Cerebral Vessel Wall Diseases

11

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Abstract

The cerebral arterial wall is composed of three layers, the tunica intima, tunica media, and adventitia, which are common structures in human systemic arteries. As the composition and cellular origin of each component differ according to the vessel locations, such as intracranial, extracranial, anterior, and posterior, the response and vulnerability to injury vary for each arterial site. Cerebral vessel wall diseases are characterized by the partial or complete involvement of vascular wall components by an inciting factor. Typical manifestations include transient ischemic attack, cerebral infarction, or intracranial bleeding by luminal narrowing, thrombus formation, or rupture. The main pathophysiological sequence of cerebral vessel wall diseases includes endothelial dysfunction, smooth muscle cell proliferation or degeneration, extracellular matrix degeneration, inflammation, and rheological stress. This chapter deals with three typical cerebral vessel wall diseases including moyamoya disease, arterial dissection, and vasculitis. The cerebral vessel wall diseases may require early differential diagnosis because they are associated with different therapeutic options. However, the early diagnosis may be difficult because these diseases often share clinical manifestations and angiographic features. Recently, the advent of vessel wall imaging techniques and the increasing availability of pathological studies prompt us to better differentiate the diseases and identify the pathomechanism of each disease. This chapter reviews the advances in the histopathological and clinical data of cerebral vessel wall diseases with the aim of unraveling their pathophysiology.

11.1 Introduction

The peculiar anatomy of cerebral arteries and a variety of pathophysiological signals contribute to the development of various cerebrovascular diseases, providing a unique classification of cerebral vessel wall disease. Common nonatherosclerotic, cerebral large-vessel wall diseases include moyamoya disease, arterial dissection, and cerebral vasculitis. The current stroke classification system defines these disease entities as uncommon causes of stroke. In particular, these cerebral vessel wall diseases are considered an important differential diagnosis in young age-onset stroke.

Detection of cerebral vessel wall disease is largely based on vascular imaging modalities such as transcranial Doppler (TCD), computed

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tomography angiography, magnetic resonance angiography (MRA), and digital subtraction angiography (DSA). However, these conventional imaging techniques have often missed the presence of wall disease, because they merely monitor blood flow within the vascular lumen. Increased flow velocity on TCD might indicate the presence of good collateral vessels as well as stenosis. While CTA, MRA, and DSA sensitively detect the luminal narrowing, flow velocity or luminal narrowing is dependent on the volumetric change of the total artery, total wall, concentric wall, and eccentric wall [1]. The cerebral arteries undergo positive and negative remodeling during the disease course, the characteristics of which may be different according to each disease entity. Classical luminal imaging is critically limited by poor delineation of the wall status that is not helpful in the diagnosis of cerebral vessel wall diseases or in understanding their pathophysiology (Fig. 11.1). Currently, with the advent of black blood imaging techniques and higher magnetic field strengths, high-resolution vessel wall images have become feasible in clinical practice. Indeed, imaging the vessel wall of cerebral arteries may improve our ability to detect unrecognized cerebral vessel wall disease.

Diagnostic evaluation typically focuses on clinical features and radiological findings. However, there is significant overlap in the angiographic

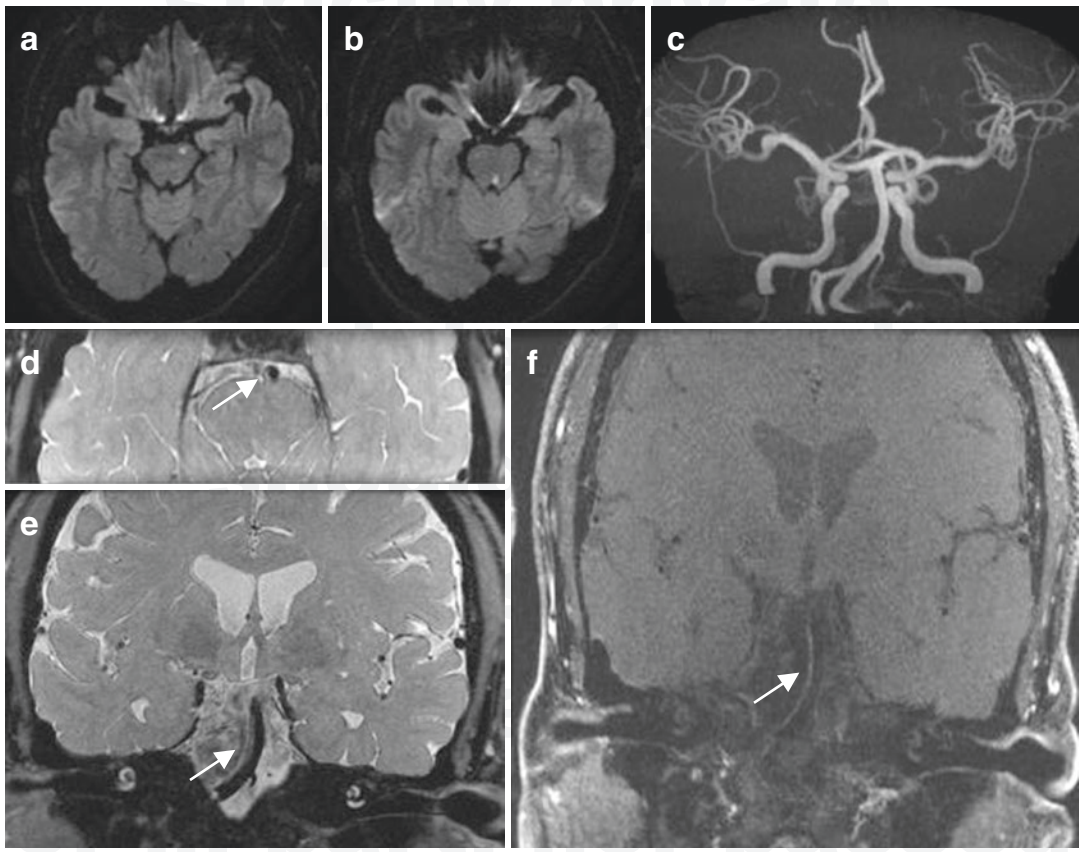

Fig. 11.1 Limitation of luminal imaging for evaluating the cerebral vessel wall disease. A 62-year-old man visited us because of sudden dizziness and diplopia. Brain DWI-MRI (**a**, **b**) showed two tiny infarcts involving the left anterior pons and the left pontine tegmentum. Time-of-flight (TOF) MRA (**c**) showed no luminal narrowing in the basilar artery. However, high-resolution MRI (**d**–**f**) displayed the eccentric enhancing atherosclerotic plaque (white arrows), which was identified by axial (**d**) and coronal view (**e**) of proton density images, and contrast-enhanced T1-weighted images (**f**)

patterns of cerebral vessel wall diseases. Moreover, moyamoya disease, cerebral artery dissection, and cerebral vasculitis share clinical, pathological, and genetic traits. The frequency of each disease is higher in patients with another vessel wall disease than in the general population. The pathophysiologies of moyamoya disease, cerebral artery dissection, and cerebral vasculitis are largely unclear as of yet. The majority of knowledge regarding their pathophysiology is derived from histological data based on biopsy or autopsy and, in part, from non-invasive radiological findings. This review will address the anatomy, embryology, and pathology of cerebral arteries, with the primary focus on the common cerebrovascular diseases occurring in the arterial wall.

11.2 Anatomy of the Cerebral Vessel Wall

Anatomical integrity is crucial to maintain the functional homeostasis of cerebral vessel walls and its perturbations eventually lead to the development and progression of cerebral vessel wall disease. Moyamoya disease, cerebral artery dissection, and cerebral vasculitis commonly involve anatomical and functional changes in the vessel wall. Knowledge of the pathophysiological characteristics of each disease should stem from a detailed recognition of the structural anatomy and embryological origin of cerebral arteries, and its differences from other systemic arteries.

11.2.1 Common Arterial Structure

The cerebral arterial wall consists of three layers, the tunica intima, tunica media, and tunica adventitia [2], which are also characteristic of other systemic arteries (Fig. 11.2). The tunica intima refers to the luminal side of arteries lined with endothelial cells. The internal elastic lamina is situated as a partition between the tunica intima and tunica media. Endothelial cells produce elastin and maintain the integrity of the internal elastic lamina by interacting with smooth muscle cells in the tunica media. The tunica intima is essential in maintaining the homeostasis of blood and adjacent vascular cells, whereas it contributes little to the structural support of vessels.

