

Causes of Ischemic Stroke

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2.1 Introduction

Ischemic stroke is a heterogeneous disease and occurs due to a multitude of underlying pathologic processes. The brain is such an exquisitely sensitive reporting system that small infarctions, well below the size that causes clinical signs in other organ systems, can cause major disability in the brain. About 85% of all strokes are due to ischemia, and in the majority of ischemic stroke, the mechanism responsible is understood (Fig. 2.1) [1]. An illustration of the causes of the majority of ischemic strokes is shown in Fig. 2.2, including atherosclerotic, cardiogenic, and lacunar (penetrating vessel) mechanisms. Large series have failed to identify a definite cause in 25–39% of patients with ischemic stroke, depending on the quality, completeness, and quickness of the clinical workup [1]. This group of strokes of unknown causes is known as cryptogenic stroke. This chapter reviews the pathways that lead to ischemic stroke.

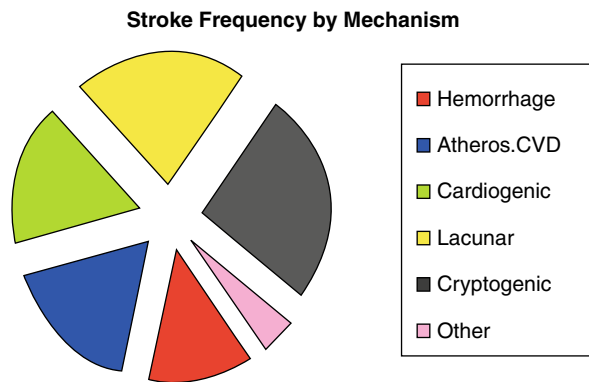


Fig. 2.1 Stroke frequency by mechanism (CVD cardiovascular disease)

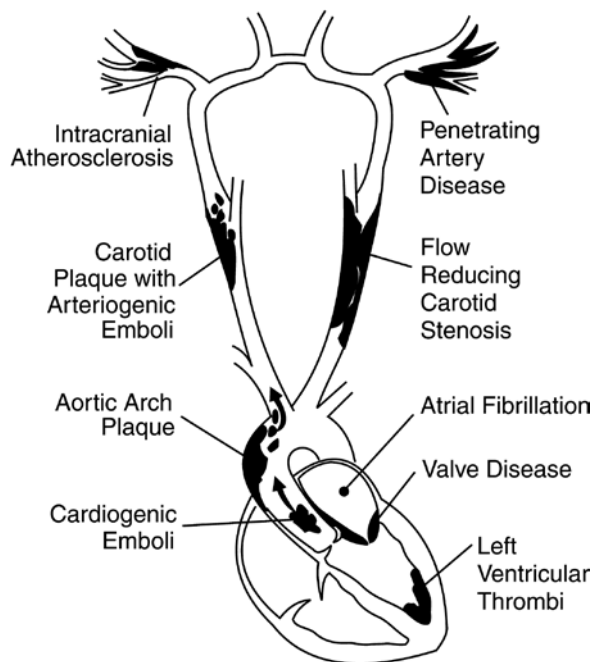


Fig. 2.2 The most frequent sites of arterial and cardiac abnormalities causing ischemic stroke. Adapted from Albers et al. [92]

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2.2 Key Concept: Core and Penumbra

Before discussing the causes of ischemic stroke, it is useful to consider the concepts of infarct core and penumbra. These terms were initially given specific scientific definitions. Ischemic penumbra was first defined as underperfused brain tissue at a level within the thresholds of functional impairment and morphological integrity, which has the capacity to recover if perfusion is restored [2]. As applied in the clinic, their definitions have become operational, with the core generally defined as that part of the ischemic region that is irreversibly injured, while the penumbra is the area of brain that is underperfused and is in danger of infarcting [3]. These are useful concepts for several reasons. If they can be identified in the acute ischemic stroke patient, they provide prognostic information and may help guide the patient management. Importantly, it is now clear that neuroimaging can provide excellent estimates of the core and the penumbra in individual patients [3, 4] (Fig. 2.3).

