5 Pathophysiology of Stroke Resulting from Large-Artery Atherothrombosis

Jae Guk Kim and Soo Joo Lee

Abstract

Atherosclerosis is the most common cause of the local disease within the large extracranial and intracranial arteries that supply the brain. Cerebral infarction due to large-artery atherothrombosis primarily caused by rupture of the plaque, thrombus formation, occlusion, and hypoperfusion. The atherosclerotic plaque that is easy to rupture consists of a lipid core, an intra-plaque hemorrhage, and thin fibrous capsule. The atherothrombotic lesion in large extracranial and intracranial arteries cause symptoms by reducing blood flow beyond obstructive lesions, and by serving as the source of intra-arterial emboli. The cerebral infarction varies according to the stability, the location of the plaque, and the degree of the stenotic vessel. Occasionally, the atherosclerotic plaque at the entrance of the penetrating artery gradually becomes larger and may cause occlusion. The atherothrombotic strokes of large artery can be divided into four mechanisms as follows: in situ thrombosis, artery-to-artery embolism, hemodynamic infarct, and branch atheromatous disease. The ischemic strokes can be expressed in two or more complex mechanisms, not actually one.

5.1 Introduction

Atherosclerosis is the most common cause of in situ arterial disease within the extracranial and intracranial arteries that supply the brain. White platelet-fibrin and red erythrocyte-fibrin thrombi are often superimposed upon the atherosclerotic lesions, or they may develop without severe vascular disease in patients. The atherothrombotic lesions in cervical and cerebral large arteries cause symptoms by reducing blood flow beyond obstructive lesions, and by serving as the source of intra-arterial emboli. At times a combination of mechanisms is working. Severe stenosis can promote the formation of thrombi which can break off and cause embolization, and the reduced blood flow caused by the arterial obstruction makes the circulation less competent at washing out and clearing these emboli [1].

Thrombosis refers to obstruction of a blood vessel due to in situ occlusive process within a blood vessel. The obstruction may occur acutely or gradually. In many cases, underlying pathology such as atherosclerosis may cause narrowing of the diseased vessel [2]. This may lead to restriction of blood flow gradually, or in some cases, platelets may adhere to the atherosclerotic

J. G. Kim · S. J. Lee (✉)
Department of Neurology, Eulji University Hospital,
Eulji University School of Medicine,
Daejon, Republic of Korea
e-mail: sjoolee@eulji.ac.kr

S.-H. Lee (ed.), *Stroke Revisited: Pathophysiology of Stroke*, Stroke Revisited,
https://doi.org/10.1007/978-981-10-1430-7_5

plaque forming a clot leading to acute occlusion of the vessel. Identification of the specific localized vascular lesion, including its nature, severity, and localization, is important for treatment because specific therapy may be effective (e.g., surgery, angioplasty, intra-arterial thrombolysis). In most patients, it should be possible clinically to determine whether the local vascular disease is within the carotid or vertebral-basilar circulation and whether the disorder affects large or small penetrating arteries. Delivery of adequate blood due to a blocked or partially blocked artery depends upon many factors, including blood pressure, blood viscosity, and collateral blood flow. Local vascular lesions also may throw emboli off, which can cause transient symptoms. In patients with thrombosis, the neurologic symptoms often fluctuate, remit, or progress in a stuttering pattern. Although the formation of atherothrombotic plaque must be a long and gradual process over many years, the clinical symptoms usually occur acutely and tend to cluster in time. For example, stroke tend to occur sooner after transient ischemic attack rather than later, perhaps as a result of recent breakdown and instability of atherothrombotic plaque [3, 4].