The tunica media is composed of two main components, smooth muscle cells, and elastin. Smooth muscle cells are located in a direction circumferential to the lumen, whereas elastin fibers run in a parallel direction to the longitudinal axis of the artery and perpendicular to the smooth muscle layer [3]. The density of smooth

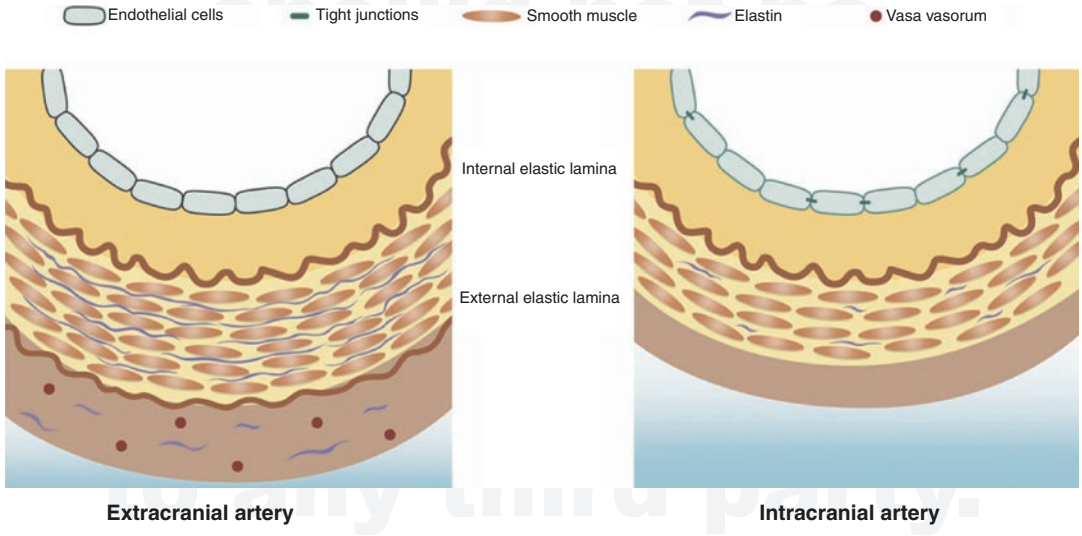

Fig. 11.2 Structural difference of extracranial and intracranial artery wall

muscle cells within the tunica media diminishes from the proximal to the distal vascular tree. Smooth muscle cells in the tunica media play two critical roles in maintaining the integrity of the vascular wall. One is a contractile function, which is important in regulating blood flow in small and medium-sized arteries. The other is a regulatory function on extracellular matrix production, which is crucial for enduring the blood pressure in large arteries. The structural network of extracellular matrix produced by smooth muscle cells typically confers a mechanical strength for vascular health. The two principal components of the extracellular matrix are the elastin and collagen generated by smooth muscle cells in the media layer. There are other cellular and matrix elements supporting the tunica media including fibroblasts, proteoglycans, and fibrillin. Elastin is assembled into a three-dimensional, stratal network that assists in resolving the pressure stress. There are collagen bundles between the lamellar layers of elastin, which shift their arrangement according to blood pressure changes. The proper organization of elastin and collagen is achieved by lysyl oxidases that facilitate lysine-derived cross-linking in elastin and collagen. Along with the structural support, the extracellular matrix is also imperative for maintaining the functional integrity of the artery as a reservoir for growth factors or transcriptional factors. The matrix molecules act as instructive signals that regulate vascular cellular function. In the tunica media, proliferative rates of smooth muscle cells and elastic fibers are low, and the turnover of collagen fibers occurs more rapidly than that of other elements. The layers of elastin are laid down during the early developmental period and have a half-life of about 40 years [4]. Therefore, the original elastin structure organized in the developmental stage is important for vascular health over a lifetime and is not easily rescued once injured.

The adventitia is the outermost layer of the vessel, which is demarcated from the tunica media by the external elastic lamina. It is composed of fibroblasts and collagen-rich extracellular matrix produced by myofibroblast cells. The relatively high level of collagen in the adventitia is advantageous in preventing rupture resulting from abrupt pressure increase. This layer is also supported by the vasa vasorum and innervated by nerve endings. The intradural segments of intracranial arteries have no vasa vasorum and receive essential nutrients directly from the blood or cerebrospinal fluid.

11.2.2 Characteristics of the Intracranial Arteries

There are two different types of arteries in the systemic vasculature, i.e., muscular and elastic arteries. The two types of arteries differ primarily in terms of the composition of the tunica media. While the elastic arteries are composed of elastic fibers, the muscular arteries are composed of smooth muscle cells. Among the extracranial arteries, the common carotid artery is an elastic artery, and the internal carotid artery is a muscular artery. The intracranial arteries are muscular arteries, but they have anatomically unique structures that are distinct from other muscular arteries of a similar caliber. The extradural and intradural portions of the internal carotid artery have different anatomical structures. The adventitia is thicker in the extradural segment than in the intradural segment. While the intradural segment has a firm internal elastic lamina, the external elastic lamina disappears from the intradural segment of the internal carotid artery, the cavernous portion of the internal carotid artery. Marked attenuation of elastic fibers and the absence of an external elastic lamina are also noted in the vertebral arteries entering the cranium. The fact that the intracranial artery has a minimal number of elastic fibers in the media with no external elastic lamina suggests that the intracranial artery is more vulnerable to rupture than the other muscular arteries. The adventitial layer of the intracranial arteries is typically thin compared to that of other systemic arteries. They have no vasa vasorum and are in direct contact with cerebrospinal fluid, such that the adventitia of the intracranial artery is referred to as the rete vasorum.

The intracranial artery accommodates a disease process via compensatory remodeling.

Remodeling can vary in direction and degree depending on the nature of the injury and the vessel inflicted. Positive outward remodeling of the cerebral artery preserves upwards of 60% of the lumen. Posterior circulation is more capable of positive remodeling compared with the anterior circulation [5]. In contrast, inward remodeling, so-called negative remodeling, can occur in certain vessel wall pathologies such as moyamoya disease with constriction of the vessel area and induction of stenosis.

11.2.3 Embryological Origins of Cerebral Smooth Muscle Cells

Endothelial cells are originated from mesodermal precursors that generate angiogenic cells, whereas vascular smooth muscle cells are derived from either different origins of progenitor cells according to the vessel location or different segments of the same vessel [6]. The different types of vascular smooth muscle cells play different roles in maintaining the structural integrity of mature vessels. Two distinct populations give birth to the smooth muscle cells of the large elastic vessels such as the aorta and cerebral arteries. The first is the somatic and splanchnic mesoderm constituting the dorsal aorta. Smooth muscle cells of mesodermal origin primarily provide mechanical strength by exerting a contractile function. The second population is the neural crest cells, which differentiate to smooth muscle cells in the aortic valvular cusps, ascending and arch of the aorta, the ductus arteriosus, the brachiocephalic and subclavian arteries, and the carotid and intracranial arteries. A major function of the vascular smooth muscle cells of neural crest origin is to synthesize and organize the elastin and collagen, such that the walls of the elastic arteries show impaired formation of the elastic lamellae when the neural crest cells are not appropriately positioned.

The muscular arteries in the large part of head and neck are also derived from neural crest cells. The neural crest is a unique structure in the early embryogenesis of vertebrates with a high degree of migration and differentiation throughout the body. The neural crest cells detach from the neural folds, migrate into the anterior and ventral head, and encounter mesoderm-derived endothelial precursors. The neural crest cells and endothelial precursors are expanded and merged into a vascular tree of head, neck, and heart outflow tracts [7]. In contrast, the dorsal and posterior parts of the head and neck are mainly supplied by the vessels of mesodermal origin. The two vascular trees of neural crest and mesodermal origin are connected and re-diverge at the level of the circle of Willis.

Although the lineage-specific smooth muscle cell populations share phenotypic properties, there are critical differences in the responses to factors that contribute to the development of cerebral vessel wall disease. In the context of the shared origin of the cerebral wall, the patients with bicuspid aortic valve are also vulnerable to dilatation, aneurysm formation, and rupture of the ascending aorta, as well as dissection of the aorta and the cervical and intracranial arteries [8]. Bicuspid aortic valve has been detected in the genetic connective tissue diseases such as Marfan syndrome and Ehlers–Danlos syndrome. The concurrent development of theses arterial abnormalities is primarily associated with a common embryonic origin of inflicted vessels and tissues [9].

11.3 Common Pathway for Cerebral Vessel Wall Disease

The solid structure of the cerebral vessel wall is changed into a disorganized pattern in response to injury signals relevant to the disease process. Histopathological studies over the past decades have identified several unifying components leading to structural fragility in the arterial wall. The main histopathological alterations include endothelial dysfunction, functional and structural degeneration of smooth muscle cells, extracellular matrix degradation, inflammation, and hemodynamic factors (Fig. 11.3). There are close pathogenetic interactions between each of the components.

