these lesions may also occur in the pons or cerebellar white matter, and in severe cases, deep gray matter such as the basal ganglia and thalamus can also be involved. WMHs can be found as low-density lesions in CT but are more sensitively diagnosed as high-signal intensity in T2-weighted or FLAIR sequences on MRI. The etymology of the term WMH originates from MRI findings. The term used to refer to these lesions had not been unified, causing confusion in academic communications for a long time. For example, first there was the term "leukoaraiosis" that Dr. Hachinski originally used [30]. He developed a kind of compound word with Greek etymology, where leuko- means "white" and -araiosis means "rarefaction." The word was popular for a time, but is now subsumed under WMHs.

WMHs are frequently found in normal older people, so a minimal amount of WMHs need not be considered pathological. Therefore, clinical grading of WMHs is necessary, though there are more than 19 reported image analysis methods [31]. Among them, the most readily available method is a grading scale that Fazekas et al. proposed by grading WMH in the centrum semiovale: grade 0: none or minimal; grade 1 (mild), punctate; grade 2 (moderate), early confluent; grade 3 (severe), confluent [32]. This method is quite easy and practical in that WMHs can be simply graded by visual inspection, and therefore is very useful for academic purposes as well as clinical practice. However, this method only evaluates WMH status in the centrum semiovale, disregarding the periventricular white matter, deep gray matter, and pons. Another disadvantage is its reliance on subjective judgment. As for the natural course, it is quite well known that WMHs progress more rapidly at moderate to severe grades (grade 2 or 3) than at minimal or mild levels [33, 34]. In other words, the status of WMHs is initially stationary, but with poor control of risk factors, conditions deteriorate rapidly after a certain period.

WMHs naturally affect cerebral function to various extents. They do not cause sudden and severe neurologic deficits as in stroke but induce chronic progressive cerebral dysfunction with insidious onset. If the lesions significantly affect white matter functions such as cognition, emotion, and sensorimotor coordination, there would be vascular cognitive impairment or dementia, depression or psychological dysfunctions, and gait disturbance or even vascular parkinsonism, respectively. Depending on the extent of the WMHs, the effects vary from person to person,

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but the more severe the WMHs, the more likely deficits are. In addition, since it is a representative subclinical manifestation of SVD, WMHs are a crucial radiologic marker for future stroke occurrence or recurrence [35–37]. In particular, the predictability of stroke by SVD mechanisms (lacunar infarction or ICH) is relatively high. In addition, even with the same stroke, patients with more severe WMH have significantly worse outcomes [37]. In terms of ischemic stroke, severe periventricular WMHs were significantly associated with poor functional outcome at 3 months, independent of other factors, such as diabetes and age [37]. As for ICH, in Korea's ICH nation-wide cohort study by Kim et al., moderate-to-severe WMHs exhibited severe Glasgow Coma Scale (GCS) scores at admission (odds ratio, OR 2.45) and 30-day mortality (OR 2.52) [38]. Severe WMHs in white matter damage neurons and the physical structures of synapses, and in turn, reduce the activity or effectiveness of neurofunctional circuits. In addition, it is obvious that if stroke occurs in patients with advanced WMHs, the functional reservoir needed for patient recovery would be insufficient, thus long-term outcomes ultimately worsen.

The underlying pathologic findings of WMH are well established. In neural tissues, selective loss of neurons and oligodendrocytes, as well as demyelination and axon damage, is found, and lipohyalinosis is frequently observed in relevant penetrating arteries [39]. These findings suggest that WMHs may cause problems in the transmission of electrical signals through neural axons. Even without complete necrosis, as in a stroke, a partial pathological change would cause progressive damage in neurofunctional circuits for higher cortical functions. These pathological findings are traditionally explained by chronic hypoperfusion caused by advanced microangiopathies in small arteries. The centrum semiovale, receiving dual perfusion on both sides by basal penetrating arteries at the bottom of the cerebral cortex and leptomeningeal arteries at the top, is a representative watershed area called the internal border zone. When blood vessels are not affected, blood perfusion from both sides is enough to maintain cerebral blood flow (CBF). However, if both penetrators deteriorate due to generalized SVD, with poor control of risk factors, the watershed area is the first to be impacted by CBF reduction. If this condition persists, damage begins in the tissues most sensitive to CBF. These findings present as ischemic demyelination and associated axonal damage. In severe cases, some neurons and oligodendrocytes may also be lost, even showing incomplete infarction in some areas. In addition to this explanation, leakage of plasma fluid and venous collagenosis due to BBB breakdown have recently been suggested as a mechanism of action, and will be discussed in the later part of this chapter [3].