Occlusion secondary to atheromatous plaque occurs by three mechanisms. First, thrombus may occur on atheroma lesions that cause in situ occlusion. Second, embolization of a part of plaque and thrombi may occlude more distal arteries. Third, the origin of small artery may be blocked by the growth of plaque in the parent of artery. In the other situation without occlusion, when atheromatous plaque growth cause severe stenosis of arterial lumen and hypoperfusion of distal brain region, that may lead to hemodynamic (watershed) infarction following severe hypotension or hypoxia. The atherothrombotic stroke of large artery can be summarized in the following four mechanisms: in situ thrombosis, artery-to-artery embolism, hemodynamic infarct, and branch atheromatous disease [1]. The ischemic strokes can be often expressed in two or more complex mechanisms, not actually one (e.g., hemodynamic failure and arterial-artery embolism, or atherosclerosis and arterial-artery embolism).

5.2 Territorial Infarct

Knowledge of the vascular territories is important, because it enables you to recognize infarctions in arterial territories, in watershed regions and also venous infarctions. It also helps you to differentiate infarction from other pathology.

The intracranial circulation can be divided into anterior and posterior circulation, on the basis of internal carotid artery and vertebral artery supply respectively [1]:

- Anterior circulation (carotid artery territory)
  - Anterior choroidal artery
  - Anterior cerebral artery (ACA)
    - Medial lenticulostriatal arteries
  - Middle cerebral artery (MCA)
    - Lateral lenticulostriatal arteries
- Posterior circulation (vertebral artery territory)
  - Posterior cerebral artery (PCA)
  - Basilar artery
  - Superior cerebellar artery (SCA)
  - Anterior inferior cerebellar artery (AICA)
  - Posterior inferior cerebellar artery (PICA)

The presence of acute infarction with stenosis or occlusion of the relevant artery is essential for diagnosis of infarct resulting from large-artery atherothrombosis. Since the original TOAST classification scheme was developed in the early 1990s, advances in stroke evaluation and diagnostic imaging have allowed more frequent identification of potential vascular and cardiac causes of stroke. An evidenced-based modification of the TOAST criteria called SSS-TOAST was developed [5]. The SSS-TOAST system divides each of the original TOAST subtypes into three subcategories as “evident,” “probable,” or “possible” based upon the weight of diagnostic evidence as determined by predefined clinical and imaging criteria. In a further refinement, an automated version of the SSS-TOAST called the Causative Classification System (CCS) was devised to improve its usefulness and accuracy for stroke subtyping [6].

In this classification criteria of cerebral infarction commonly used in clinical practice [6],

atherothrombotic stroke of large artery becomes evident when the following criteria are met; (1) either occlusive, or stenotic (≥50% diameter reduction or <50% diameter reduction with plaque ulceration or thrombosis or plaque with ≤50% diameter reduction that is seated at the site of the origin of the penetrating artery supplying the region of an acute lacunar infarct) vascular disease judged to be due to atherosclerosis in the clinically relevant extracranial or intracranial arteries. (2) The absence of acute infarction in vascular territories other than the stenotic or occluded artery (Table 5.1).

Table 5.1 Causative classification system (CCS) of ischemic stroke etiology: diagnostic criteria of large-artery atherothrombotic stroke

Level of confidence	Criteria
Evident	1. Either occlusive or stenotic (≥50% diameter reduction or <50% diameter reduction with plaque ulceration or thrombosis) vascular disease judged to be caused by atherosclerosis in the clinically relevant extracranial or intracranial arteries, and 2. The absence of acute infarction in vascular territories other than the stenotic or occluded artery.
Probable	1. History of ≥1 transient monocular blindness (TMB), TIA, or stroke from the territory of index artery affected by atherosclerosis within the last month, or 2. Evidence of near-occlusive stenosis or non-chronic complete occlusion judged to be caused by atherosclerosis in the clinically relevant extracranial or intracranial arteries (except for the vertebral arteries), or 3. The presence of ipsilateral and unilateral internal watershed infarctions or multiple, temporally separate, infarctions exclusively within the territory of the affected artery
Possible	1. The presence of an atherosclerotic plaque protruding into the lumen and causing mild stenosis (<50%) in the absence of any detectable plaque ulceration or thrombosis in a clinically relevant extracranial or intracranial artery and history of ≥2 TMB, TIA, or stroke from the territory of index artery affected by atherosclerosis, at least 1 event within the last month, or 2. Evidence for evident large-artery atherosclerosis in the absence of complete diagnostic investigation for other mechanisms