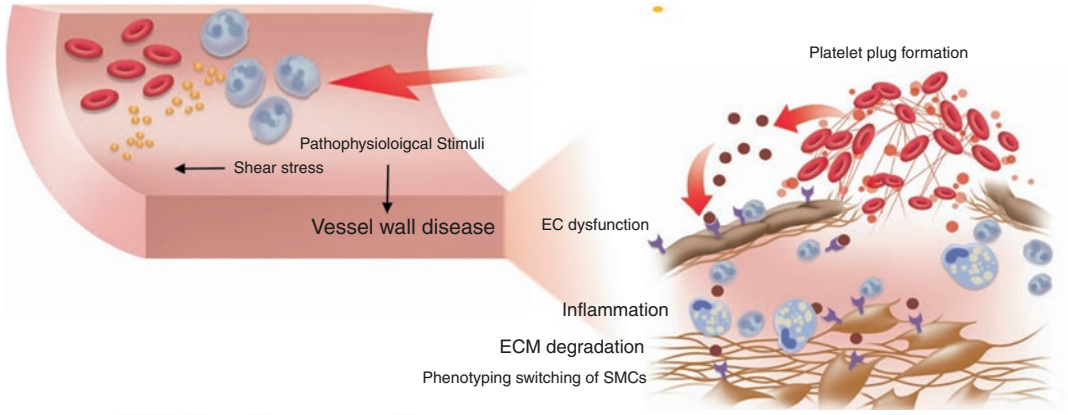

Fig. 11.3 Common pathophysiological pathway incurring cerebral vessel wall disease. EC, endothelial cell; ECM, extracellular matrix; SMC, smooth muscle cell

11.3.1 Endothelial Dysfunction

Endothelium is characterized by the continuous cellular lining of the systemic vasculature and is widely distributed in the human body. It plays the most vital role in maintaining the homeostasis of organs and supporting their healthy functionality. Healthy endothelial lining is a good container for blood. The luminal surface secretes vasculoprotective molecules and prevents the intrinsic coagulation cascade or platelet adhesion, thereby inhibiting leukocyte infiltration, smooth muscle proliferation, and thrombus formation [10]. Moreover, endothelial cells act as biomechanical transducers for mechanical forces into biological signals. Endothelial cells show morphological and functional changes in response to hemodynamic changes. The morphological changes of endothelial cells give adaptation to flow alterations and protect the vessel wall, whereas stress may activate the injury signals including inflammatory cascades. Finally, in response to growth factors, pro-inflammatory cytokines, or endotoxins, they play a regulatory role in the balance of pro- and anti-inflammatory actions within the arterial wall. Thus, dysfunction of the endothelium generally leads to thrombus formation, smooth muscle cell proliferation, extracellular matrix degeneration, and vessel wall inflammation.

Endothelial cell damage or dysfunction is a universal pathological feature seen in various cerebral vessel wall diseases. Pathological changes of the endothelium are noted in the initial stage of disease. Endothelial cell dysfunction initiates a complex pathophysiological sequence due to loss of the selective barrier function. It accelerates the adhesion of blood monocytes into the intima, where they differentiate into macrophages, and activates the inflammatory process. Growth factors and cytokines are also stimulated by activated endothelial cells, and these mediators in turn stimulate the nearby smooth muscle cells. In response to various pathophysiological signals, dysfunctional endothelial cells further increase specific local pathological processes within the arterial wall. Endothelial cell dysfunction is a reversible process, and treatment targeting endothelial dysfunction may be effective to prevent the subsequent damage in the vessel wall.

11.3.2 Phenotypic Switching of Smooth Muscle Cells

The smooth muscle cells maintain the structural integrity of the vessel wall. Vascular smooth muscle cells normally occupy 70% of the media, and this composition is altered under conditions of cerebral vessel wall disease. In response to injury signals, vascular smooth muscle cells undergo phenotypic modulation in a way to produce a pro-inflammatory signal, and some proliferate and induce vascular narrowing. In normal cerebral arteries, smooth muscle cells express a wide array

of smooth muscle cell markers including myosin heavy chain, 22-kDa SMC lineage-restricted protein, ACTA2, and smoothelin. However, in disease states, smooth muscle cells lack these markers and instead acquire the markers and properties of macrophages. The cells undergoing phenotypic switching secrete various extracellular matrix proteins and cytokines, acquire increased proliferative and migratory properties, and promote inflammatory signals [11]. The proinflammatory phenotypes are followed by the promatrix remodeling process. The signals driving the switching of smooth muscle cells to macrophage-like cells vary according to the nature of the vessel wall disease. Under a certain injury signal, the smooth muscle cells migrate into the intima and proliferate, resulting in the presence of a large number of intimal smooth muscle cells, which is called intimal hyperplasia.

While vascular smooth muscle cells with phenotypic switching eventually go into apoptosis, smooth muscle cell degeneration may be a primary and early event in some vessel wall diseases. Smooth muscle cell apoptosis accelerates the features of medial degeneration including decreased density of smooth muscle cells, elastin fragmentation, and increased glycosaminoglycans [12]. It also critically affects the integrity of the vascular wall and makes the vessel prone to rupture. Smooth muscle cell degeneration is induced by macrophages through death ligand and death receptor interactions [13]. Dying cells release IL-1 and subsequently activate the inflammatory cascade.

11.3.3 Extracellular Matrix Degradation

Arterial tensile strength depends on the integrity of the smooth muscle cells and extracellular matrix of the tunica media. However, loss of smooth muscle cells is not associated with a significant reduction in the static mechanical properties of the arteries, suggesting that the mechanical properties of the large arteries are primarily attributable to the elastin and collagen components. The vessel walls have a high degree of the cross-linking of elastin and collagen and rarely undergo a wear and tear process throughout life. Elastin production begins in midgestation, and there is minimal synthesis throughout the life. The longevity of elastin is estimated to be the human life span. Hence, if the vessels undergo extracellular matrix degradation, the disease course may be irreversible.

Extracellular matrix components show a different distribution according to the specific location of the vasculature. Various types of defects of the elements comprising the extracellular matrix have been reported in patients with connective tissue disease, which has also been commonly associated with concomitant cerebral vessel wall disease. Collagen types I and III are the vascular components that impart strength to the vessel wall. Osteogenesis imperfecta has complications of bone fragility in association with mutations in collagen type I, and collagen type III is defective in vascular Ehlers–Danlos IV syndrome. Fibrillin-1 is essential for the firm organization of the extracellular matrix, including the maintenance of elastic fibers. Marfan syndrome has mutations of the fibrillin-1 gene on chromosome 15, and it is characterized by cardiac, skeletal, and ocular abnormalities [14].

Changes in the extracellular matrix components occur as a consequence of vascular remodeling. Matrix metalloproteinases (MMPs) and their inhibitors (tissue inhibitors of metalloproteinases [TIMPs]) are involved in the process of vascular remodeling. MMPs are produced by smooth muscle cells and leukocytes, and they digest the extracellular matrix, causing further injury via the production of other proteinases. Overexpression of various proteases, particularly MMP2, has been identified in the plasma of patients with cerebral vessel wall disease [15]. Altered regulation of MMPs and TIMPs actively contributes to vascular remodeling and the progression of cerebral vessel wall disease.

11.3.4 Inflammation

Various patterns of the inflammatory response have been identified as triggers and accelerators

to cerebral vessel wall disease. Within the arterial wall, various components of the innate and adaptive immune response operate in an orchestrated manner. As a common pathway of inflammatory reaction, monocytes/macrophages infiltrate into the vessel wall and play a key role in vascular remodeling via the release of MMP [16]. Endothelial dysfunction is associated with the impaired barrier function between the bloodstream and the tunica media, which provokes the infiltration of inflammatory cells and downstream inflammatory cascades. Monocyte chemoattractant protein 1 (MCP1) and NF-kB are pivotal in recruiting monocytes into the vessel wall, initiating the inflammatory reaction, and leading to the phenotypic modulation of smooth muscle cells. Phenotypically switched smooth muscle cells further evoke pro-inflammatory responses, by producing various cytokines and chemokines to mediate macrophage and T cell function. Conversely, smooth muscle cells and extracellular matrix also display anti-inflammatory properties. The balance between the two opposing signals determines the characteristics of medial pathology. Alongside macrophages, T cells and mast cells also actively participate in the inflammatory reaction of vascular diseases. Cytokines, soluble short-acting proteins, have also been studied as pathogenetic contributors of various cerebral wall diseases. Cytokines are produced by monocytes, macrophages, and T cells, and they function as key mediators of the immune response. IL1β, IL6, and tumor necrosis factor-α (TNFα) have been principally involved in the pathogenesis of various vessel wall diseases. Therapeutic approaches targeting the inflammatory pathway may be effective in some cerebral vessel wall diseases.

Inflammation accompanies the proliferation of the adventitial vasa vasorum with extension of the neovessels into the media. The endothelial cells near the lumen are partly fed by the luminal fluid, and nutrition beyond this zone is supplied by the vasa vasorum. Therefore, if the vascular cells in the tunica media activate in response to injury signals, there is a robust increase in the density of the vasa vasorum, extending into tunica media. Therefore, in diseases with active inflammation, vessel density increases threefold over that of stable lesions. Recent advancements in the field of neuroimaging have enabled the imaging of inflammation and neovascularization in the arterial wall. As a site of immunoprivilege, the avascular media may be spared by some disease conditions such as immune-mediated disorders, whereas leukocyte infiltration in the tunica media and media degeneration may be significant in other conditions such as vasculitis.

11.3.5 Hemodynamic Change on the Wall

It is natural that the vascular lesions are distributed randomly throughout the arterial tree, because the whole vasculature is exposed to similar insults. However, the involved sites of disease are far from random; rather, they include areas with specific arterial geometries. This phenomenon supports the hypothesis that unique hemodynamic patterns in particular areas may be important in the development of cerebral vessel wall disease. A pulsatile blood flow through the vasculature provokes various mechanical stimuli. Laminar flow within the vessel maintains the normal function of vascular components and prevents vascular disease [17]. When the luminal area of vessel and blood flow is not disturbed, a hemodynamic force leads endothelial cells to downregulate inflammatory cytokines and growth factors. Within a normal range, this force prevents atherogenesis, thrombosis, adhesion of inflammatory cells, smooth muscle migration and proliferation, and extracellular matrix degeneration. However, disturbed laminar flow or turbulent flow can occur during the disease course, especially in areas with complex geometry. Initially, hemodynamic changes in the vessel wall direct the regulatory mechanism in favor of maintaining the normal range of force. Endothelial cells are actively trying to adapt to changes of hemodynamic stress by various compensatory mechanisms. However, sustained alteration of the hemodynamic force associated with endothelial maladaptation may initiate the cerebral vessel wall disease, and accelerate the disease progression. Unregulated hemo-

dynamic force causes endothelial cells and smooth muscle cells to upregulate the levels and activities of MMP-2 and MMP-9 and to degrade the extracellular matrix, which results in vascular remodeling [18].

