3 Epidemiology, Risk Factors, and Stroke Mechanisms

Philip B. Gorelick and Jong S. Kim

Prevalence of Posterior Circulation Stroke

Based on previous registry data using admitted stroke patients, posterior circulation stroke (PCS) was reported to account for 20–30% of stroke [1, 2]. However, the prevalence may vary depending on (1) the frequency of using MRI in the initial diagnosis of stroke and (2) the policy or criteria of each center for patient admission. For example, centers where MRI is frequently used for symptoms such as dizziness, small PCS will be more often detected. Some tertiary centers of South Korea have reported that PCS accounted for about 40% of admitted patients with ischemic stroke [3, 4].

In the studies that compared between ACS and PCS, [5–10] PCS accounts for 16–51%. (Table 3.1). Thus, almost all the studies showed that PCS is less common than ACS, although its portion varies. As discussed later, atrial fibrillation is a more important cause of ACS than PCS. This may explain why PCS is relatively more prevalent in Asian countries [6, 8], where atrial fibrillation is less common than in Caucasians [5, 9]. Patients with PCS were generally younger and more often males than those with ACS, although one study from China did not show such a trend [8]. This demographic difference seems to be in line with the more widespread presence of atrial fibrillation in ACS than in PCS patients.

In a multicenter registry study from South Korea, authors enrolled patients with ischemic stroke or transient ischemic attack (TIA) associated with cerebral atherosclerosis. They found that the proportion of PCS was 26%. In this study, the locations of symptomatic cerebral atherosclerosis were middle cerebral artery (MCA) (34%), internal carotid artery (29%: proximal 23%, distal 6%), vertebral artery (10%: proximal 4%, distal 6%), basilar artery (8%), posterior cerebral artery (6%), and anterior cerebral artery (5%) [11]. Between ACS and PCS, there were no differences in age and sex, probably because strokes associated with atrial fibrillation were excluded.

P. B. Gorelick
Davee Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Population Health Research Institute, Faculty of McMaster University Health Sciences and Hamilton University Health Science, Hamilton, ON, Canada

Department of Translational Science and Molecular Medicine, Michigan State University College of Human Medicine, Grand Rapids, MI, USA

Department of Neurology and Rehabilitation, University of Illinois College of Medicine at Chicago, Chicago, IL, USA

Thorek Memorial Hospital, Chicago, IL, USA
e-mail: pgorelic@thorek.org

J. S. Kim (✉)
Department of Neurology, Asan Medical Center, University of Ulsan, Seoul, South Korea
e-mail: jongskim@amc.seoul.kr

J. S. Kim (ed.), *Posterior Circulation Stroke*, https://doi.org/10.1007/978-981-15-6739-1_3

Table 3.1 Studies that compared characteristics between PCS and ACS

Author	Subramanian	Miyamoto	Zeng	Li	Sommer	Zurcher	Toyoda	Kim	Kim#
Published (year)	2009	2010	2015	2017	2018	2019	(unpublished)	(unpublished)	2012
Region	Canada	Japan	China	China	Austria	Switzerland	Japan	South Korea	South Korea
Study design	Multicenter	Retrograde	Retrograde	Retrospective	Nationwide	Single center	NCVC Stroke Registry	AMC registry	Multicenter
	Registry	Single center	Single center	Single center	Stroke unit registry	Registry		Stroke unit registry	Registry
Number (ACS/PCS) (%, PCS)	5844/2645 (26)	1089/430 (39)	1763/482 (21)	364/187 (51)	23,447/4604 (16)	983/466 (32)	2301/662 (22)	2773/833 (23)	736/264 (26)
Mean age (ACS/PCS, year)	74/70*	69/66*	63/62	61/66	49/40	70/67*	42/32*	67/65*	67/67
Sex (ACS/PCS, % female)	51/44*	36/27*	41/33*	39/34	49/40	46/39	75/73*	39/33*	35/36
Risk factors (%, ACS/PCS)									
Hypertension	69/67	50/57*	48/48	67/69*	81/78	66/64	76/82*	65/66	69/82*
Diabetes	24/27*	25/33*	14/21*	20/20	25/25	15/12	32/31*	29/37*	32/45*
Dyslipidemia	34/36	21/20	7/6	6/4	54/57	61/67*	50/53	29/35*	48/49
Smoking	37/39	18/33	33/38*	37/31	ND	23/20	18/18	32/39*	36/29*
Atrial fibrillation	20/16*	27/17*	8/3*	ND	29/22	31/16*	38/26*	15/16	
Past history of stroke	35/32	7/8	ND	22/9*	23/21	26/28	31/34	ND	26/22
Stroke subtype (%, ACS/PCS)	ND	*	*	ND			*	*	
LAD		20/34*	27/29		13/12	15/10	14/15	33/28*	
SVD		36/32	37/38		23/21	5/21	16/21	23/34*	
CE		31/20*	13/5*		29/24	41/25	38/23	27/20*	
NIHSS (at admission, ACS/PCS)	ND	ND	6.4/5.2*	4.3/3.2*	5/3	10.6/5.9*	5/3*	6.0/3.7*	

PCA posterior circulation stroke, *ACS* anterior circulation stroke, *LAD* large artery disease, *SVD* small artery disease, *CE* cardiac embolism, *ND* not described

#This study enrolled patients with atherosclerotic strokes only

*Data with statistical difference

Table 3.2 Ten factors accounting for approximately 90% of stroke attribution

Hypertension
Current smoking
Waist-to-hip ratio
Diet risk score
Exercise
Diabetes mellitus
Alcohol (consumption >30/month or binges)
Psychosocial stress and depression
Cardiac causes
Ratio of apolipoprotein B to A1

Table 3.3 Stroke risks by category according to the American Heart Association/American Stroke Association

Generally nonmodifiable risks
Age
Low birth weight
Race (e.g., blacks and some Hispanic/Latino Americans)
Genetic factors
Well-documented and modifiable risks
Physical inactivity
Dyslipidemia
Diet and nutrition
High blood pressure
Obesity and body fat distribution
Diabetes mellitus
Cigarette smoking
Atrial fibrillation
Other cardiac conditions
Asymptomatic carotid artery stenosis
Sickle cell disease
Less well-documented or potentially modifiable risks
Migraine
Metabolic syndrome
Alcohol consumption
Drug abuse
Sleep-disordered breathing
Hyperhomocysteinemia
Elevated lipoprotein (a)
Hypercoagulability
Inflammation and infection

Risk Factors

General Risk Factors

Stroke is not an accident as the traditional term "cerebrovascular accident (CVA)" would imply. Instead, there are well-documented modifiable risk factors for stroke and other risks that are part of the causal web leading to stroke. Based on a large-scale international case–control study, it has been estimated that 90% of ischemic stroke may be attributed to ten factors: hypertension, current smoking, waist-to-hip ratio, diet risk score, exercise, diabetes mellitus, alcohol consumption >30/month or alcohol binges, psychosocial stress and depression, cardiac causes, and the ratio of apolipoprotein B to A1 [12]. Table 3.2 lists the aforementioned factors. General stroke risk factors may be categorized according to the following scheme: generally nonmodifiable risks, well-documented and modifiable risks, and less well-documented or potentially modifiable risks [13]. Table 3.3 lists stroke risks in general by category according to the American Heart Association/American Stroke Association (AHA/ASA) [13].