6.2.2.3 Microbleeds

Cerebral microbleeds are small amounts of hemosiderin deposited in the brain parenchyma, leading to local inhomogeneity around the lesions on MRI, resulting in small lesions of low-signal intensity on GRE or susceptibility-weighted images (SWI) (Fig. 6.4f). The most important point in diagnosing microbleeds is to exclude other lesions or artifacts that may be confused with microbleeds. This is because the GRE or SWI sequences used to diagnose microbleeds visualize all the substances that cause the susceptibility effect. Typically, calcifications, iron deposits, and deoxyhemoglobin inside the blood vessels are substances that cause susceptible effects. Controversy still exists about the size criteria for microbleeds [40]. In general, the minimum diameter is set to 2 mm, but the maximum diameter varies from 5 to 10 mm. However, considering the results from a series of clinical studies, the most appropriate determinant between microbleeds and intraparenchymal bleeding would be 5.7 mm [41]. Using GRE imaging, it is adequate that microbleeds are defined as a circular low-signal intensity lesion within 2–5 mm, but the definition under SWI may be applied differently. The diagnostic criteria illustrated in Table 6.2 are relatively widely accepted [40]. Microbleeds are most frequently found in the deep gray matter—the basal ganglia and thalamus—but are also found in the infratentorial and lobar locations [42–44]. Microbleeds in the deep area are usually caused by the vascular risk

Table 6.2 Recommended criteria for cerebral microbleeds identification

1. Black on T2∗-weighted MRI
2. Round or ovoid (rather than linear)
3. Blooming on T2∗-weighted MRI
4. Devoid of signal hyperintensity on T1- or T2-weighted sequences
5. At least half surrounded by brain parenchyma
6. Distinct from other potential mimics such as iron/calcium deposits, bone, or vessel flow voids
7. Clinical history excluding traumatic diffuse axonal injury

MRI: magnetic resonance imaging. Adapted from Lancet Neurology, Copyright Elsevier [40]

factors of stroke, particularly hypertension, but lobar microbleeds are more frequent in patients with CAA [45]. General pathological findings of microbleeds consist of minute hemosiderin deposition around the lipohyalinotic small arteries and hemosiderin-laden macrophages in the periphery. Therefore, microbleeds describe a small amount of blood leaking through a weak vessel wall, in other words, a subclinical, minute ICH. In patients with CAA, pathological observations showed hemosiderin deposition and inflammatory lesions due to blood leakage from vulnerable vessels with β-amyloid pigmentation [46]. The microbleeds seen on GRE and SWI appear to be exaggerated in size by the blooming effect, so the actual area of hemosiderin deposition is expected to be smaller.

In asymptomatic adults, the prevalence of microbleeds is approximately 3–7% [47, 48]. Old age and hypertension are important risk factors, but the effect of diabetes on microbleeds has been questioned. In the Rotterdam Scan Study, which examined microbleeds in 1062 asymptomatic adults, the prevalence of hypertension was 71.9%, and age was strongly correlated with the presence of microbleeds: 17.8% in 60–69 year-olds, 31.3% in 70–79 year-olds, and 38.3% in patients aged 80 years or older [47]. According to studies with ischemic stroke patients, the incidence of microbleeds among this group is significantly higher than that of normal individuals, ranging from 35 to 71% [48]. There is a clear difference in reporting rates of microbleeds as subtypes of ischemic stroke, characteristics of recruited patients, MRI sequences of microbleeds, and MRI parameters. Microbleeds are more frequent in lacunar infarctions, rather than in cardioembolic or atherothrombotic strokes [49]. The prevalence of microbleeds in ICH is the highest, ranging from 47 to 80% [48]. Further, microbleeds were observed more frequently in Asian ethnic groups than in non-Asian ethnic groups [50]. A higher prevalence of microbleeds in SVD-related strokes, lacunar infarction, and ICH can be easily understood considering the mechanism of development. With regards to this association, my colleagues and I reported that the presence of microbleeds in basal ganglia or lobar areas was strongly related to ICH development in the same regions [44]. Accordingly, the relationship between microbleeds and ICH is stronger than those of any SVD features, such as WMHs or lacunes [40].