The major mechanical forces on the endothelial cells are cyclic stretch, pulsatile pressure, and wall shear stress. Of these mechanical forces, wall shear stress has been proposed as a trigger for disease initiation and progression. Wall shear stress is calculated by the shear rate multiplied by the fluid viscosity. The shear rate is a velocity gradient in the axial plane of the vessel, which depends on the luminal diameter and flow velocity [19]. Decreasing vessel diameter inversely increases the shear rate and subsequently wall shear stress. Variations in arterial wall geometry can influence the distribution and magnitude of wall shear stress, which is a strong determinant in maintaining vascular health and contributing to site-specific disease distribution. Wall shear stress regulates endothelial function, and the presence of mechanoreceptors on the endothelium is thought to change flow signals into biological signals. Shear stress stimulates gene expression, activation of channel and receptor, and the cytoskeletal alignment. Endothelial cells activate different pathological pathways in the course of cerebral vessel wall disease depending on the type and magnitude of shear stress. While stable levels of shear stress promote genes related to the vasculo-protective phenotype, sustained high or low levels of shear stress have been implicated in cerebral vessel wall disease. Biological responses to high wall shear stress include increased endothelial cell damage, endothelial cell turnover, extracellular matrix degradation, medial thinning, and smooth muscle cell apoptosis formation. Meanwhile, low wall shear stress induces pro-inflammatory changes of endothelial cells that are leaky and sticky, impairs nitrous oxide-dependent dilation, and increases inflammatory cell infiltration, thrombus formation, and smooth muscle cell proliferation and migration. The evaluation of wall shear stress as a contributor to cerebral vessel wall disease may help to identify individuals at risk of disease progression and to predict long-term outcomes.

11.4 Pathophysiology of Cerebral Vessel Wall Diseases

It is very hard to define the pathophysiology of moyamoya disease, cerebral artery dissection, and cerebral vasculitis owing to the nonspecific nature of the radiological findings and the lack of convincing histopathological data. Further complicating our knowledge are the unpredictable phenotypes that each disease can exhibit during different time periods of the disease. Nevertheless, significant progress has been made for elucidating the critical pathways that initiate and progress the disease (Table 11.1). Recent information on the pathophysiologies of moyamoya disease, cerebral artery dissection, and cerebral vasculitis, as well as unsolved issues awaiting future research are addressed here.

Table 11.1 Pathological features for common cerebral vessel wall diseases

	Moyamoya disease	Cervical artery dissection	Primary CNS vasculitis
Smooth muscle cells	Migration into intima, proliferation and concentric thickening, transformation from contractile to synthetic type	Cell apoptosis, medial degeneration	Phenotypic switching from contractile to inflammatory type
Extracellular matrix	Alteration of collagen to elastic ratio, matrix degradation	Inherited deformity of collage and elastin cross-link	Matrix degradation
Inflammation	Elevated levels of MMPs, VCAM-1, ICAM-1, E-selectin	Elevated levels of MMPs	Increased macrophages, lymphocytes, proteases, cytokines
Internal elastic lamina	Fragmentation and wavy appearance	Breakdown and degradation	Degradation

11.4.1 Moyamoya Disease

Moyamoya disease is primarily a disease of the medial layer of the arterial wall that is characterized by the progressive steno-occlusion of the distal internal carotid artery and proximal vessels of the circle of Willis. The occlusive changes of the major basal arteries are accompanied by the formation of dilated, fragile arterioles at the base of brain, designated as moyamoya vessels. The latter phenotype is recognized as primary aberrant neo-vascularization or a compensatory process due to the reduced cerebral blood flow. Moyamoya disease manifests as transient ischemic attack, cerebral infarction, or intracranial bleeding with separate age peaks for children and adults and a female predominance. Transient ischemic attack and cerebral infarction result from hemodynamic compromise or artery-to-artery embolism from the thrombosed neovessels, whereas intracranial bleeding occurs owing to rupture of the fragile moyamoya vessels or associated aneurysms. Moyamoya disease is most prevalent in Asian countries or those of Asian ancestry, and founder mutations have been discovered in Asians [20]. Given the distinct genetic architecture of Asian and European ancestry, various subtypes of moyamoya disease may exist [21]. Moyamoya disease is diagnosed by clinical and imaging criteria: idiopathic stenosis or occlusion of both distal internal carotid arteries, followed by characteristic hypertrophy and proliferation of the small lenticulostriate arteries (Fig. 11.4). The current diagnostic guidelines that were revised by the Research Committee of MMD of the Japanese Ministry of Health, Labor, and Welfare in 2015 include patients with both bilateral and unilateral disease. However, it remains unclear whether unilateral moyamoya disease is an early form of bilateral disease or a unique disease entity. Differently from moyamoya disease, moyamoya syndrome indicates a moyamoya disease-like condition secondary to atherosclerosis, vasculitis, dissection, sickle cell disease, and inherited coagulopathy. The natural course of moyamoya disease is not well known and the progression of arterial stenosis has variable courses. The five-year risk of recurrent

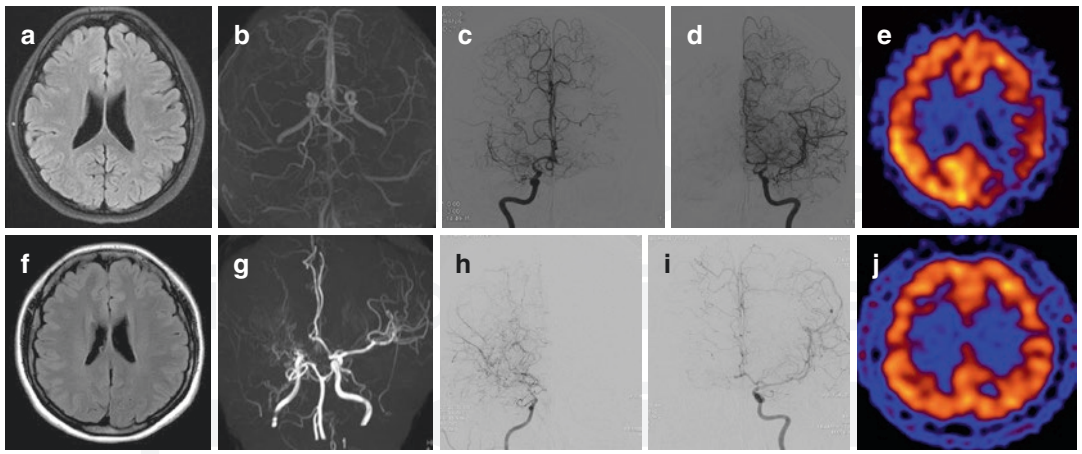

Fig. 11.4 Phenotype of moyamoya disease. Moyamoya disease manifests as various clinical and radiological phenotypes. Upper panel (**a**–**e**) indicates bilateral moyamoya disease. A 37-year-old woman complained of recurrent transient aphasia and right-sided weakness. FLAIR image (**a**) showed no abnormal lesions, but MRA (**b**) showed near occlusions of the bilateral MCAs. Conventional angiography (**c**, **d**) revealed complete occlusions of the bilateral MCA with distal reconstitution via basal collaterals. Brain SPECT (**e**) showed a significant reduction of blood flow in the left frontoparietal area. Lower panel (**f**–**j**) indicates a unilateral moyamoya disease. A-32-year-old woman presented with recurrent headache and dizziness. FLAIR image (**f**) showed no abnormal lesions, but MRA (**g**) showed near occlusion of right MCA. Conventional angiography (**h**, **i**) revealed occlusion of the right ACA and MCA with distal reconstitution via basal collaterals, and mild stenosis of the left proximal MCA and ACA. Brain SPECT (**j**) showed a slightly decreased blood flow in both frontal areas

ipsilateral stroke is 65% in the medically treated symptomatic cases and 82% in patients with bilateral symptoms of ischemia [22].

Histological findings of moyamoya disease include reduced outer diameters of the involved arteries, unregulated proliferation of smooth muscle cells and fibroblasts and migration into the intima, breakdown of the internal elastic lamina, intima thickening, and media thinning. Moyamoya vessels show fibrin deposits in the wall, fragmentation of elastic lamina, attenuated media, and microaneurysm, which are all prone to rupture. Various cerebrovascular diseases can display similar angiographic findings with conventional imaging techniques. Recently, high-resolution vessel wall MRI has provided some information for the differentiation of moyamoya disease from other arteriopathies. This imaging can more clearly visualize luminal stenosis associated with concentric negative remodeling. The most common vessel wall MRI findings for moyamoya disease are non-enhancing, negative-remodeling lesions without T2 heterogeneity [23]. Based on our study, moyamoya disease could be differentiated from atherosclerosis in that moyamoya disease shows more homogenous wall thickening with faint contrast enhancement, with more prevalent spring-like vascular structures around the stenotic area [24]. In another study, decreased wall area and remodeling index and concentric enhancement in the arteries at the circle of Willis were noted in moyamoya disease, whereas focal eccentric enhancement was noted in atherosclerotic lesions [25]. Diffuse concentric enhancement might indicate the hyperproliferation of smooth muscle cells and extracellular degradation by increasing levels of matrix metalloproteinase. The difference in the enhancement pattern between studies is likely due to the different ethnic populations at varying stages of the disease.