Source: Ay H, Benner T, Arsava EM. A computerized algorithm for etiologic classification of ischemic stroke: the causative classification of stroke system. Stroke 2007; 38:2979 [6]

5.3 In Situ Thrombosis and Artery-to-Artery Embolism

In Situ Thrombosis Atheromatous plaque may promote platelet adhesion, activation, and aggregation, which can stimulate the blood coagulation pathway and produce mural thrombus form an early stage [2]. The atheroma and atherothrombotic plaque gradually grows because of repeated event of mural thrombosis layering one on top of the other, finally the arterial lumen may be occluded. The intraluminal thrombus can then propagate to the proximal portion of artery or distal portion of the artery. But it usually propagates no further than the next branching point of the artery. The balance of pro-thrombotic and anti-thrombotic factors may determine whether a thrombus superimposed on atheromatous plaque or an occlusive embolus grows, lysed or become incorporated into the arterial wall and produce the gradually enlarging atherothrombotic plaque. As with acute myocardial infarction, it is not uncommon to have a severe cerebral infarction due to cervical carotid artery occlusion. The rupture of an unstable atherosclerotic plaque results in a fatal occlusion. However, symptomatic acute in situ atherothrombotic occlusion rather than artery-to-artery embolism does not often appear as a cause for ischemic stroke or transient ischemic attack in the carotid system. For example, internal carotid artery can be better observed than middle cerebral artery (Figs. 5.1, 5.2, and 5.3). This may be because atheroma affects the larger arteries and it take a very large plaque to occlude them or because the collateral blood flow is better distal to larger arteries [7, 8]. In situ thrombotic occlusion is not common in other intracranial arteries. Because intracranial arterial stenosis progresses for a long time and collateral blood

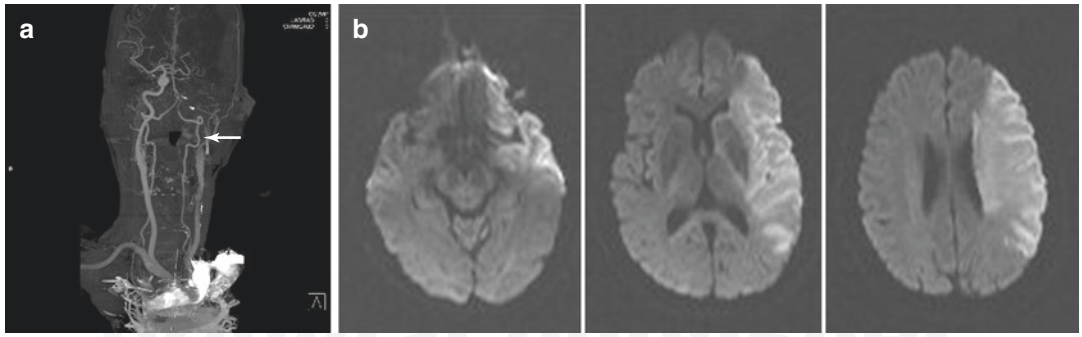

Fig. 5.1 In situ thrombosis, internal carotid artery (ICA). (**a**) Occlusion of left proximal ICA on CT angiography. (**b**) Acute infarct of insular and striatocapsular region, frontotemporal cortex and subcortical white matter area on diffusion-weighted image