Based on the assumption that microbleeds reflect the tendency of the brain tissue to bleed, it has been tested that microbleeds can be used as an indicator of the risk of future hemorrhagic stroke. In Hong Kong, an analysis of 121 patients with acute ischemic stroke showed that patients with baseline microbleeds were more likely to experience hemorrhagic stroke [51]. In addition, the number of microbleeds was proportional to the risk of subsequent hemorrhagic stroke. This suggestion was repeatedly demonstrated in a prospective study of 112 patients with ICH, which found this relationship was more pronounced in patients with WMHs [52]. Overall, a systematic analysis concluded that microbleeds are likely to predict future hemorrhagic stroke [53]. Especially in patients undergoing anticoagulation with atrial fibrillation after recent ischemic stroke or transient ischemic attack, identifying microbleeds may be useful for the prevention of future ICH. According to the CROMIS-2, a prospective large-sized cohort study conducted in the United Kingdom for this purpose, the symptomatic ICH rate in patients with microbleeds was approximately 3.8 times higher than in those without microbleeds (9.8 per 1000 patient-years versus 2.6) with statistical significance [54]. There is no doubt regarding the predictive value of microbleeds on future ICH. We may need a meticulous tuning of strategies for secondary prevention

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among ischemic stroke patients with microbleeds. To date, however, no consensus on anticoagulant therapy in patients with microbleeds and atrial fibrillation has been reached. In order to clarify the benefits and losses in these patients, a large-scale clinical trial is urgently needed to identify the risk of microbleeds. Further, new oral anticoagulants (NOAC) are being actively used for the prevention of atrial fibrillation-related stroke. Meanwhile, the effects of microbleeds on NOAC-related bleeding is another topic for further analysis.

6.2.2.4 ePVS

Perivascular space, also called Virchow–Robin space, refers to a space in which the subarachnoid space extends into the brain parenchyma along penetrating arteries branching from the large cerebral arteries (Fig. 6.5). Filled with CSF, it extends along the penetrating arteries at a close distance. In normal adults, it is hardly distinguishable on conventional CT or MRI. However, in aging brains or brains that have been exposed to advanced vascular risk factors such as hypertension, the perivascular spaces are enlarged (hence the term ePVS) and can be clearly visualized on MRI. These lesions are observed in terms of CSF density, mainly on T2-weighted MRI, but are rather indistinguishable on FLAIR MRI or CT. They can be distinguished relatively well in several ways with lacunes: (1) ePVSs are usually smaller with a diameter within 3 mm; (2) ePVSs are distributed more proximally to the brain surface than lacunes, at the base of the basal ganglia, and the juxtasubcortical area near the cortex; (3) they are rarely found as a sole lesion, and a large number of lesions are usually observed at once; (4) there is no perilesional gliotic rim in ePVSs.

There are a few theories about the mechanism of development. Among them, vascular tortuosity-related expansion is a hypothetic mechanism that has long been considered