Despite diagnostic advancements, an etiologic answer cannot yet be given to patients with moyamoya disease. The symmetrical involvement feature of the disease suggests this arteriopathy may be genetically or developmentally determined. However, cerebral manifestations along without evidence of systemic involvement suggests a complicated genetic etiology. Approximately 10% of patients with moyamoya disease have a familial occurrence. Moyamoya disease is often inherited and several genetic mutations have been discovered. ACTA2 mutation has been suggested as the key mediator of vascular occlusion in familial moyamoya disease [26]. More recently, the ring finger 213 (RNF213) gene has also been suggested as a susceptible gene for moyamoya disease but with a low penetrance rate. Various RNF213 genetic variants have been robustly detected in Japanese moyamoya diseases [27] and in Caucasian and Chinese populations [28]. Polymorphisms in the MMP-3 gene and the TIMP-2 promoter gene have also been associated with familial moyamoya disease.

Alternatively, exposure to environmental factors in a critical period, such as maternal infection or inflammation, in genetically susceptible patients may trigger the vascular changes of moyamoya disease. Some epidemiological observations have indicated that infection during the early postnatal period may lead to the development of moyamoya disease, although no specific infective pathogens have been identified [29]. Immune-related factors have been involved in the anatomical changes of the vascular wall. Immunohistochemical studies of intracranial vessels from moyamoya patients display the aberrant expression of immunoglobulin G, alpha-smooth muscle actin (αSMA), and S100A4 protein in the vessel wall [30]. The proteins of αSMA and S100A4 are robustly detected in the thickened intima. IgG binds to the internal elastic lamina, deposits, and disrupts the internal elastic lamina. It is plausible that the damaged internal elastic lamina allows the S100A4-positive smooth muscle cells to migrate into the intima, proliferate, and result in luminal narrowing. This observation compels us to consider the influence of fetal environmental factors on the risk of moyamoya disease in the future. Maternally derived immunologic factors may affect the vessel wall integrity of the fetus. Given the female dominance and a higher association with maternal moyamoya disease, there seems to be a fetal environmental exposure resulting in an increased

risk of moyamoya disease rather than a heritable factor, although mitochondrial or X-linked inheritance remains a theoretical possibility. On the other hand, there exists a link between moyamoya disease and autoimmune disease, including Graves's disease, diabetes mellitus, and systemic lupus erythematosus, supporting the contribution of an autoimmune component of moyamoya disease.

There are several lines of mediators implicated in the pathophysiology of moyamoya disease. Growth factors have been implicated as a pathogenetic contributor to smooth muscle cell migration and intima thickening. Various growth factors including basic fibroblast growth factor, cellular retinoic-acid-binding protein I (CRABP-1), and hepatocyte growth factor are robustly detected in the cerebrospinal fluid of patients with moyamoya disease [31]. Overexpression of MMP-9 and the reduced expression of MMP-3, TIMP-1, and TIMP-2 in moyamoya disease are thought to be involved in the concentric remodeling process. However, these growth factors might also mediate the formation of moyamoya vessels during the disease course. Cytokines including vascular-cell adhesion molecule type 1, intercellular adhesion molecule type 1, and E-selectin enhance the vasculo-proliferative process. Circulating endothelial progenitor cells have been involved in the disease course and progression. Indeed, endothelial progenitor cell function is impaired and their levels are increased or decreased according to the different stages of moyamoya disease [32]. In addition, smooth muscle progenitor cells derived from the blood of patients with moyamoya disease were characterized by unique features that differed from those of healthy subjects, such as irregularly arranged and thickened tubules and altered gene expression [33].

The predilection for particular regions of the intracranial vasculature of moyamoya disease may be primarily explained by hemodynamic stress on the vessel. The vessels are more vulnerable to hemodynamic stress at the site of vascular branching, where the flow is substantially fast and branches are in an acute angle. Moreover, moyamoya disease dynamically changes the geometrical parameters of the diseased vasculature. Elevated wall shear stress at the non-occluded lesions is associated with moyamoya disease progression and an increased risk of vascular events [34]. In addition, the dynamic changes of arteriogenesis can cause a local increase in wall shear stress, which may be associated with aneurysm formation and rupture. In contrast, the magnitude of wall shear stress at the near-occluded lesions is considerably lower, making the vessels more susceptible to occlusion. Under the low level of shear stress during concentric negative remodeling, endothelial cells increase the genes related to cell growth and thrombosis. A detailed evaluation of shear stress may assist in predicting the progression of moyamoya disease.

11.4.2 Cerebral Artery Dissection

The extracranial segments of the cerebral arteries are more susceptible to dissection than the intracranial segments because they are more frequently exposed to injury by bony structures such as the vertebrae and styloid processes in association with the high mobility and the wide directional changes of the vessels [35]. As previously mentioned, the intracranial arteries have no external elastic lamina and have an attenuated tunica media where the elastic fibers are only one-third as thick as the extracranial artery, and the majority of elastic fibers are located in an internal elastic lamina. Since there is so little tissue buffering the changes in mechanical strength, intracranial arterial dissections show a higher rate of subarachnoid hemorrhage than do extracranial dissections, constituting about 50–60% of all reported series of intracranial artery dissection. Collectively, the dissections of the intracranial artery and cervical artery have different mechanisms, symptoms, and outcomes. In terms of intracranial artery dissection, the risk factors and the predisposing conditions are also unknown. There are only small case series of intracranial artery dissection in association with trauma and rare genetic disorders. Further studies of intracranial artery dissection are required to provide a firm link between wall fragility and

hemodynamics and dissection. In this section, we focus on dissection at the cervical level, which is of greater clinical impact.

Cervical artery dissection is defined as the splitting of the carotid and vertebral artery wall. It is rare, accounting for about 2% of all ischemic strokes, though it constitutes 20% of incidences of ischemic stroke in young adults [36]. The internal carotid artery is 3–5 times more affected than the vertebral artery. Cervical artery dissection occurs equally by sex, but females show more frequent involvement of the vertebral artery and multiple vessels. About 85% of cases of cervical artery dissections manifest as transient ischemic attack or stroke, whereas the minor manifestations include headache, neck pain, cranial nerve palsy, and Horner's syndrome [37]. The ischemic events essentially result from thromboembolic or hemodynamic mechanisms, and severe stenosis or occlusions are more likely to be associated with ischemic events than are cases without steno-occlusion. Aneurysmal dilatation is associated with cervical artery dissection in about one-third of cases, and cervical artery dissection is occasionally associated with subarachnoid hemorrhage when the dissection extends to the intradural segment of the vessel. Although neck trauma or strenuous exertion can cause cervical artery dissection, the majority of cervical artery dissection occurs spontaneously. Occasionally, cervical artery dissection presents with minor trauma histories associated with hyperextension, rotation, or lateroversion of the neck. Various clinical situations that increase shear stress, such as hypertension, systemic inflammation, and peripartum cardiomyopathy can also increase the risk of cervical artery dissection. The dissection of the internal carotid artery occurs most frequently 2–3 cm from the bifurcation and rarely extends over the petrous bone. Vertebral artery dissection typically occurs at the V2/V3 junction where the arteries emerge from the axis vertebra and suddenly curve to enter the cranium. Vertebral artery dissection can also involve the V1 portion of the vertebral artery, since the vertebral artery is highly mobile until reaching the intervertebral foramen at C5 or C6. The dissection in the V4 portion of vertebral artery may extend to the intracranial segment. Neck pain, history of chiropractic procedure, and bilateral involvement are more common in patients with vertebral artery dissection than in those with carotid artery dissection [37].

CT angiography, TOF-MRA, and MRA with gadolinium infusion are considered sensitive techniques for the diagnosis and follow-up of cervical artery dissection. The main angiographic patterns of dissection include stenosis, occlusion, and aneurysmal dilatation (Fig. 11.5). Conventional angiography is the gold standard in imaging for cervical artery dissection, but it is only considered when endovascular intervention is anticipated owing to its invasiveness. MRA and conventional angiography are greatly limited in that they reveal only indirect signs such as a tapered vessel or aneurysms. Recent advances have been made by the use of high-resolution MRI that enables the high-quality imaging of large vascular walls. Vessel wall imaging may yield the pathognomonic findings of arterial dissection, such as an intramural hematoma or a double lumen in the damaged artery. The clinical course of cervical artery dissection is highly variable, which complicates the physician's process of selecting a therapeutic strategy. Overall, patients have a 0.3% rate of symptomatic dissection recurrences per year after the first cervical artery dissection event [38]. Patients with connective tissue disease or family history would account for the majority of the recurrences. Most steno-occlusive lesions re-canalize within weeks or months; however, some may persist in 10–20% of patients, and recanalization of cervical artery dissection is mainly achieved within the first 6 months after dissection. Apart from neurological deficits incurred by incident stroke, the long-term prognosis of cervical artery dissection is fairly good. Large, multicenter studies including the CADISS trial (Cervical Artery Dissection in Stroke Study) and the CADISP study (Cervical Artery Dissection and Ischemic Stroke Patients) showed a stroke recurrence rate of 2–3% at 3 months, with all recurrences occurring within the 2 weeks after onset [39–41]. The natural history of dissection depends on the initial angiographic features. The dissections with