Differences in the Risk Factors Between Posterior Circulation and Anterior Circulation Stroke

There have been studies that compared risk factors between ACS and PCS (Table 3.1). Overall, atrial fibrillation is more often associated with ACS than with PCS. Atherosclerotic risk factors such as diabetes and hypertension appear to be more prevalent in PCS than in ACS. This difference may be attributed to the fact that cardiac embolism is less frequent in PCS. However, in the study that enrolled only the patients with symptomatic cerebral atherosclerosis, atherosclerotic risk factors such as diabetes mellitus and hypertension were still more closely associated with PCS than with ACS [11]. This result suggests that the impact of each atherosclerotic risk factor may be different between anterior and posterior circulation. An alternative explanation would be that nonatherosclerotic diseases (e.g., moyamoya disease) may have been misdiagnosed as anterior circulation (e.g., MCA) atherosclerosis in certain cases, especially in Asia [14].

Finally, the genetic variant, ring finger protein 213 (RNF213) c.14576G>A (rs112735431), which was originally identified as a susceptibility

genetic variant for moyamoya disease, is shown to be present in patients with intracranial cerebral atherosclerosis. In a study from Japan, RNF213 heterozygotes were present in 10 of 43 patients in patients with the anterior intracranial atherosclerosis, but none in the patients with PCS [15]. In another study from South Korea, RNF 213 heterozygotes were found in 13 of the 240 large artery disease (LAA) patients (5.4%), but none of the patients with PCS had this polymorphism [16]. Thus, this genetic variant may be one of the determinants for the location of cerebral atherosclerosis.

Stroke Mechanisms

As in ACS, PCS is caused by large artery disease, small artery disease, cardiogenic embolism, and other mechanisms.

Large Artery Disease

The main pathology of large artery disease consists of thrombosis superimposed on atherosclerosis. The pathologic features of PCS are not fundamentally different from those of ACS [17, 18]. In the posterior circulation, atherosclerosis is prone to occur in the proximal extracranial vertebral artery (VA), distal intracranial VA, lower-middle portion of the basilar artery (BA), and proximal posterior cerebral artery (PCA) [11, 19] (Fig. 3.1, left image). In the stenotic atherosclerotic vessel, thrombus may be superimposed. Thrombus formed within the intracranial VA often extends into the proximal BA [20]. Within the BA, atherosclerotic stenosis is common in the proximal 2 cm, more often seen on the ventral than in the dorsal side [17, 20]. Thrombi within the BA tend to have limited propagation [21], occasionally extending only to the orifice of the next long circumferential cerebellar artery such as anterior inferior cerebellar artery (AICA) or superior cerebellar artery (SCA).

Mechanisms of Stroke in Large Artery Disease

Detailed stroke mechanisms of large artery disease include artery-to-artery embolism, in situ thrombotic occlusion, branch occlusion, hypoperfusion, and their combinations.

Artery-to-Artery Embolism

A thrombus may occur in stenosed atherosclerotic vessels, especially when atherosclerotic plaques are eroded or ulcerated [22, 23]. The thrombus arising from the proximal vessels (e.g., extracranial VA) can be detached and can travel all the way to the distal arteries such as the PCA, SCA, PICA, and distal BA (embolization) [24] (Fig. 3.1, right image). This phenomenon has been described as "artery-to-artery embolism." Stenoses in the intracranial arteries such as intracranial VA, BA, or proximal PCA also produce embolism, although they may also produce infarction through other mechanisms such as branch occlusion [25, 26]. Embolism seems to occur more frequently in the setting of posterior fossa hypoperfusion associated with significant bilateral VA occlusive disease, due in part to ineffective washout of emboli in hypoperfused areas [27] (Fig. 3.2). Although uncommon, arterial embolisms may develop from more proximal arteries, such as the subclavian artery, the ascending aorta, and aortic arch [28].

In Situ Thrombotic Occlusion

In patients with intracranial artery atherosclerosis, thrombus formation in areas of plaque can result in total arterial occlusion, leading to an infarction in the relevant territory. In the posterior circulation, in situ thrombotic occlusion is often observed in the territories of PCA, and BA branches such as AICA or PICA [11, 29]. In situ thrombotic occlusion produces relatively large territorial infarction. However, unlike cardiogenic embolism, it less often produces massive "malignant" infarction because of relatively well-developed collateral circulation in the setting of