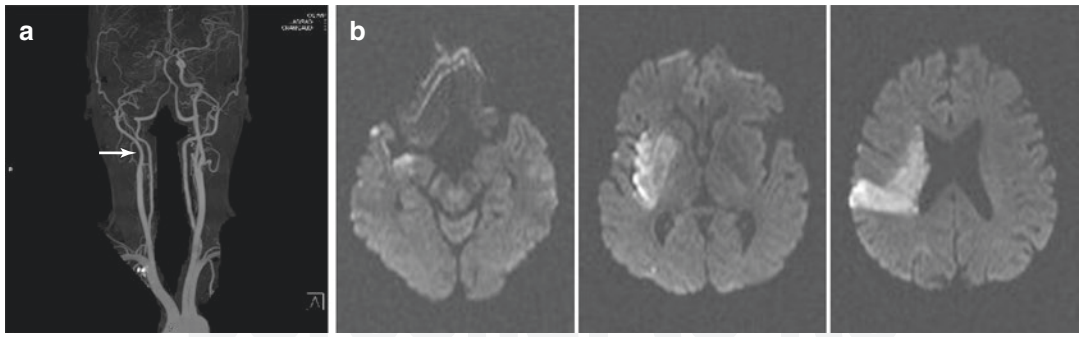

Fig. 5.2 In situ thrombosis, internal carotid artery (ICA). (**a**) Occlusion of right proximal ICA with faintly visible right distal ICA on CT angiography. (**b**) Acute infarct of insular, basal ganglia, and some frontotemporal cortex on diffusion-weighted image

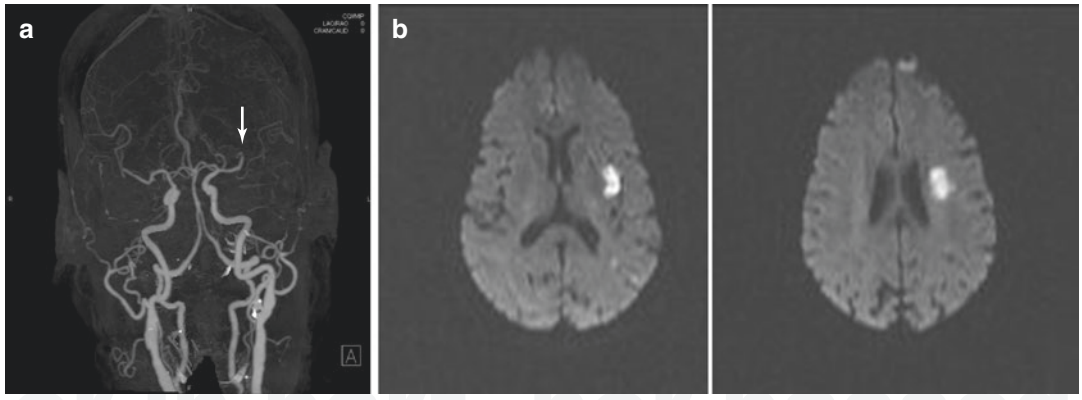

Fig. 5.3 In situ thrombosis, middle cerebral artery (MCA). (**a**) Occlusion of left MCA (M1) on CT angiography. (**b**) Acute infarct of insular and striatocapsular region on diffusion-weighted image

flow is well developed, cerebral infarcts involving whole area of the arterial territory usually occur in the rare. Infarcts usually occur in deep areas such as striatocapsular or border zone area. Symptoms are also mild and may appear as TIA. On the other hand, in situ atherothrombotic occlusion may be more common in the posterior circulation such as basilar artery but even here