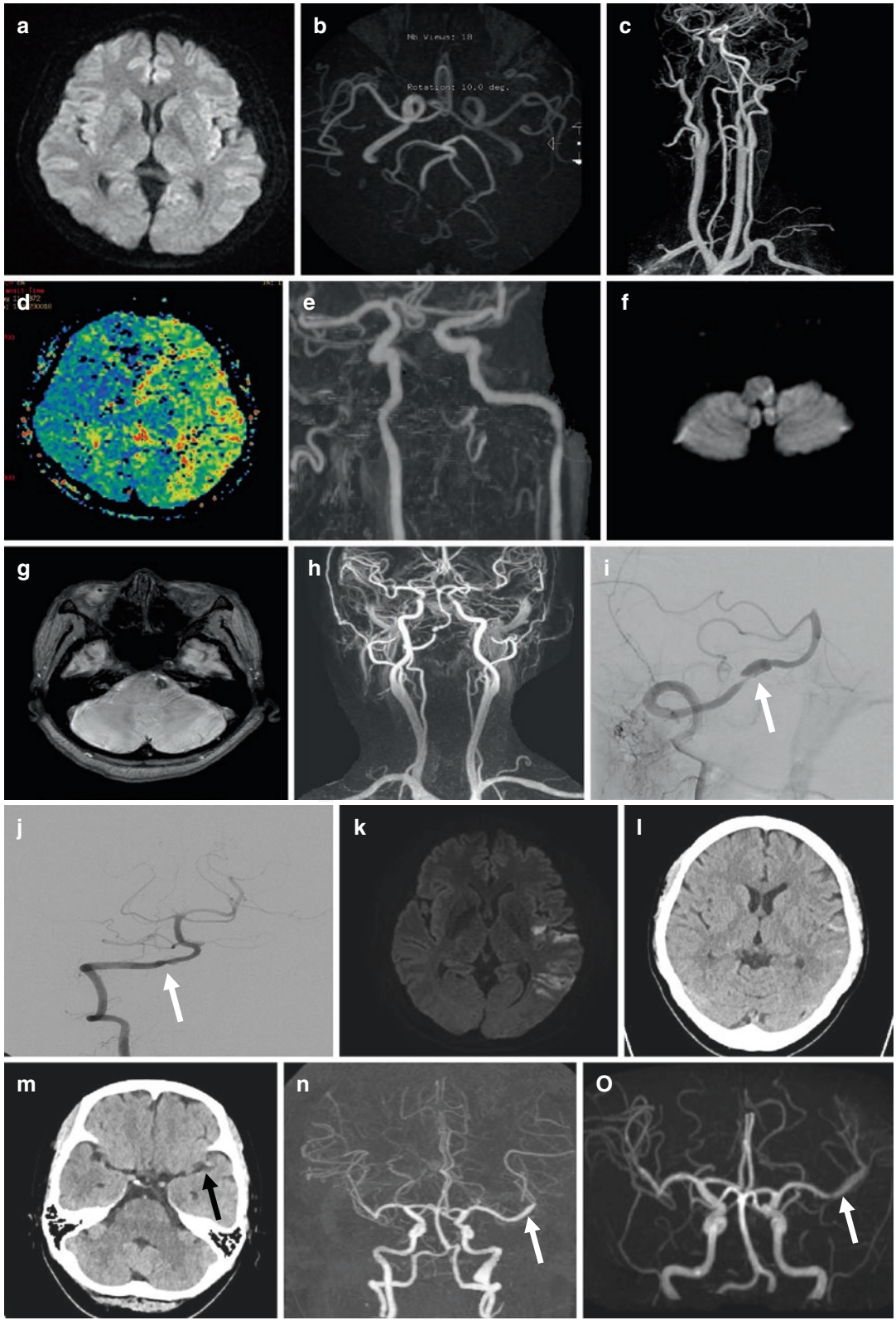

Fig. 11.5 Phenotype of cervical artery dissection. Cerebral artery dissection occurs in various segments of the cervical and intracranial arteries. Images (**a**–**e**) indicates a carotid artery dissection. A 45-year-old man experienced a transient right-sided weakness. DWI (**a**) showed no abnormal lesions, but MRA (**b**, **c**) showed a severe stenosis of long segment of the left carotid artery. PWI (**d**) showed a perfusion delay in the left MCA territory. Follow-up MRA (**e**) revealed a significant resolution of the dissected carotid artery. Images shows a vertebral artery dissection (**f**–**j**). DWI (**f**) shows a lateral medullary infarction, and SWI shows acute thrombus in the distal left vertebral artery. MRA (**h**) and conventional angiography (**i**) showed severe stenosis of the bilateral vertebral arteries and dissecting aneurysm in the right distal vertebral artery (white arrow). Follow-up MRA (**j**) showed an improvement of stenosis and aneurysmal dilatation. Images (**k**–**o**) indicates a case of intracranial artery dissection. DWI (**k**) shows a left MCA infarction, and brain CT (**l**, **m**) showed subarachnoid hemorrhage and intramural hematoma (black arrow) in the left MCA. MRA (**n**) revealed a severe stenosis of the left distal MCA (white arrow), and follow-up MRA (**o**) showed a recannalization of left MCA but with a mild dilatation

arterial occlusion are most significantly associated with a poor outcome, whereas those with aneurysm and mildly stenotic features have favorable outcomes [42]. In general, patients with dissecting aneurysms carry a very low risk of clinical complications and good anatomic outcomes [42]. Therapeutic strategies include antiplatelet agents or anticoagulants and, occasionally, invasive treatments such as endovascular procedures. These options confer some risks, which must be applied by balancing harm and benefit and predicting the probable natural history. Antithrombotic therapy may no longer be required once the flow in the dissected artery has been restored.

Cervical artery dissection is relatively uncommon in the very elderly, possibly because of arterial stiffening or accumulating atherosclerosis during the aging process. Indeed, some age-related risk factors are negatively associated with arterial dissection. Lipid accumulation in the vessel wall and decreased compliance may change a weak artery into a resistant artery. Considering that females have more frequent vertebral artery dissection and occurrences of multiple dissections, sex hormones may contribute to the arteriopathies. It has been reported that hormones affect the integrity of vessel walls by changing collagen deposition, matrix metalloproteinases, and arterial compliance [15]. While there is no convincing evidence that the conventional vascular risk factors are related to the dissection, migraine is highly associated with patients with this disorder. Although the underlying mechanisms are unknown, there are a variety of overlapping genetic polymorphisms between migraine and arterial dissection, suggesting a common genetic predisposition. Migraine is also associated with a higher level of serum elastase activity, which usually indicates extracellular matrix degradation.

In terms of the pathophysiology of cervical artery dissection, it has been histologically proven that intima tears cause the luminal blood to burst subintimally, leading to intramural hematoma (Fig. 11.6). An alternative pathway is that the sudden intramural hematoma results from the rupture of the vasa vasorum from intrinsic factors. The pathological changes associated with cervical artery dissection primarily include the fragmentation of the elastic lamellae, focal loss of smooth muscle cells, accumulation of proteoglycans, and blood in the border of the media and adventitia. It is generally accepted that cervical artery dissection results from the interaction of a genetically determined frailty of the vessel wall and acquired factors such as minor trauma, blood dyscrasia, and infection. A significant association between the MTHFR 677TT genotype and cervical artery dissection has been noted. An association between cerebral artery dissection and connective tissue diseases, such as Marfan syndrome, neurofibromatosis type 1, Ehlers–Danlos syndrome, and Loeys–Dietz syndrome has also been suggested [43]. Connective tissue disorders usually involve dissections of multiple vessels, which favor the link between cervical artery dissection and underlying arteriopathy. However, a multifactorial genetic predisposition more frequently underlies the pathogenesis of cervical artery dissection as opposed to a single genetic disorder. The geneti-