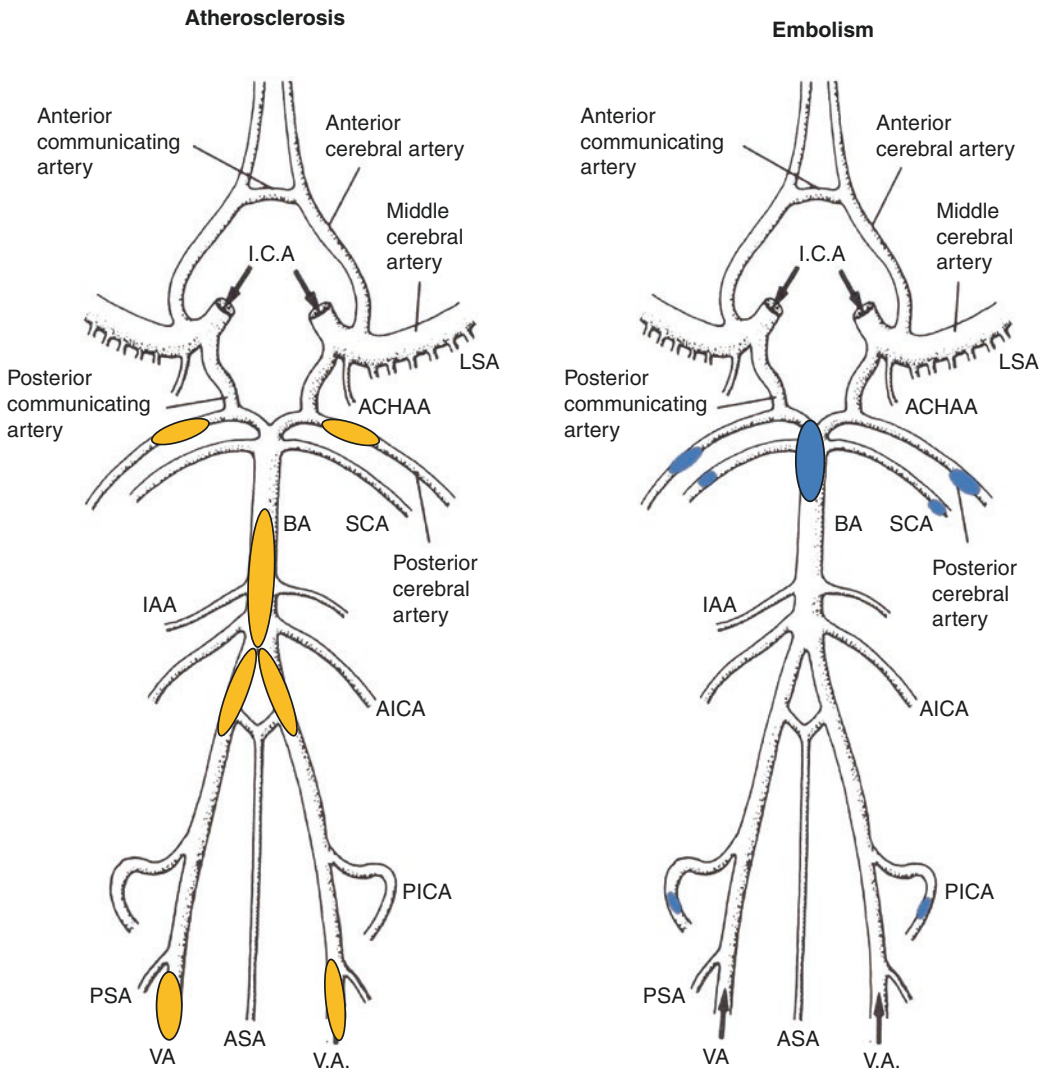

Fig. 3.1 Left image: Frequent location of atherosclerosis in the posterior circulation. Right image: Frequent site of embolic occlusion

the chronic atherosclerotic process [30]. With persistent occlusion, however, the initial infarct frequently grows, leading to progressive neurological worsening. Thus, the ultimate infarct volume varies according to the size of the occluded vessel, the speed of arterial occlusion, and the status of the collateral circulation. Patients with this mechanism more often experience transient ischemic attacks (TIAs) preceding main infarction (Fig. 3.3) than in those with cardiogenic embolism.

Branch Occlusion

Atherosclerotic plaques in an intracranial artery can occlude the orifice of one or several perforators, causing infarcts limited to the perforator territory [31] (Fig. 3.4A). Pathological features of this "atheromatous branch occlusion" were described [32, 33]. It seems that branch occlusion is more often observed in PCS than ACS; one study showed that this was the mechanism of stroke in 16% of symptomatic MCA atherosclerosis, whereas it occurred in 64% of the BA

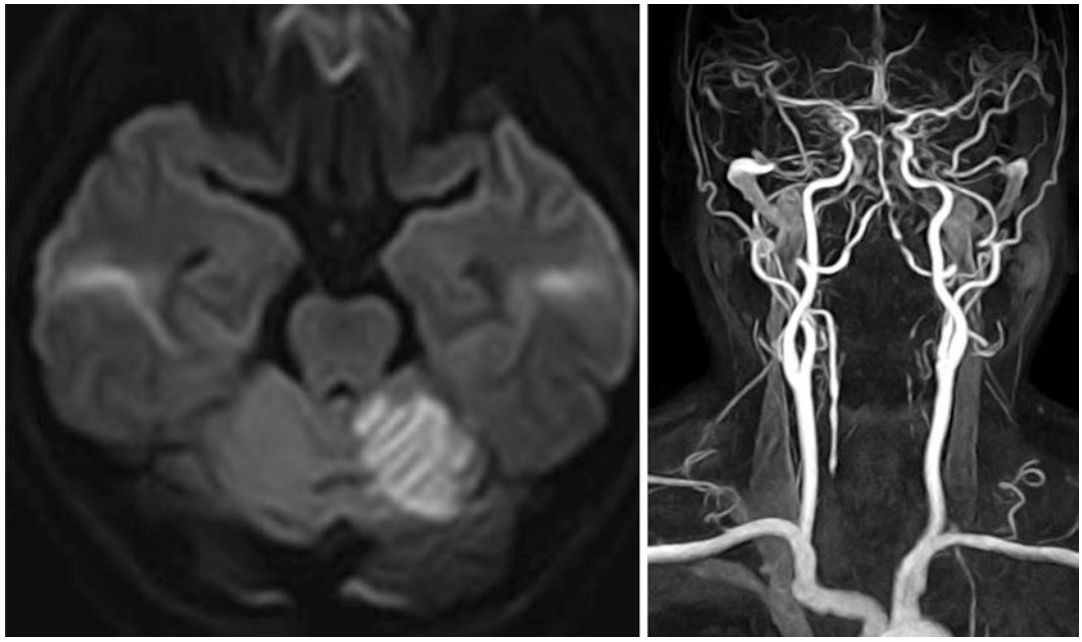

Fig. 3.2 A 64-year-old hypertensive man suddenly developed dysarthria and gait difficulty. Neurological examination showed dysarthria and limb ataxia on the left side. Diffusion-weighted MRI showed an infarction in the left superior cerebellar artery territory (left image). MRA showed bilateral proximal atherosclerotic occlusion of the vertebral arteries (right image). The probable stroke mechanism was artery-to-artery embolism

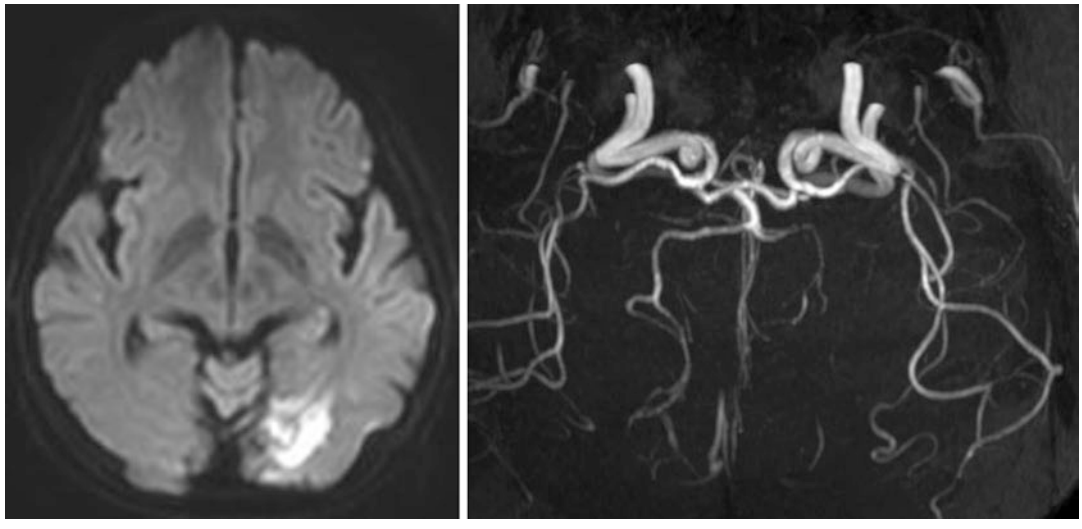

Fig. 3.3 A 72-year-old hypertensive and diabetic woman developed visual dimness on the right side, which was preceded by recurrent episodes of right limb tingling sensation that lasted approximately 10 min. Neurological examination showed normal findings except for right upper quadrantanopia. Diffusion-weighted MRI showed an infarction in the left occipital lobe (left image). MRA showed left posterior cerebral artery (PCA) occlusion (right image), which was not recanalized on follow-up MRA 5 days later. Cardiac examination and Holter monitoring findings were normal. The presumed stroke mechanism was in situ atherothrombotic occlusion of the left PCA