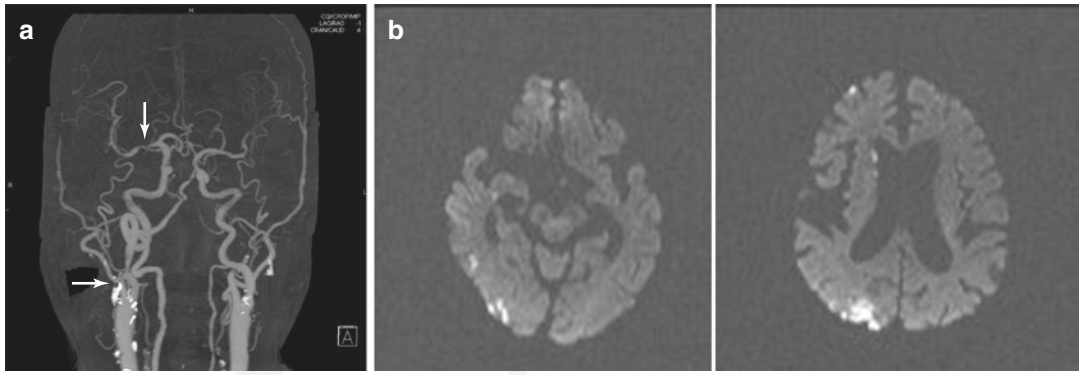

Fig. 5.4 Artery-to-artery embolism. (**a**) Severe stenosis at right ICA and focal stenotic lesion of MCA on CT angiography. (**b**) Acute scattered infarct of right occipitotemporal area and small frontal cortex on diffusion-weighted image

artery-to-artery embolism is also often found. Figures 5.1, 5.2, and 5.3 show cases with in situ thrombosis.

Artery-to-Artery Embolism One of the most common aspects is the ulcer or rupture of the surface of the plaque, resulting in distal embolism, which blocks the blood vessels at the distal end, resulting in cerebral infarction. Atheroma and/or thrombus may become emboli to obstruct a smaller distal artery, usually at a branching point. Emboli consist of platelet–fibrin particles, combined red thrombi, cholesterol crystals, and other debris from plaque, calcified particles, and any combinations. Depending on the size and nature of emboli, the embolus can be lyzed, fragmented, and then swept on into microcirculation. In other case, emboli permanently can block the distal artery and produce antegrade and retrograde thrombosis form platelets. In most cases, severe vascular stenosis is accompanied by perfusion defects, which may be due to the inability of blood clot wash-out if perfusion is impaired. Cerebral infarction due to this mechanism can be suspected as multiple small cerebral cortical infarctions suggesting embolism in diffusion-weighted images and microemboli can be observed by monitoring with transcranial Doppler ultrasound.

Emboli can be delivered to the brain or eye through blood vessels. An embolus from a plaque at the origin of the internal carotid artery normally goes to the eye or anterior two-third cerebral hemisphere. On occasion, it may go to the occipital cortex if blood can flow from the internal carotid artery via posterior communicating artery to the posterior cerebral artery. If the artery is already occluded, then an embolus may travel via the collateral circulation and impact in an unexpected area. The emboli from cervical arteries seldom seem to enter the small perforating arteries of the deep brain to cause lacunar infarct. It may be a consequence of the fact that the perforating arteries arise at 90-degree angle from the parent artery. For example, Fig. 5.4 shows case with artery-to-artery embolism.

5.4 Hemodynamic (Watershed) Infarction

Reduced cerebral blood flow secondary to large atheroma may develop when plaque growth causes severe stenosis of arterial lumen and hypoperfusion of distal brain region. That may lead to border zone infarct following severe hypotension or hypoxia.

The reduction of arterial blood pressure can be systemic or local. In either case, if perfusion pressure falls, cerebral arterioles dilate. When this vasodilatation is maximal, autoregulation stops, and if pressure is further reduced, cerebral blood flow also decreases. In such situation, the boundary or watershed zones between arterial territories become to be oligemic. The distribution of brain

damage caused by profound hypotension is determined by the balance between the vulnerability of regional brain tissues and the degree of collateral blood flow.