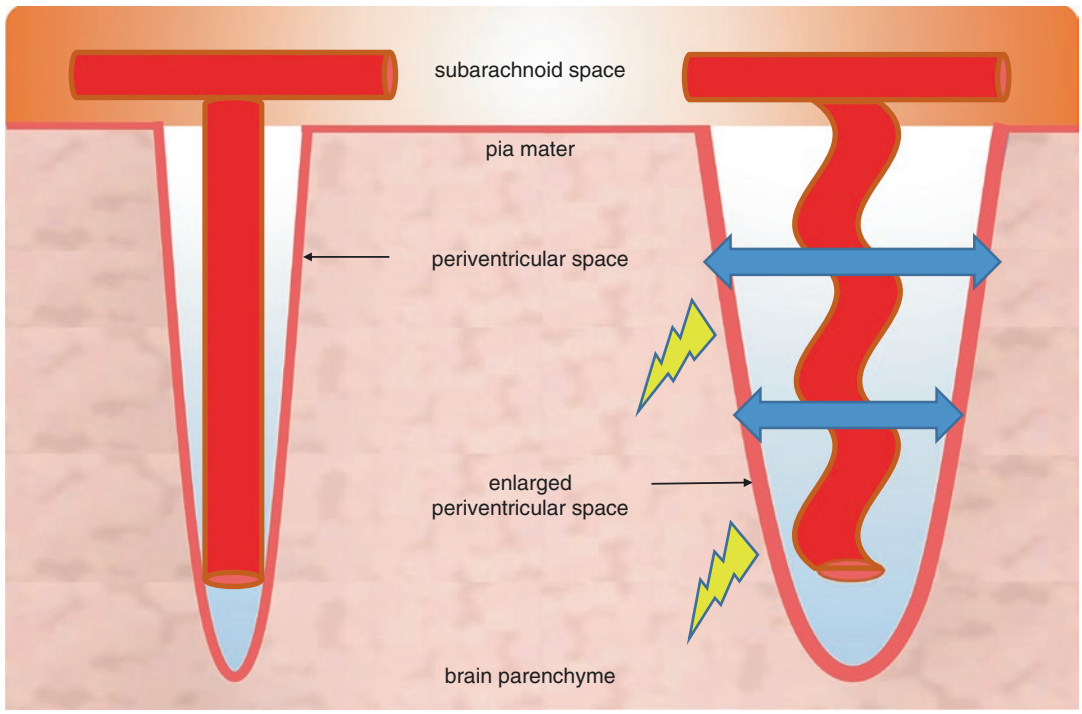

Fig. 6.5 The pathophysiology of enlarged periventricular space. Periventricular spaces are cerebrospinal fluid-filled canals surrounding perforating arteries in the parenchyma of the brain. Their close anatomical structure to arteries brings mechanical expansion of periventricular space by vascular tortuosity, which is a main phenomenon caused by hypertension or aging process

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(Fig. 6.5). When penetrating arteries are exposed to hypertension or aging, they can morphologically become tortuous from increased blood pressure. The tortuous arteries progressively push the surrounding brain tissue to the periphery, which gradually widens the perivascular spaces. Since these changes may occur even in the early stages of hypertension, ePVS is frequently found even in the absence of other SVD features, such as WMHs or lacunes. Considering the effects of vascular risk factors on the interface of blood vessels and brain tissue, ePVS seems to be a lesion when blood vessels still tolerate vascular stress. This is because there are no noticeable changes to brain tissue around the ePVS. On the contrary, WMHs, lacunes, and microbleeds seem to be lesions that extend beyond blood vessels, affecting surrounding brain tissue. Accordingly, ePVS may indicate an end-organ damage finding during early to mid-term hypertension, or relatively good stress tolerance in brain tissue, while WMHs, lacunes, and microbleeds may indicate advanced tissue damage beyond the tolerance of the blood–tissue interface. Alternatively, it was suggested that sterile inflammation and exudation of plasma protein are involved in ePVS development, although this hypothesis warrants further evaluation [3].

6.3 Risk Factors

The vascular risk factors that cause SVD are not fully understood. Patients with SVD possess a variety of common atherosclerosis risk factors, such as hypertension, diabetes, hyperlipidemia, and smoking. Moreover, it is difficult to distinguish the risk factors that influence them on an individual level. Based on results from previous clinical studies, it is possible to categorize risk factors into high, moderate, and controversial degrees.