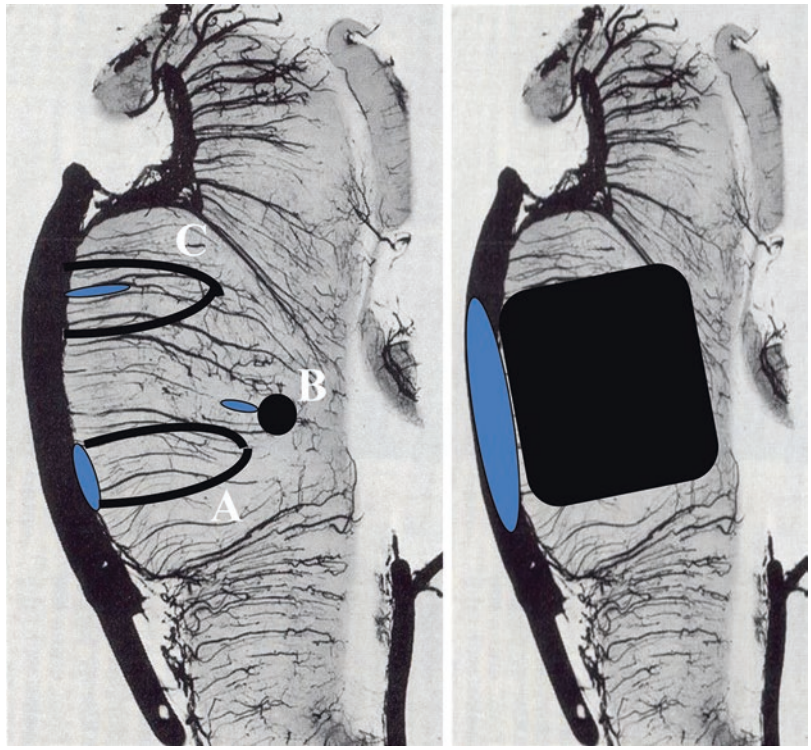

Fig. 3.4 Schematic drawing of the mechanism of brainstem infarction. Left image; A. atherothrombosis occurring in the basilar artery obliterates the orifice of the perforator. B. lipohyalinotic distal small artery occlusion. C. Atherosclerotic occlusion of the proximal portion of the perforator. A and C are referred to as "branch atheromatous disease." They produce infarcts abutting on the basal surface, whereas B (lypohyalinotic disease) produces an island-like deep infarction. Right image; Extensive atherosclerotic occlusion (or plaque rupture) producing multiple, bilateral branch occlusions leading to a large brainstem infarction. An embolic occlusion can also produce this syndrome. Single (or a few) branch occlusion (A, C in the left image). Extensive branch occlusion (right image)

atherosclerosis [11]. Thus, branch occlusion is the major mechanism of the isolated brainstem (e.g., pontine and medullary) (Fig. 3.5, upper panel) infarctions [25, 26, 34–36].

Brainstem infarcts associated with branch occlusion tend to extend to the basal surface (Figs. 3.4A and 3.5), whereas those caused by small artery lipohyalinotic disease (see below) produce a deep, island-like infarction within the parenchyma (Fig. 3.4B). The former is more often associated with atherosclerotic characteristics, [37] larger lesion volume, and an unstable and unfavorable clinical course than the latter [26, 38, 39] (Fig. 3.6).

Occasionally, the proximal small vessel disease also harbors characteristics of atherosclerosis, and the resultant brainstem infarction looks similar to that of branch occlusion due to BA atherosclerosis (Fig. 3.4C). Thus, this condition has been included in the category of atherosclerotic branch occlusion [31], although this is classified as small vessel disease in our clinical practice given that there is no large, atherosclerotic parenteral artery disease. Nevertheless, atheromatous branch occlusion cannot be ruled out in patients with normal-looking parenteral arteries on an angiogram. Nowadays, high-resolution vessel wall MRI (HR-MRI) can identify the small plaque that occludes the perforator, even in patients with apparently normal MRA findings [40, 41] (Fig. 3.5, lower panel; see also Chap. 9).

Compared with atherosclerotic lesions producing embolism or in situ thrombotic occlusion, branch occlusion is associated with less severe arterial stenosis [42]. However, the stenosis degree may be severe in occasional cases.

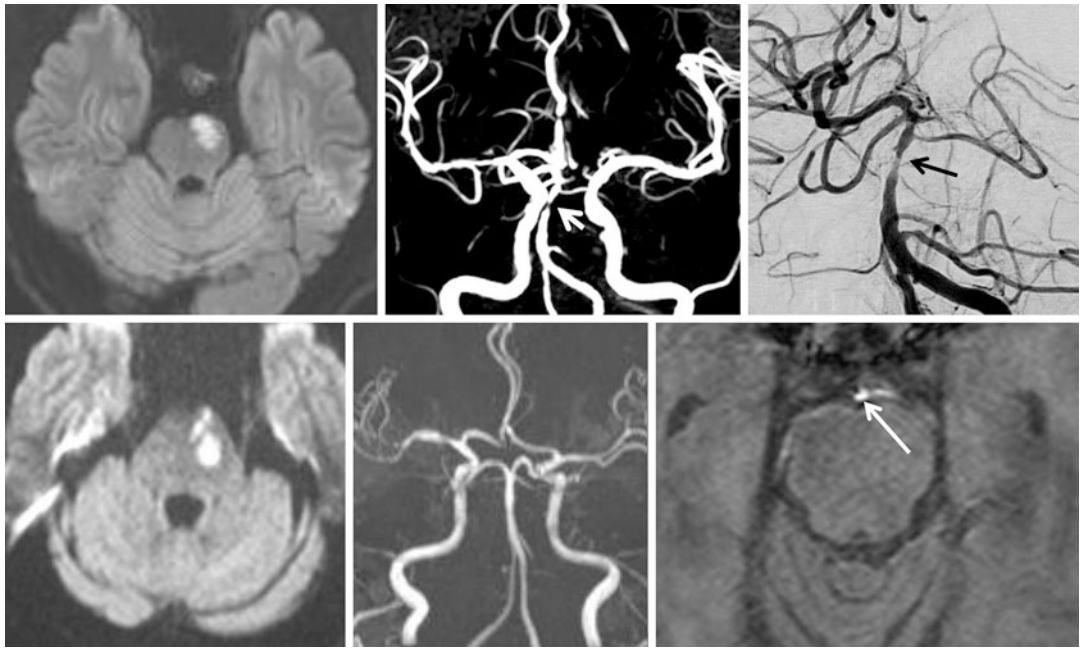

Fig. 3.5 Examples of atheromatous branch occlusion producing unilateral pontine infarction. Upper panel; Diffusion-weighted MRI shows a left pontine infarction (left image) caused by branch occlusion associated with basilar artery stenosis identified by MRA (middle image, arrow) and conventional angiogram (right image, arrow). Lower panel; Diffusion-weighted MRI shows a left pontine infarction (left image). Although MRA did not show significant basilar artery disease (middle image), high-resolution vessel wall MRI shows thickened, enhanced vessel wall in the dorsal portion of the basilar artery (arrow) that probably obliterated a perforator (right image)