To illustrate the core/penumbra concept, let us consider the hypothetical case of an embolus to the main stem portion (M1) of the middle cerebral artery (MCA). The MCA along with the anterior cerebral artery (ACA) arise from the internal carotid artery (ICA) at the base of the frontal lobe (Fig. 2.4). When an embolus lodges in the M1 segment of the MCA, the MCA territory of the brain becomes underperfused (Fig. 2.5). However, in many cases the collateral circulation from the ACA and posterior cerebral artery (PCA) can compensate to some degree. Collateral blood flow to the brain after a large vessel occlusion may occur through the circle of Willis or by communications between small pial vessels on the surface of the brain (pial collaterals). The amount of collateral flow determines the size of the core and the penumbra (Figs. 2.6 and 2.7) [5]. However, it is critical to understand that both the core and penumbra are dynamic entities that depend on the complex physiology that is playing out in the acutely ischemic brain. If the occlusion is not removed, the core size usually increases, while the salvageable penumbra decreases with time. Ischemic penumbra is present for a limited period of time even in the center of ischemia. Irreversible necrosis then radiates to the surrounding tissue over time. The rate of change in the size of the core and the penumbra depends on the blood flow provided by the collaterals [4, 5].

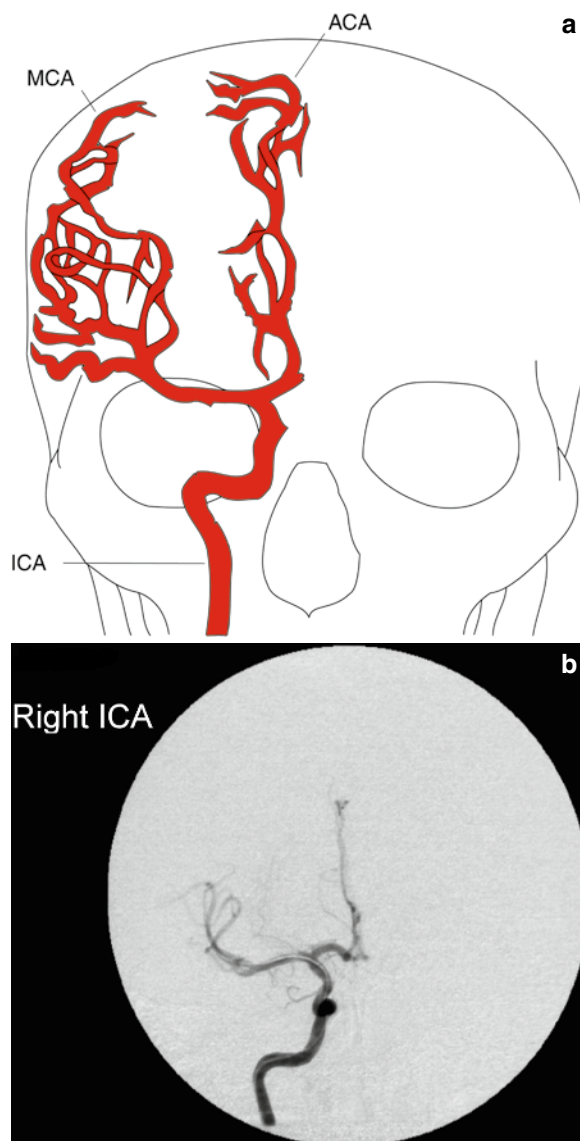


Fig. 2.3 (a) Internal carotid artery feeds the middle cerebral artery (MCA) and anterior cerebral artery (ACA). (b) Right internal carotid artery (ICA). Adapted from Fisher [93]

2.3 Risk Factors

In many respects stroke is a preventable disorder. Prevention is the target of a variety of programs to reduce risk factors for stroke. The aim of primary prevention is to reduce the risk of stroke in asymptomatic people. Hypertension, carotid artery stenosis, atrial fibrillation and certain other cardiac conditions, cigarette smoking, diabetes mellitus, dyslipidemia, sickle