The combination of cardiac disease or arterial hypotension of the other causes and severe carotid arterial stenosis are principal risk factors for hemodynamic watershed infarcts [9, 10]. These stenotic lesions are composed of stable fibrous sheets with many fibrous tissues and fewer lipid centers and are predominantly caused by severe stenosis of the extracranial and intracranial carotid arteries and middle cerebral artery. When the vascular stenosis progresses to a level that is almost obstructed, hemodynamic end-diastolic blood flow is reduced (hypoperfusion), and the degree of development of the leptomeningeal collateral determines the extent of the blood flow disturbance. The lesion may become larger due to changes in blood pressure or position such as dehydration or excessive blood pressure drop. In the early diffusion-weighted images, there is a high risk of progression if the perfusion defect appears large in the perfusion-weighted image.

The onset and progression of hemodynamic stroke is characteristic. Unlike embolic stroke that occur suddenly or atherothrombotic and lacuar stroke that often occur in a stuttering pattern of discrete steps, many hemodynamic strokes gradually worsen over hours to days. Some hemodynamic strokes also progress in a stepwise pattern. Syncope at the onset is seen more commonly in hemodynamic stroke than in other types.

Watershed infarctions are of two types as follows: cortical watershed infarct and internal watershed infarction. These infarctions that occur in cortical border zones mostly commonly affect the watershed between those cortical portions perfused by the middle cerebral artery and those portions perfused by anterior cerebral artery or posterior cerebral artery. Internal watershed infarction occurs in the cerebral white matter border zones between medullary arteries in superficial pial arteries and the deep penetrating arteries that are branches of the basal cerebral arteries. Figure 5.5 shows example case with hemodynamic infarct.

5.5 Branch Atheromatous Disease

Small deep brain infarcts are often caused by two different vascular pathologies: (1) atheromatous occlusion at the orifice of large caliber

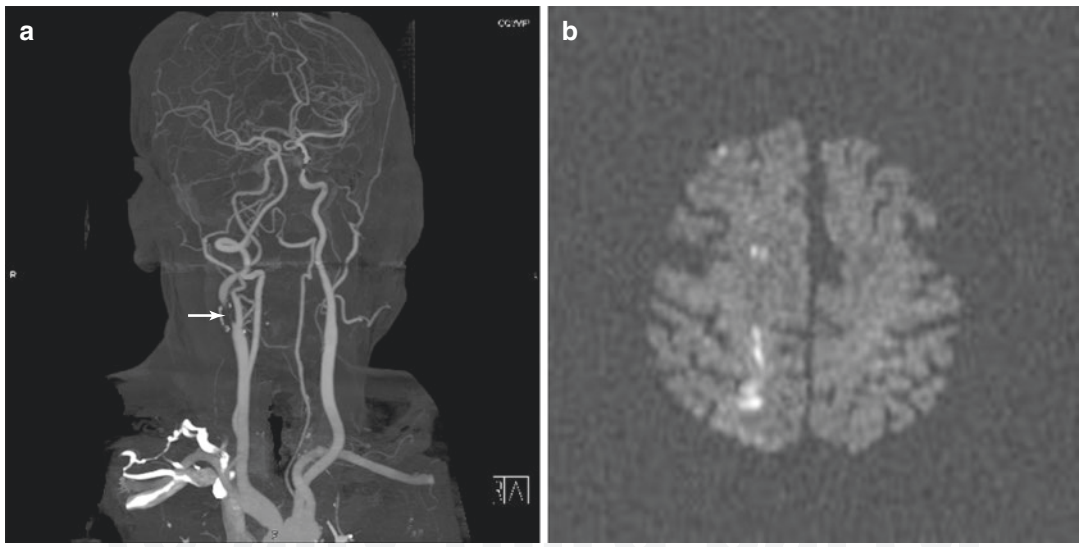

Fig. 5.5 Hemodynamic infarct. (**a**) Severe stenosis at right proximal ICA on CT angiography. (**b**) acute linear infarct of frontoparietal cortex on diffusion-weighted image