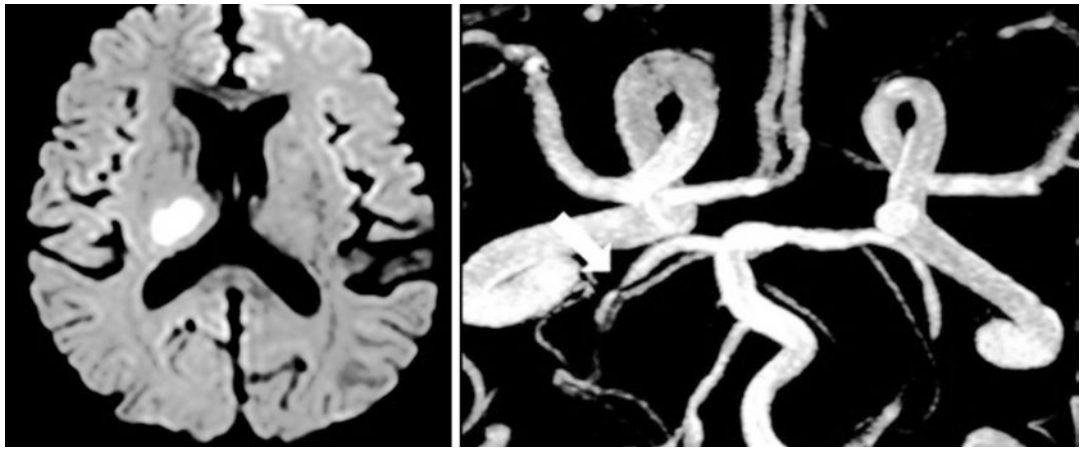

Fig. 3.6 A hypertensive 64-year-old man developed sudden numb sensation in the left limb. The next day, he additionally experienced left limb weakness and ataxia. Diffusion-weighted MRI showed an infarction in the right thalamus (left image). MRA showed focal stenosis in the P2 portion of the right posterior cerebral artery (right image) that probably occluded the orifice of the thalamic perforators

Sudden, extensive BA thrombotic occlusion due to either atherosclerotic rupture or embolization from proximal sources may produce extensive brainstem infarction by way of multiple, bilateral branch occlusions (Fig. 3.4, right image).

Hypoperfusion

In patients with severe vascular stenosis/occlusion and insufficient collaterals, hemodynamic TIAs can occur. Typically, symptoms such as dizziness, diplopia, and visual disturbances occur briefly and stereotypically in patients who are dehydrated or fatigued. When stroke develops, the symptoms may fluctuate widely according to the degree of hydration, blood pressure, and the position of the patient's head. Improving perfusion with hydration or induced hypertension may be of help in such patients [43, 44]. Although the efficacy has not yet been proven, [45] revascularization therapies, such as angioplasty/stenting or bypass surgeries (see Chap. 13), may relieve these symptoms.

Unlike ACS, MRI lesion patterns of hemodynamic infarction are not clearly established in the PCS, due in part to considerable normal variations and collateral patterns that influence perfusion. Small infarcts occurring in the cerebellar border zone (areas bordering PICA, AICA, and SCA) may be attributed to hypoperfusion associated with cardiac arrest or severe VA or BA occlusive disease (see Chap. 6). However, infarcts of the similar pattern are also produced by embolism to small arteries within the border zone areas [46]. Thus, the MRI imaging alone is not a reliable sign predicting hypoperfusion.

The stroke mechanism is often difficult to assess partly because severe vertebrobasilar atherosclerosis can induce both hemodynamic and embolic strokes and partly because the territory of each cerebellar artery often overlaps. PCS solely attributable to hemodynamic failure seems to be distinctly uncommon. More often, hypoperfusion plays an additive role in the development or progression of stroke, together with other major stroke mechanisms, e.g., small embolic infarcts in the border zone areas, progressive enlargement of infarction in patients with in situ thrombotic occlusion (see above).

Location of Large Artery Disease

Extracranial Vertebral Artery

The most frequent location of extracranial VA atherosclerotic disease is at the origin from the subclavian arteries. Atheroma may originate in the subclavian artery and spread to the proximal VA. Despite the high incidence of extracranial VA atherosclerosis, serious PCSs are relatively uncommon in this condition [47]. When stroke develops, it is almost always related to embolism from thrombi formed in the proximal VA [9, 31, 48–50]. Compared to unilateral VA lesions, bilateral steno-occlusive lesions (or unilateral disease with contralateral hypoplasia) generate embolism more often, probably related to hypoperfusion in the posterior fossa, which may promote thrombus generation and inefficient washout of emboli (Fig. 3.2). Hypoperfusion, in turn, is related to the effective development of collateral circulation, especially when the VA occlusion occurs gradually. Important sources of collaterals include occipital branches of the external carotid artery, the ascending cervical and transverse cervical branches of the thyrocervical trunk, and retrograde flow from the contralateral VA or from the posterior communicating system.

Intracranial Vertebral Artery

Generally, intracranial VA occlusive disease is more often symptomatic than extracranial VA disease. Unilateral intracranial VA disease may produce medullary (either lateral or medial) infarction through occlusion of the medullary perforators (branch occlusion, Fig. 4.4 in Chap. 4) or PICA. Cerebellar infarction with or without medullary involvement may also occur through the occlusion of the ostium of the PICA. Thrombi within the stenosed intracranial VA may also generate emboli that occlude distal vessels (artery-to-artery embolism). Bilateral intracranial VA occlusion is less well tolerated and often leads to TIAs or cerebellar and brainstem infarction [51–53] (Fig. 11.2 in Chap. 11), although some patients who have adequate collateral circulation may survive without the development of major infarction [53].

Basilar Artery

Pathologically [54] and angiographically [55] documented BA occlusion often leads to catastrophic bilateral pontine infarction (Fig. 3.4, right image), but some patients have only limited or transient deficits [48–50, 56]. The variable outcome depends on the extensiveness of the thrombus and the status of collateral circulation (e.g., backward flow from the well-developed posterior communicating artery or SCA). The collateral status may, in turn, be influenced by the extent of the atherothrombotic diseases in individuals. For example, collateral circulation through the PICA would be poor when the intracranial VA is also obstructed. When thrombus propagates to the distal BA, collateral circulation from the SCAs and the posterior communicating arteries becomes limited. The speed of BA occlusion also matters; BA embolism and dissection tend to result in sudden coma and quadriparesis, while progression of brainstem ischemia related to atherothrombosis is slow and progressive and earns time for collateral development. Early plaques associated with mild stenosis generally produce unilateral pontine infarcts through the mechanism of branch occlusion (Fig. 3.5).