Factors that convey a high risk for SVD include old age and hypertension. As an irreversible risk factor, the association between old age and SVD is clear. Even with hypertension, SVD is rarely identified before age 40, but no matter how healthy, WMHs are generally profuse after age 70. This suggests that aging, namely vascular aging, is closely related to the development of SVD. Aging is associated with all types of SVD and is also implicated in the development of other risk factors. So, distinguishing the effects of aging alone is only statistically possible and practically difficult. A second high risk factor for SVD is hypertension [55]. Hypertension has long been known to be the most potent risk factor for SVD; it is now undoubtedly acknowledged that treatment of hypertension is the most effective means of inhibiting SVD progression [56]. Hypertension is a strong risk factor for all forms of SVD, but long-standing, uncontrolled hypertension conveys greater risk than an acute hypertensive crisis. It is uncertain whether diastolic or systolic blood pressure is more important, with reports that both are relevant or not. A prospective observational study showed that control of hypertension inhibits the progression of WMHs [33]. Among the radiological features of SVD, microbleeds are the type with the strongest effect of hypertension [57]. Although microbleeds in the lobar area are also related to CAA, microbleeds in the deep gray matter or pons are closely associated with hypertension [45]. This was supported by a clinical report which found a dose–response relationship between the burden of hypertension (based on the levels of left ventricular mass index using transthoracic echocardiography) and the number of microbleeds [57].

Meanwhile, smoking and diabetes are moderate risk factors for SVD. The Rotterdam Scan Study, which conducted follow-up MRI in 1077 patients, showed that current smoking was a significant risk factor for WMH progression (OR, 2.63) [58]. However, in a cross-sectional study of 1797 patients from Singapore, Hong Kong, and Korea, only age and hypertension were positively correlated with SVD features—WMHs, lacunes, and microbleeds—but other factors, including smoking, were irrelevant [59]. In addition, the relationship between diabetes and SVD was also inconsistent. A clinical study with an Asian sample showed no effect of diabetes on the likelihood of WMH, lacunes, and microbleeds [59]. In contrast, a study of Caucasian stroke patients showed a clear correlation between diabetes and SVD

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features (OR, 2.74) [60]. Smoking is likely to be a risk factor affecting SVD, as well as large-artery atherosclerosis, but diabetes has been regarded as a risk factor only for large-artery atherosclerosis. As for ICH, an important clinical manifestation of SVD, no clear relationship between diabetes and the incidence of ICH has been established. It has also been repeatedly reported that diabetes has a minimal effect on the development of microbleeds. In summary, diabetes is a critical risk factor for the progression of atherosclerosis in large arteries but exerts a limited effect on the development of SVD [61].

Hyperlipidemia has long been misunderstood in association with SVD. A high level of low-density lipoprotein (LDL) cholesterol is the strongest risk factor for large-artery atherosclerosis. It is well known that the use of lipid-lowering agents, such as statins, greatly reduces the risk of coronary artery disease or stroke. Because of its strong association with large-artery atherosclerosis, there has been a prejudice that hyperlipidemia has a significant effect on SVD. However, it is largely unrelated to SVD, and in terms of hemorrhagic SVD manifestations, it was reported to have a protective function that inhibits the development. With regards to WMHs, hyperlipidemia was not associated with the development of the lesions, as indicated by the Rotterdam Scan Study and a clinical study in Asia [58, 59]. Moreover, low, rather than high, serum cholesterol levels are a strong risk factor for microbleeds and ICH [62]. However, these results do not suggest that statins should be prohibited for patients with SVD. Low levels of serum cholesterol in the clinical studies, which were associated with the incidence of microbleeds and ICH, were not generated by the lipid-lowering agents, but other systemic conditions, such as nutrient deficiency and alcohol consumption. Although the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial showed that high doses of atorvastatin increase the risk of ICH, there is much evidence that statin use does not increase the incidence of ICH in other situations [63]. At the very least, it is important to recognize that there is no association between hyperlipidemia and SVD.

In addition, there are some reports that nutrients such as homocysteine, B12, and folate are associated with the development of SVD. However, this connection is not only sporadic, but also very difficult to clearly distinguish from other risk factors for SVD. Regardless of how advanced statistical methods are, it is unlikely that we will be able to establish a clear relationship.