penetrating arteries termed branch atheromatous disease and (2) lipohyalinotic degenerative changes termed lipohyalinotic degeneration (lacunar infarct). The type of pathology that causes small deep infarcts involves the large arteries that give rise to penetrating artery branches rather than intrinsic disease of the branches themselves. The orifices of these penetrating arteries branches could be obstructed by atherosclerotic plaque lesions. Caplan described the vascular pathology in these branches, and named the condition intracranial branch atheromatous disease [11]. The location and mechanism of the pathology within the parent arteries are following. The orifices of the penetrating branches can be blocked by atheroma in the parent artery, atheroma can originate in the parent artery and extend into the branch (so-called junctional atheromatous plaques), or microatheroma can arise at the origin of the branch itself. Thrombus may be sometimes superimposed on the atheroma and occasionally a microdissection may develop in the parent artery and spread into the first millimeters of the branch. It is now possible to image intracerebral branch atheromatous disease using high resolution MRI. Plaques in the middle cerebral artery and basilar artery can be shown to impinge upon or occlude penetrating branches by MRI techniques that show axial sections of the origins of branches from the parent arteries. The location within the parent artery is critical in blocking lenticulostriatal, thalamostriatal, and basilar artery branches. Figures 5.6 and 5.7 shows cases with branch atheromatous disease.

The lesion size may be less than 20 mm in diameter (similar to the size of the lacunar infarction) and mild stenosis of less than 30% in the corresponding vessel is found. It is more common in the basilar artery than in the middle cerebral artery. In the case of the middle cerebral artery, more than one ischemic lesion is observed in two or more images of the axial view, and the basal artery is a form in which the ischemic lesion extends to the basal surface. Although early lesions and symptoms may be misinterpreted as lacunar infarction, it is common to see progression of the neurological disorder as the lesion becomes larger than the lacunar infarction due to lipohyalinosis [12].

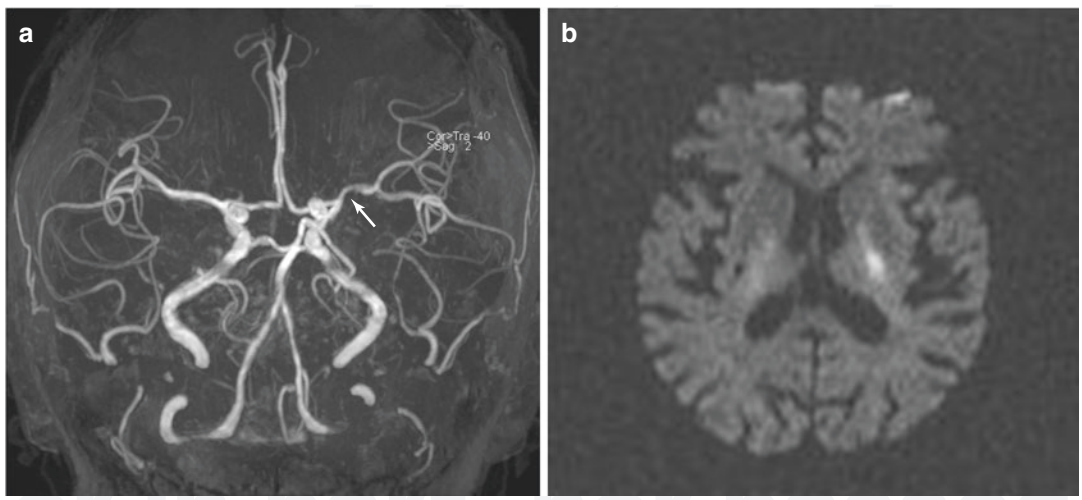

Fig. 5.6 Branch atheromatous disease, middle cerebral artery (MCA). (**a**) Mild focal stenosis at left proximal MCA on MR angiography. (**b**) Small capsular infarct on diffusion-weighted image