Small Artery (Penetrating Artery) Disease

A single subcortical or brainstem infarct usually results from disease of penetrating arteries [57] (Fig. 3.4B). Its pathological hallmarks include irregular cavities, less than 15–20 mm in size, located in subcortical, brainstem, and cerebellar areas. Penetrating arteries associated with these lesions have disorganized vessel walls, fibrinoid material deposition, and hemorrhagic extravasation through arterial walls, first called "segmental arterial disorganization" and then lipohyalinosis by Fisher [33, 57–63]. These vascular changes develop in arteries or arterioles 40–400 μm in diameter and frequently affect the perforating arteries from the PCA or BA. Penetrating artery disease is the main mechanism of brainstem infarction, although brainstem infarctions may also be caused by atheromatous branch occlusion [31], as discussed before.

Cardiac Embolism

Given the fact that blood flow to the posterior circulation is only 1/5–1/4 of the anterior circulation, we can understand that a thrombus arising in the heart more often travels to the anterior circulation than to the posterior circulation system. Nevertheless, previous studies showed that about 1/5–1/4 of PCS result from cardiogenic embolism (Table 3.1). These emboli commonly occlude the PCA, rostral BA, SCA, and PICA (Fig. 3.1, right image). Infarcts are typically larger than those associated with large artery atherosclerotic disease, partly because the clots are larger and partly because of the insufficiently developed collateral circulation [64]. The onset is usually abrupt. Additional infarcts may be seen in the anterior circulation as well. The occluded artery is often spontaneously recanalized, and hemorrhagic transformation of an infarct is common, which may cause worsening headache or neurological deterioration.

It has been recognized that patent foramen ovale (PFO) with a large amount of shunt is an etiology of embolic infarcts (paradoxical embolism), especially in young patients without vascular risk factors [65, 66]. The posterior circulation seems to be a predilection site for embolism in patients with PFOs as compared to the anterior circulation [67, 68]. A recent study showed that embolic infarctions associated with PFO more often occurred in the posterior circulation than those associated with atrial fibrillation (44.4% versus 22.9%) [68]. Relatively poor adrenergic innervation in the vertebrobasilar circulation and inefficient response to sympathetic stimuli at the time of Valsalva maneuvers may explain the increased chance of blood clot to travel to the vertebrobasilar system. Given the evidence that PFO closure is effective in the prevention of PFO-related stroke in patients with a large amount of shunt, [69] PFO has been increasingly recognized as a treatable cause of stroke, especially in young patients. Identification of PFO through extensive cardiac workup (e.g., transesophageal echocardiogram) is important given the fact that lifelong administration of antithrombotics may be not needed if closure procedure is successfully performed (Fig. 3.7).

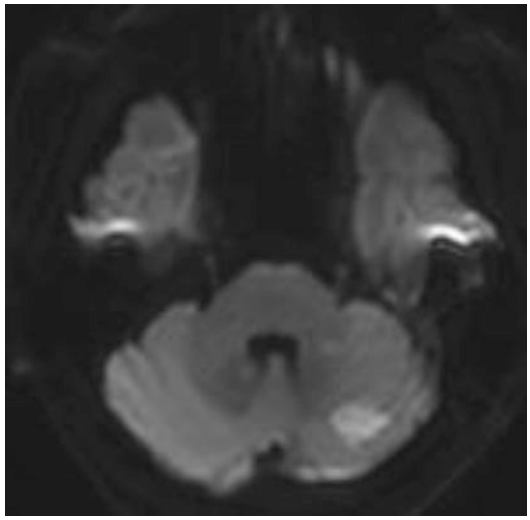

Fig. 3.7 A 36-year-old woman without any vascular risk factors suddenly developed dizziness and gait ataxia. Diffusion-weighted MRI showed a left cerebellar infarction. MRA showed normal findings. Holter examination was normal. Transesophageal echocardiography showed patent foramen ovale (PFO) with a large amount of right-to-left shunt. The probable stroke mechanism was paradoxical embolism due to PFO. PFO closure was performed by a cardiologist

Embolic infarction associated with cardiac catheterization also occurs preferentially in the posterior circulation [70, 71].

Differences in Stroke Mechanisms Between ACS and PCS

Stroke mechanisms differ from ACS and PCS; in most of the registry studies, CE is more common in ACS than in PCS (Table 3.1). LAD and SVD are relatively more prevalent in PCS.

In addition, detailed mechanisms appear to be different even in patients with "atherosclerotic" stroke. When the stroke mechanisms were compared between ACS and PCS patients who had atherosclerosis, the prevalence of artery-to-artery embolism, in situ thrombotic occlusion, local branch occlusion, and hemodynamic mechanism were 53 vs. 34, 21 vs. 14, 12 vs. 40 and 5 vs.0 [11]. Thus, branch occlusion is more important, and artery-to-artery embolism is less important mechanism in PCS than in ACS patients. This is in part due to the location of the symptomatic atherosclerosis. Atherosclerosis of the proximal internal carotid artery accounted for 34% of ACS atherosclerosis, whereas proximal VA atherosclerosis accounted for only 14% of PCS atherosclerosis. In other words, compared with atherosclerosis in ACS, atherosclerosis in PCS patients is more often located in the intracranial artery. Nevertheless, even in patients with intracranial atherosclerosis, stroke mechanisms may still differ between ACS and PCS. For example, while MCA atherosclerosis often produces artery-to-artery embolism, BA atherosclerosis is more often associated with branch occlusion [11]. Although the reason remains unclear, shorter perforating arteries arising from the BA or VA may be more vulnerable for occlusion in the presence of parental artery disease compared with the relatively longer lenticulostriate arteries arising from the MCA.

Less Common Causes

Less common causes include arterial dissections, fibromuscular dysplasia, moyamoya disease, vasospasm, and infectious or immunologic vasculitis. Details are discussed in Chap. 14.

When large arteries are involved, the stroke mechanisms in patients with uncommon diseases are identical with what was discussed so far, i.e., artery-to-artery embolism, branch occlusion, hemodynamic insufficiency, and their combination. However, the importance of each mechanism differs among various diseases.

References

1. Bogousslavsky J, Van Melle G, Regli F. The Lausanne Stroke Registry: analysis of 1,000 consecutive patients with first stroke. Stroke. 1988;19(9):1083–92.
2. Moulin T, Tatu L, Crepin-Leblond T, Chavot D, Berges S, Rumbach T. The Besancon Stroke Registry: an acute stroke registry of 2,500 consecutive patients. Eur Neurol. 1997;38(1):10–20.
3. Lee BI, Nam HS, Heo JH, Kim DI. Yonsei Stroke Registry. Analysis of 1,000 patients with acute cerebral infarctions. Cerebrovasc Dis. 2001;12(3):145–51.
4. Lee JH, Han SJ, Yun YH, Choi HC, Jung S, Cho SJ, et al. Posterior circulation ischemic stroke in Korean population. Eur J Neurol. 2006;13(7):742–8.