6.4 Pathophysiology of SVD

As mentioned before, the mechanisms underlying the occurrence of SVD features have already been described. This section will provide a comprehensive description of the known mechanisms of SVD features. With uncontrolled hypertension and aging, microangiopathic changes such as lipohyalinosis are developed in penetrating small arteries and arterioles. These changes cause mechanical disruption, dissection, and thrombosis on the vessel wall. When one vessel is suddenly blocked, lacunar infarction may occur with associated neurological symptoms. If the infarction occurs in the non-active functional area, noticeable neurological symptoms do not occur, but the lesion may later be discovered as a lacune on MRI. If the ischemic intensity is not enough to develop a complete infarction, the lesion may become a WMH lesion or may disappear in the chronic stage. Lacunar infarctions or lacunes are due to hypertension-related microangiopathic changes occurring in penetrating arteries and are common in areas vulnerable to high blood pressure—the basal ganglia, internal capsules, thalamus, corona radiata, and pons. The vessel walls of these penetrating arteries are not thick enough to maintain their integrity with advanced hypertension, and they may rupture and develop a hemorrhage into the brain parenchyma. Small amounts of extravasated blood with a diameter less than 5 mm are usually asymptomatic and can be detected as microbleeds on GRE or SWI sequences. When the extravasated lesions are large enough to develop an abrupt neurological deficit, they may be identified as an acute ICH. The locations of microbleeds and ICH are

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quite similar, because the development mechanisms are identical despite the difference in amount of blood. Deep gray matter, such as the basal ganglia and thalamus, are vulnerable to high blood pressure, and are the most common areas for lacunes, microbleeds, and ICH. Looking in detail, we can see that lacunes occur at some distance from a vessel occlusion, whereas microbleeds and ICH occur just at the site of a vascular rupture. Accordingly, microbleeds are found at sites proximal to penetrating arteries branching from parent arteries traveling through subarachnoid space, and lacunar infarctions are more common at distal sites such as the internal capsules and corona radiata. Microbleeds in the lobar area are not uncommon in patients with hypertension but occur more frequently in those with CAA. Even in this case, microbleeds are largely found in juxtacortical areas—sites more proximal to parent branching vessels. Microbleeds in the periventricular area or centrum semiovale are infrequent. Tiny ruptures of leptomeningeal arteries denatured by CAA result in lobar microbleeds. In contrast, when an intraluminal disruption in the same vessels occurs, a small infarction—called a cortical microinfarct—may occur. As microangiopathic changes progress throughout the brain, deep internal areas—called internal border zones—may face problems with blood perfusion. The periventricular area and the centrum semiovale are the representative internal border zones. Chronic hypoperfusion at this site causes incomplete infarction and ischemic demyelination to be observed as WMHs on MRI. Figure 6.6 is a general illustration showing the location and mechanisms of these SVD features [64].

The development of SVD can be explained in most cases by the above overview. Recently, it has been suggested that the development of SVD, particularly WMHs, is due to endothelial failure and subsequent sterile inflammation. Wardlaw