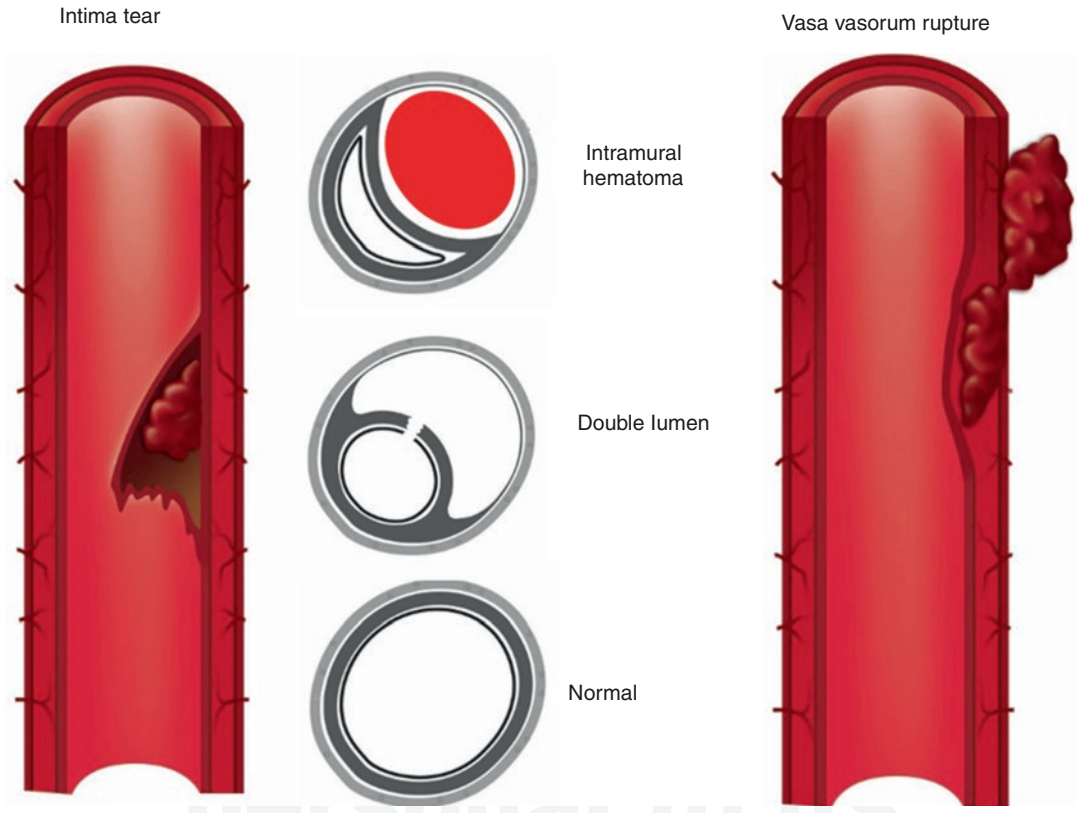

Fig. 11.6 Pathophysiology of cervical artery dissection

cally determined conditions prone to dissection share the pathogenetic feature of tunica media degeneration. An electron microscopy study of the skin of patients with cervical artery dissection displayed pieces of evidence of underlying connective tissue orders in 50%, while only 3% showed clinical manifestations [44]. In addition, cervical artery dissection commonly presents with aortic-root dilation, intracranial aneurysm, and arterial redundancies (kinks, coils, or loops) [45]. The abnormal development of neural crest-derived cells in the tunica media of the cervical and intracranial arteries is highly associated with dissection at multiple levels of the cerebral arteries. Thus, the patients with proven cervical artery dissection need extensive investigation for the underlying connective tissue disease. Shear stress is a strong trigger for the development of cervical artery dissection in predisposed individuals. Shear stress on the cervical arteries is highest at 90° of lateral rotation or 45° of rotation with neck extension [46]. Dissection induces complex flow patterns in vessels with distinct geometric properties, which might play a considerable pathophysiological role in the development, recurrence, and healing of the disease. As previously mentioned, the wall shear stress stabilizes vascular integrity and promotes remodeling. The wall shear stress might confer an adaptive role by inhibiting the growth of intimal tears, expansion of mural hematoma, and formation of luminal thrombi during the acute phase, eventually promoting anatomical recanalization. In contrast, minimal or no flow impairs arterial remodeling and reversibility, which is associated with a poor functional outcome. It was recently determined that the initial absence of antegrade flow reduces the likelihood of complete recanalization with a poor long-term outcome [42].

11.4.3 Primary Central Nervous System Vasculitis

Central nervous system (CNS) vasculitis is a heterogenous disease entity with the hallmarks of inflammation and destruction of cerebral arterial walls. It can be divided into primary CNS vasculitis and CNS vasculitis secondary to a systemic condition. In this section, we provide an overview of the primary type of CNS vasculitis. Primary CNS vasculitis is a rare inflammatory disease of unknown origin involving the medium-sized vessels of the brain and spinal cord [47]. The incidence peaks at 50 years affecting men and women equally. Neurological symptoms and signs are nonspecific and extremely variable according to the involved vessels and brain regions. Multi-territorial and bilateral acute stroke is the most common pattern found on MRI, while patients may experience recurrent strokes or diffuse progressive encephalopathy. Primary CNS vasculitis should be suspected in the setting of strokes of unknown causes with abnormal angiography. Widely adopted diagnostic criteria include the presence of neurologic or psychiatric symptoms, typical angiographic or histopathological features of vasculitis within the CNS, and exclusion of other mimicking diseases.

The common diagnostic tool for primary CNS vasculitis is a conventional cerebral angiography, while the gold standard for the confirmatory diagnosis of primary CNS vasculitis is cerebral and meningeal biopsy. Typical angiographic findings include segmental stenosis and dilatation of multiple mid-sized arteries in both hemispheres (Fig. 11.7). However, the sensitivity and specificity of angiographic findings are not optimal and it is unclear whether angiographic findings are well correlated with those from cerebral biopsy. In pathologically proven cases of primary CNS vasculitis, angiography was found to have a sensitivity and specificity of only about 30%. The low sensitivity is probably because a significant proportion of primary CNS vasculitis involves the distal segment of cerebral arteries below its spatial resolution. The advance in neuroimaging holds promise for differentiating primary CNS vasculitis from other non-inflammatory conditions. The advent of high-resolution MRI for the intracranial arteries may help to differentiate CNS vasculitis from other vasculopathies. In patients with multiple arterial stenoses, the enhancement of the arterial wall with gadolinium is more prominent in primary CNS vasculitis than in other mimicking arteriopathies [23, 48].

Given the non-specificity of cerebral angiography, patients with suspected primary CNS vasculitis should undergo biopsy. The biopsy provides essential information for identifying vasculitis and also in evaluating infectious and neoplastic diseases. In contrast, cerebral biopsy is not generally indicated in cases of negative angiography because conventional cerebral angiography is associated with a high negative predictive value for primary CNS vasculitis. Since primary CNS vasculitis involves vessels in a skipped and segmental pattern, the sensitivity is low with a false negative rate of 25% and a negative biopsy does not rule out the likelihood of CNS vasculitis. Thus, the site for biopsy should be carefully selected so that areas of radiological abnormalities and meningeal sampling are targeted. For tissue biopsy, open-wedge biopsy of a radiologically positive lesion is recommended to increase the biopsy efficiency. Typical histological findings include granulomatous vasculitis with vasculocentric mononuclear inflammation, diffuse lymphocytic vasculitis with occasional plasma cells, and necrotizing vasculitis characterized by transmural fibrinoid necrosis in the leptomeningeal and parenchymal arteries (Fig. 11.8) [49]. The intracranial arteries usually undergo stenosis or occlusion by thrombosis and inflammation in the vessel wall. The lesion is often accompanied by hemorrhagic transformation or hemorrhagic complications such as subarachnoid hemorrhage. The mechanism by which blood leaks into the subarachnoid space is not well understood, though the interaction between the inflammatory vascular lesion and ischemia reperfusion secondary to steno-occlusion is involved in this complication. The pathogenesis of primary CNS vasculitis is also not fully under-