5. Subramanian G, Silva J, Silver FL, Fang J, Kapral MK, Oczkowski W, et al. Risk factors for posterior compared to anterior ischemic stroke: an observational study of the Registry of the Canadian Stroke Network. Neuroepidemiology. 2009;33(1):12–6.
6. Miyamoto N, Tanaka Y, Ueno Y, Tanaka R, Hattori N, Urabe T. Comparison of clinical backgrounds with anterior versus posterior circulation infarcts. J Stroke Cerebrovasc Dis. 2010;19(5):393–7.
7. Zeng Q, Tao W, Lei C, Dong W, Liu M. Etiology and risk factors of posterior circulation infarction compared with anterior circulation infarction. J Stroke Cerebrovasc Dis. 2015;24(7):1614–20.
8. Li Y, Cai Y, Zhao M, Sun J. Risk factors between intracranial-extracranial atherosclerosis and anterior-posterior circulation stroke in ischaemic stroke. Neurol Res. 2017;39(1):30–5.
9. Sommer P, Posekany A, Serles W, Marko M, Scharer S, Fertl E, et al. Is functional outcome different in posterior and anterior circulation stroke? Stroke. 2018;49(11):2728–32.
10. Zurcher E, Richoz B, Faouzi M, Michel P. Differences in ischemic anterior and posterior circulation strokes: a clinico-radiological and outcome analysis. J Stroke Cerebrovasc Dis. 2019;28(3):710–8.
11. Kim JS, Nah HW, Park SM, Kim SK, Cho KH, Lee J, et al. Risk factors and stroke mechanisms in atherosclerotic stroke: intracranial compared with extracranial and anterior compared with posterior circulation disease. Stroke. 2012;43(12):3313–8.
12. O'Donnell MJ, Xavier D, Liu L, Zhang H, Chin SL, Rao-Melacini P, et al. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. Lancet. 2010;376(9735):112–23.
13. Meschia JF, Bushnell C, Boden-Albala B, Braun LT, Bravata DM, Chaturvedi S, et al. Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014;45(12):3754–832.
14. Kim JS, Bonovich D. Research on intracranial atherosclerosis from the East and west: why are the results different? J Stroke. 2014;16(3):105–13.
15. Shinya Y, Miyawaki S, Imai H, Hongo H, Ono H, Takenobu A, et al. Genetic analysis of ring finger protein 213 (RNF213) c.14576G>A in intracranial atherosclerosis of the anterior and posterior circulations. J Stroke Cerebrovasc Dis. 2017;26(11):2638–44.
16. Kim YJ, Kim BJ, Lee MH, Lee H-B, Lee JS, Chang D-i, et al. Are Genetic Variants Associated with the Location of Cerebral Arterial Lesions in Stroke Patients?. Cerebrovascular Diseases. 2020;49(3):262–68.
17. Cornhill JF, Akins D, Hutson M, Chandler AB. Localization of atherosclerotic lesions in the human basilar artery. Atherosclerosis. 1980;35(1):77–86.
18. Schwartz CJ, Mitchell JR. Atheroma of the carotid and vertebral arterial systems. Br Med J. 1961;2(5259):1057–63.
19. Ueda K, Toole JF, McHenry LC Jr. Carotid and vertebrobasilar transient ischemic attacks: clinical and angiographic correlation. Neurology. 1979;29(8):1094–101.
20. Castaigne P, Lhermitte F, Gautier JC, Escourolle R, Derouesne C, Der Agopian P, et al. Arterial occlusions in the vertebro-basilar system. A study of 44 patients with post-mortem data. Brain. 1973;96(1):133–54.
21. Castaigne P, Lhermitte F, Buge A, Escourolle R, Hauw JJ, Lyon-Caen O. Paramedian thalamic and midbrain infarct: clinical and neuropathological study. Ann Neurol. 1981;10(2):127–48.
22. Fisher M, Paganini-Hill A, Martin A, Cosgrove M, Toole JF, Barnett HJ, et al. Carotid plaque pathology: thrombosis, ulceration, and stroke pathogenesis. Stroke. 2005;36(2):253–7.
23. Fuster V, Badimon L, Badimon JJ, Chesebro JH. The pathogenesis of coronary artery disease and the acute coronary syndromes (2). N Engl J Med. 1992;326(5):310–8.
24. Caplan LR, Amarenco P, Rosengart A, Lafranchise EF, Teal PA, Belkin M, et al. Embolism from vertebral artery origin occlusive disease. Neurology. 1992;42(8):1505–12.
25. Kim JS. Pure lateral medullary infarction: clinical-radiological correlation of 130 acute, consecutive patients. Brain. 2003;126(Pt 8):1864–72.
26. Kim JS, Cho KH, Kang DW, Kwon SU, Suh DC. Basilar artery atherosclerotic disease is related to subacute lesion volume increase in pontine base infarction. Acta Neurol Scand. 2009;120(2):88–93.
27. Caplan LR, Hennerici M. Impaired clearance of emboli (washout) is an important link between hypoperfusion, embolism, and ischemic stroke. Arch Neurol. 1998;55(11):1475–82.
28. Amarenco P, Cohen A, Tzourio C, Bertrand B, Hommel M, Besson G, et al. Atherosclerotic disease of the aortic arch and the risk of ischemic stroke. N Engl J Med. 1994;331(22):1474–9.
29. Lee E, Kang DW, Kwon SU, Kim JS. Posterior cerebral artery infarction: diffusion-weighted MRI analysis of 205 patients. Cerebrovasc Dis. 2009;28(3):298–305.
30. Wong KSCL, Kim JS. Stroke mechanisms. In: Kim JS, Caplan LR, Wong KS, editors. Intracranial atherosclerosis. Chichester, West Sussex: Blackwell; 2008. p. 57–68.
31. Caplan LR. Intracranial branch atheromatous disease: a neglected, understudied, and underused concept. Neurology. 1989;39(9):1246–50.
32. Lhermitte F, Gautier JC, Derouesne C. Nature of occlusions of the middle cerebral artery. Neurology. 1970;20(1):82–8.
33. Fisher CM, Caplan LR. Basilar artery branch occlusion: a cause of pontine infarction. Neurology. 1971;21(9):900–5.
34. Kim JS, Kim J. Pure midbrain infarction: clinical, radiologic, and pathophysiologic findings. Neurology. 2005;64(7):1227–32.
35. Park JY, Chun MH, Kang SH, Lee JA, Kim BR, Shin MJ. Functional outcome in poststroke patients with or without fatigue. Am J Phys Med Rehabil. 2009;88(7):554–8.