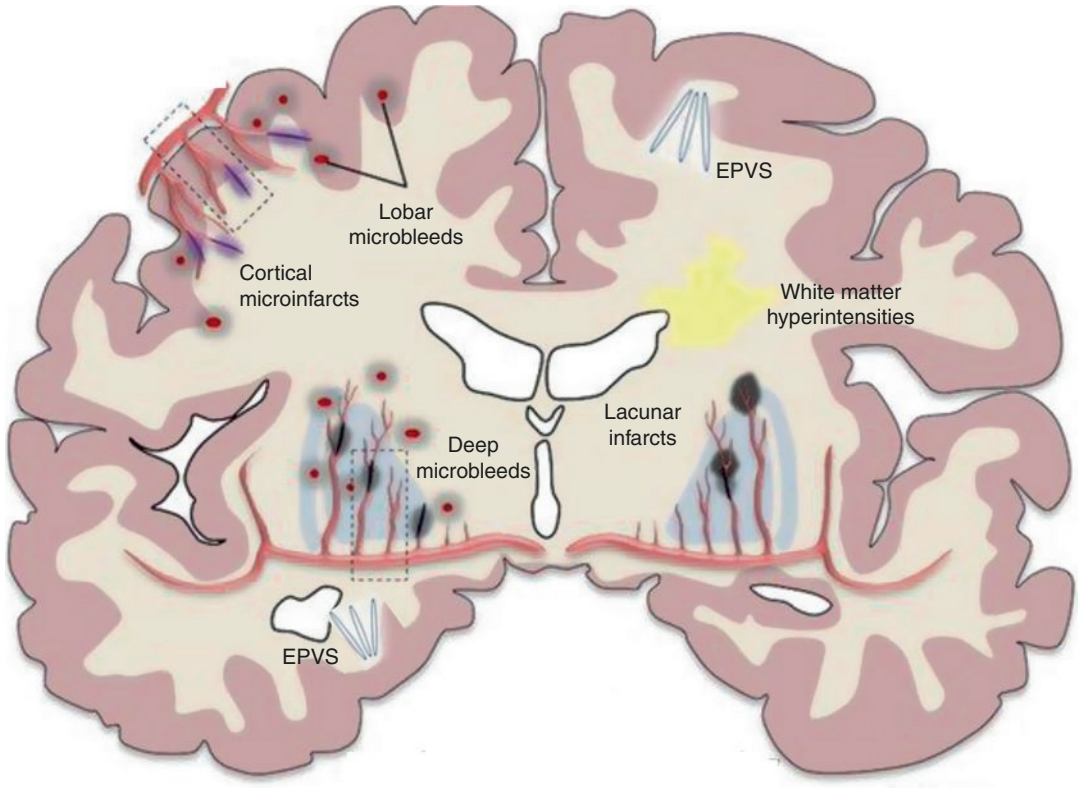

Fig. 6.6 The distribution of cerebral small vessel disease. Adapted with permission from Springer Nature [64]

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et al. analyzed the CT and MRI data of nine patients with lacunar infarction, which showed that lacunar infarction could occur as a tubular vessel-like structure around the vessel, rather than at the end of the occluded vessel [65]. The authors distinguished that this appearance might also have been caused by a leak of blood and fluid into the perivascular space around the artery. In other words, it was suggested that leakage of plasma fluid components occurs due to endothelial failure in the early stages of SVD, and the resulting perivascular edema is toxic to brain tissue cells, leading to rarefaction and demyelination. According to this theory, the capillary lacks a smooth muscle layer, resulting in immediate edema and tissue damage when endothelial failure occurs. In arterioles, autoregulatory dysfunction in the thickened vascular walls may lead to ischemia due to the loss of appropriate vasodilation. Here, the reason why endothelial failure occurs in the first place is key to the theory's novelty. They argue that endothelial failure may be caused by (1) problems with BBB integrity due to aging, (2) amyloid deposition on the vessel wall, (3) sterile inflammation, and (4) a diet high in salt. In that case, is this theory necessarily a process unrelated to hypertension? Indeed, vascular stiffness and its associated self-regulatory dysfunction are also responsible for the development of essential hypertension, and conversely, are exacerbated by hypertension. Therefore, the endothelial failure theory should be taken as one of the theories explaining the process of microangiopathy caused by hypertension, which is not a new theory in itself. Perhaps endothelial failures in the microangiopathic vessels are a naturally occurring pathological process.

6.5 Therapeutic Perspectives and Conclusion

Cerebral SVD is a disease whose clinical effects are better known to the brain than other organs. The disease has various clinical manifestations ranging from asymptomatic lesions to highly fatal lesions such as ICH. SVD occurs when adult individuals are chronically exposed to various vascular risk factors such as old age and hypertension. There is no specific treatment targeting SVD. While it is not possible to return to a healthy state once SVD has developed, it is best to minimize progression through strict management of risk factors. Since SVD is a powerful predictor of various brain diseases such as stroke, dementia, parkinsonism, and depression, it is crucial to detect it using brain imaging. SVD can also be a useful surrogate radiologic marker for determining the success of risk control. In this chapter, almost all aspects of SVD—clinicoradiological type, pathology, risk factors, and mechanisms of development have been covered. I hope that this information will be used to facilitate better understanding of cerebral SVD.

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