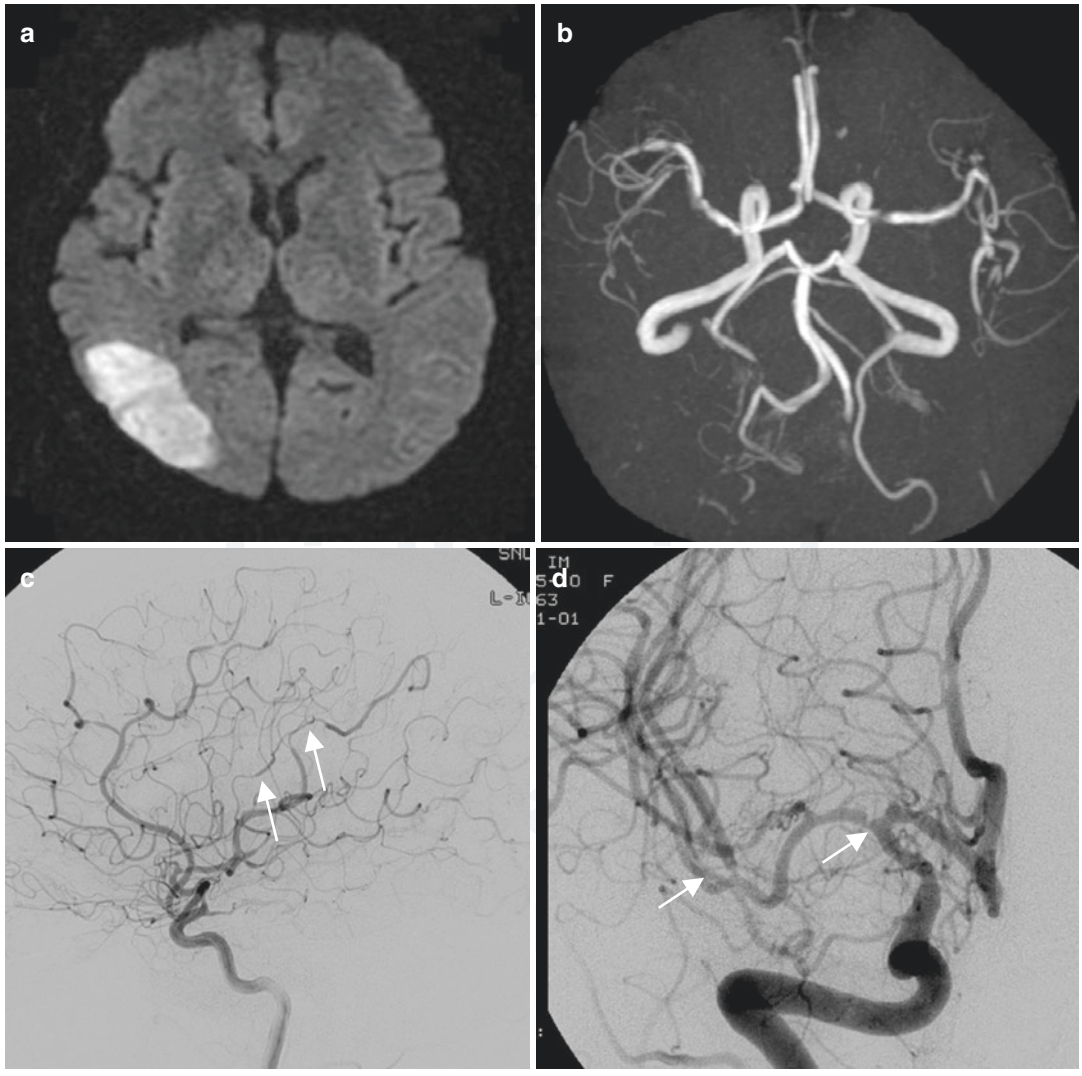

Fig. 11.7 Phenotype of primary CNS vasculitis. A 58-year-old woman visited us because of a sudden visual disturbance. She has no specific history suggestive of systemic vasculitis. DWI (**a**) showed an infarct in the right temporo-occipital area. MRA (**b**) showed a multiple segmental stenosis in the intracranial arteries. Conventional angiography (**c**, **d**) showed beaded patterns of stenosis in multiple intracranial arteries (white arrows). The clinical and angiographic phenotypes were well-controlled with immunosuppressive agents

stood. No clear genetic links have been noted in adult patients with the disease, and although the immunologic triggers have not been clearly identified, certain types of viral or mycobacterial organisms may contribute to the initiation of inflammatory cascades. The presence of memory T cells deposited in the vessel wall may represent the evidence of a cross-reaction to similar epitopes [50]. As reported in animal models of vasculitis, MMP 9 may play a primary role in the destruction of the vessel wall.

The low incidences of this disease entity and the lack of specific laboratory markers for diagnosis prompt consideration of a wide range of differential diagnoses. Radiological mimics of primary CNS vasculitis include reversible cerebral vasoconstriction syndrome (RCVS), infectious vasculitis, CNS manifestations of sys-

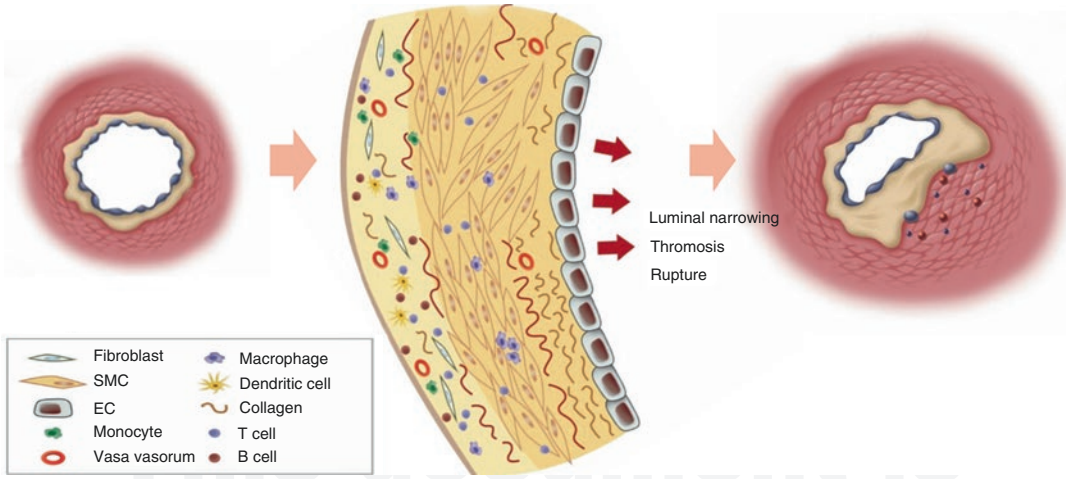

Fig. 11.8 Pathophysiology of primary CNS vasculitis. *EC* endothelial cell, *SMC* smooth muscle cell

temic vasculitis, and neoplastic conditions. The most common differential diagnosis is atherosclerotic disease. Atherosclerotic disease is more proximal, more eccentric, and involves shorter segments as compared to vasculitic lesions. RCVS is a noninflammatory vasoconstrictive syndrome characterized by severe headache and sometimes focal or diffuse neurologic signs. Cerebrospinal fluid analysis, which is essential for the differential diagnosis of the two diseases, generally shows findings of aseptic meningitis in primary CNS vasculitis and helps to exclude RCVS. Angiographic abnormalities are more diffuse in RCVS than in primary CNS vasculitis, and they typically resolve within 8–12 weeks. The convexity subarachnoid hemorrhage is present in 25% of patients with suspected primary CNS vasculitis [51]. This rate is comparable to the magnitude found in RCVS. However, the higher association with leptomeningeal enhancement supports the higher likelihood of a diagnosis of primary CNS vasculitis [52]. Vasculitis is a common mechanism of cerebrovascular complications mediated by infectious pathogens. Vasculitis arises from direct invasion of the pathogen itself or of inflammatory cells into the vessel wall, or indirectly by chemical stimulation of inflammatory exudates in the subarachnoid space. Infiltrative vasculitis occurs inward from the adventitia and is prominent in the large- and medium-sized arteries in the circle of Willis. Infectious pathogens that are most frequently associated with vasculitis are pyogenic bacteria, tuberculosis, *Treponema pallidum*, *Borrelia burgodorferi*, human immunodeficiency virus, hepatitis B and C virus, varicella zoster virus, cytomegalovirus, and Cryptococcus. Varicella zoster virus (VZV) is one of the more important pathogens linked to CNS vasculitis; therefore, cases of suspected primary CNS vasculitis should be evaluated for VZV vasculopathy. Infectious vasculopathy can be excluded by thorough microbiological testing of the cerebrospinal fluid. On the other hand, CNS vasculitis associated with systemic autoimmune diseases should also be differentiated from primary CNS vasculitis. Behcet's disease, systemic lupus erythematosus, Sjogren syndrome, and sarcoidosis can mimic all aspects of primary CNS vasculitis. Constitutional symptoms, systemic organ dysfunction, and elevation of acute phase reactants in serum suggest the presence of systemic disease rather than primary CNS vasculitis. Primary CNS vasculitis is a distinct disease entity from CNS vasculitis of other causes in that it rarely involves systemic organs or alteration of systemic inflammatory markers. Furthermore, primary CNS autoimmune disease such as NMDAR encephalitis may mimic the clinical presentation of primary CNS vasculitis. In the clinical setting, neuronal antibody testing should be performed. The radiological findings may be similar to intravas-

cular lymphoma or primary CNS lymphoma. Brain biopsy is mandatory to clinically distinguish the two disease conditions. Since the disease responds well to immunosuppressive therapy, early clinical suspicion is critical. Failure of immunotherapy should prompt reevaluation for an alternative diagnosis such as a neoplastic disorder, infection, systemic autoimmune disease, and reversible vasoconstriction syndrome.

11.5 Future Directions

Moyamoya disease, arterial dissection, and CNS vasculitis are radiologically similar arteriopathies with distinct pathophysiologies in relation to the degeneration and remodeling processes of the arterial wall. Enriched epidemiological observations and advanced imaging and laboratory profiles have enhanced our knowledge of the similarities and differences between the cerebral vessel wall diseases. Further investigation is necessary to determine the master switch and elucidate the downstream phenomenon in each disease. In the context of shared pathophysiology, small vessel disease is currently recognized as encompassing lacunes, microbleeds, and leukoaraiosis. This strategy can also be applied to the cerebral vessel wall diseases. Comprehensive multi-panel assays with high-throughput genetic or immunologic tests would offer the opportunity to classify cerebral vessel wall diseases as mechanical, inflammatory, autoimmune, or degenerative conditions.

Prompt diagnosis is necessary to improve the long-term outcome of patients with cerebral vessel wall diseases. Each cerebral vessel wall disease requires a distinct therapeutic approach. In moyamoya disease, hemodynamic support by direct or indirect bypass surgery may be helpful to prevent future ischemic events. Cervical artery dissection is usually treated using anticoagulant or antiplatelet agents, but occasionally by endovascular treatment, while various regimens of immunosuppressive therapy have been applied for CNS vasculitis. We are still in the early stages of optimizing the management of these cerebral vessel wall diseases. There is a need for an enhanced understanding of the therapeutic targets before the optimal treatment is achieved for each condition. In order to establish more effective therapeutic targets, we need to better comprehend the underlying pathophysiology and the shared associations among all the cerebral vessel wall diseases. Data regarding the natural history and genetic and molecular signatures associated with disease development should be accumulated based on the findings of large prospective multicenter cohorts. In addition, more histopathological data should be obtained with optimal targets and methods. Developments and applications of new vessel wall imaging techniques in conjunction with pathological data would enable the clear characterization of lesions with respect to injury type, injury extent, and vulnerability to thrombosis or rupture.

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