36. Kim JS, Yoon Y. Single subcortical infarction associated with parental arterial disease: important yet neglected sub-type of atherothrombotic stroke. Int J Stroke. 2013;8(3):197–203.
37. Nah HW, Kang DW, Kwon SU, Kim JS. Diversity of single small subcortical infarctions according to infarct location and parent artery disease: analysis of indicators for small vessel disease and atherosclerosis. Stroke. 2010;41(12):2822–7.
38. Bang OY, Joo SY, Lee PH, Joo US, Lee JH, Joo IS, et al. The course of patients with lacunar infarcts and a parent arterial lesion: similarities to large artery vs small artery disease. Arch Neurol. 2004;61(4):514–9.
39. Kwon JY, Kwon SU, Kang DW, Suh DC, Kim JS. Isolated lateral thalamic infarction: the role of posterior cerebral artery disease. Eur J Neurol. 2012;19(2):265–70.
40. Klein IF, Lavallee PC, Schouman-Claeys E, Amarenco P. High-resolution MRI identifies basilar artery plaques in paramedian pontine infarct. Neurology. 2005;64(3):551–2.
41. Swartz RH, Bhuta SS, Farb RI, Agid R, Willinsky RA, Terbrugge KG, et al. Intracranial arterial wall imaging using high-resolution 3-tesla contrast-enhanced MRI. Neurology. 2009;72(7):627–34.
42. Lee DK, Kim JS, Kwon SU, Yoo SH, Kang DW. Lesion patterns and stroke mechanism in atherosclerotic middle cerebral artery disease: early diffusion-weighted imaging study. Stroke. 2005;36(12):2583–8.
43. Lee MH, Kim JG, Jeon SB, Kang DW, Kwon SU, Kim JS. Pharmacologically induced hypertension therapy for acute stroke patients. J Stroke. 2019;21(2):228–30.
44. Bang OY, Chung JW, Kim SK, Kim SJ, Lee MJ, Hwang J, et al. Therapeutic-induced hypertension in patients with noncardioembolic acute stroke. Neurology. 2019;93(21):e1955–e63.
45. Markus HS, Harshfield EL, Compter A, Kuker W, Kappelle LJ, Clifton A, et al. Stenting for symptomatic vertebral artery stenosis: a preplanned pooled individual patient data analysis. Lancet Neurol. 2019;18(7):666–73.
46. Amarenco P, Kase CS, Rosengart A, Pessin MS, Bousser MG, Caplan LR. Very small (border zone) cerebellar infarcts. Distribution, causes, mechanisms and clinical features. Brain. 1993;116(Pt 1):161–86.
47. Fisher CM. Occlusion of the vertebral arteries. Causing transient basilar symptoms. Arch Neurol. 1970;22(1):13–9.
48. Fields WS, Ratinov G, Weibel J, Campos RJ. Survival following basilar artery occlusion. Arch Neurol. 1966;15(5):463–71.
49. Moscow NP, Newton TH. Angiographic implications in diagnosis and prognosis of basilar artery occlusion. Am J Roentgenol Radium Therapy, Nucl Med. 1973;119(3):597–604.
50. Pochaczevsky R, Uygar Z, Berman AJ. Basilar artery occlusion. J Can Assoc Radiol. 1971;22(4):261–3.
51. Caplan LR. Bilateral distal vertebral artery occlusion. Neurology. 1983;33(5):552–8.
52. Shin HK, Yoo KM, Chang HM, Caplan LR. Bilateral intracranial vertebral artery disease in the New England Medical Center, Posterior Circulation Registry. Arch Neurol. 1999;56(11):1353–8.
53. Bogousslavsky J, Gates PC, Fox AJ, Barnett HJ. Bilateral occlusion of vertebral artery: clinical patterns and long-term prognosis. Neurology. 1986;36(10):1309–15.
54. Kubik CS, Adams RD. Occlusion of the basilar artery; a clinical and pathological study. Brain. 1946;69(2):73–121.
55. Archer CR, Horenstein S. Basilar artery occlusion: clinical and radiological correlation. Stroke. 1977;8(3):383–90.
56. Caplan LR. Occlusion of the vertebral or basilar artery. Follow up analysis of some patients with benign outcome. Stroke. 1979;10(3):277–82.
57. Fisher CM. Lacunes: small, deep cerebral infarcts. Neurology. 1965;15:774–84.
58. Fisher CM. A lacunar stroke. The dysarthria-clumsy hand syndrome. Neurology. 1967;17(6):614–7.
59. Fisher CM. Lacunar strokes and infarcts: a review. Neurology. 1982;32(8):871–6.
60. Fisher CM. Ataxic hemiparesis. A pathologic study. Arch Neurol. 1978;35(3):126–8.
61. Fisher CM, Curry HB. Pure motor hemiplegia. Trans Am Neurol Assoc. 1964;89:94–7.
62. Fisher CM, Cole M. Homolateral ataxia and crural paresis: a vascular syndrome. J Neurol Neurosurg Psychiatry. 1965;28:48–55.
63. Fisher CM. Pure sensory stroke involving face, arm, and leg. Neurology. 1965;15:76–80.
64. Kim HJ, Yun SC, Cho KH, Cho AH, Kwon SU, Kim JS, et al. Differential patterns of evolution in acute middle cerebral artery infarction with perfusion-diffusion mismatch: atherosclerotic vs. cardioembolic occlusion. J Neurol Sci. 2008;273(1–2):93–8.
65. Mas JL, Arquizan C, Lamy C, Zuber M, Cabanes L, Derumeaux G, et al. Recurrent cerebrovascular events associated with patent foramen ovale, atrial septal aneurysm, or both. N Engl J Med. 2001;345(24):1740–6.
66. Lamy C, Giannesini C, Zuber M, Arquizan C, Meder JF, Trystram D, et al. Clinical and imaging findings in cryptogenic stroke patients with and without patent foramen ovale: the PFO-ASA Study. Atrial Septal Aneurysm. Stroke. 2002;33(3):706–11.
67. Venketasubramanian N, Sacco RL, Di Tullio M, Sherman D, Homma S, Mohr JP. Vascular distribution of paradoxical emboli by transcranial Doppler. Neurology. 1993;43(8):1533–5.
68. Kim BJ, Sohn H, Sun BJ, Song JK, Kang DW, Kim JS, et al. Imaging characteristics of ischemic strokes related to patent foramen ovale. Stroke. 2013;44(12):3350–6.
69. Abdelghani M, El-Shedoudy SAO, Nassif M, Bouma BJ, de Winter RJ. Management of patients with patent foramen ovale and cryptogenic stroke: an update. Cardiology. 2019;143(1):62–72.
70. Dawson DM, Fischer EG. Neurologic complications of cardiac catheterization. Neurology. 1977;27(5):496–7.
71. Keilson GR, Schwartz WJ, Recht LD. The preponderance of posterior circulatory events is independent of the route of cardiac catheterization. Stroke. 1992;23(9):1358–9.