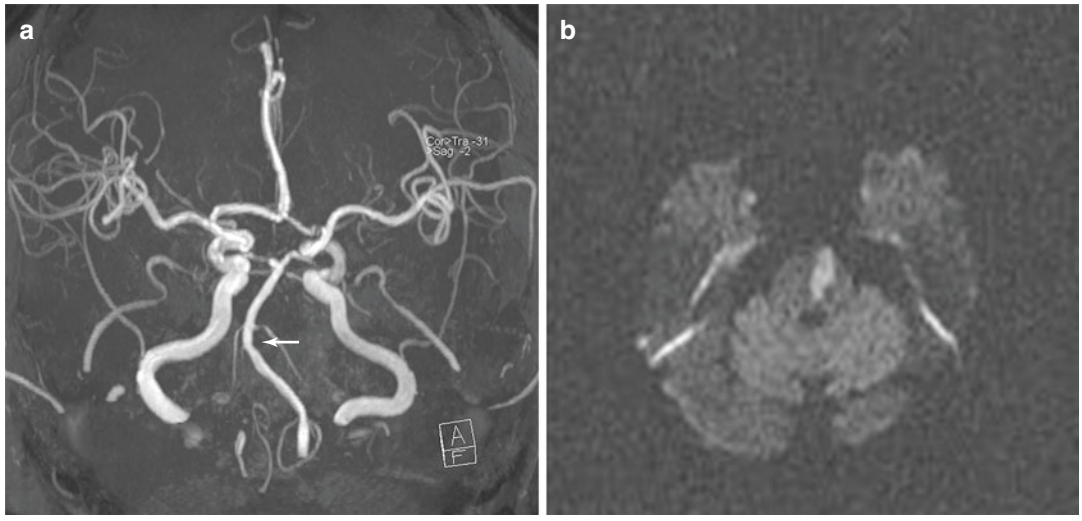

Fig. 5.7 Branch atheromatous disease, basilar artery. (**a**) Mild focal stenosis of basilar artery on MR angiography. (**b**) Acute infarct involving ventral surface of pons on diffusion-weighted image

References

1. Caplan LR. Basic pathology, anatomy, and pathophysiology of stroke. In: Caplan's stroke: a clinical approach. 4th ed. Philadelphia: Saunders; 2009. p. 22–63.
2. Viles-Gonzalez JF, Fuster V, Badimon JJ. Atherothrombosis: a widespread disease with unpredictable and life-threatening consequences. Eur Heart J. 2004;25:1197–207.
3. Rothwell PM, Warlow CP. Timing TIAs preceding stroke: time window for prevention is very short. Neurology. 2005;64:817–20.
4. Coull AJ, Lovett JK, Rothwell PM. Population based study of early risk of stroke after transient ischemic attack or minor stroke: implication for public education and organization of services. Br Med J. 2004;328:326.
5. Ay H, Furie KL, Singhal A, et al. An evidence-based causative classification system for acute ischemic stroke. Ann Neurol. 2005;58:688–97.
6. Ay H, Benner T, Arsava EM, et al. A computerized algorithm for etiologic classification of ischemic stroke: the causative classification of stroke system. Stroke. 2007;38:2979–84.
7. Lhermitte F, Gautier JC, Detrouesne C. Nature of occlusions of the middle cerebral artery. Neurology. 1970;20:82–8.
8. Bogousslavsky J, Regli F. Unilateral watershed cerebral infarcts. Neurology. 1986;36:373–7.
9. Bladin CF, Chambers BR. Clinical features, pathogenesis, and computed tomographic characteristics of internal watershed infarct. Stroke. 1993;24:1925–32.
10. Bladin CF, Chambers BR. Frequency and pathogenesis of hemodynamic stroke. Stroke. 1994;25:2179–82.
11. Caplan LR. Intracranial branch atheromatous disease: a neglected, understudied, and underused concept. Neurology. 1989;39:1246–50.
12. Petrone L, Nannoni S, Del Bene A, et al. Branch atheromatous disease: a clinically meaningful, yet unproven concept. Cerebrovasc Dis. 2016;41:87–95.