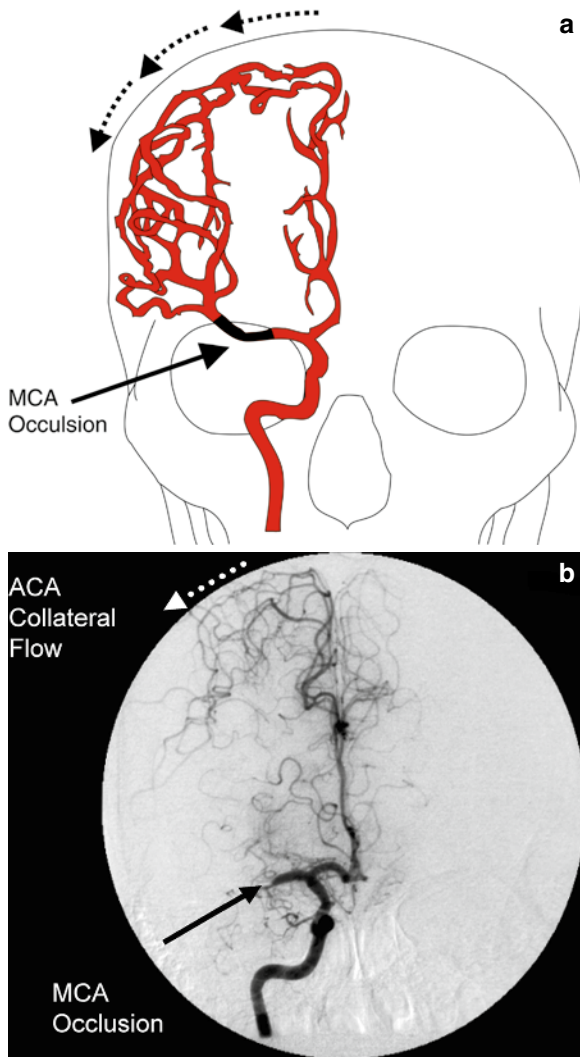


Fig. 2.4 (a) ACA collateral flow after MCA occlusion. (b) ACA collateral flow. Adapted from Fisher [93]

cell disease, poor diet, physical inactivity, and obesity are well-established risk factors for ischemic stroke [6, 7]. Less well-established risk factors include alcohol and drug abuse, the metabolic syndrome, oral contraceptive use, sleep-disordered breathing, migraine, hyperhomocysteinemia, elevated lipoprotein(a), elevated lipoprotein-associated phospholipase, inflammation, infection, and hypercoagulability (Table 2.1) [7]. The greatest stroke risk, however, occurs in those with previous transient ischemic attack or previous stroke (Table 2.1) [7]. For these patients, risk factor reduction for secondary prevention is essential. Secondary vascular risk has been shown to decrease with treatment

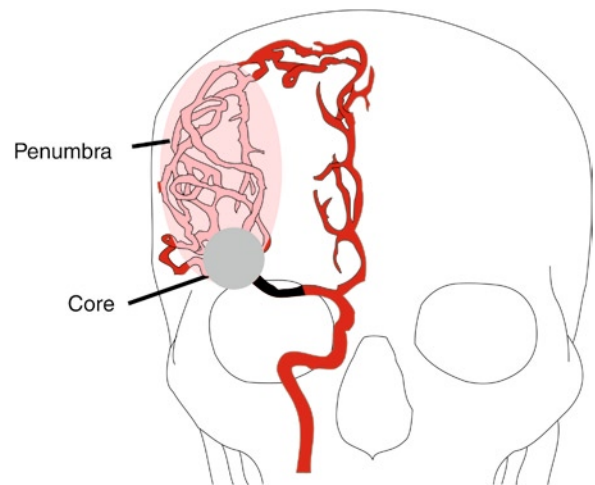


Fig. 2.5 Core and penumbra after MCA occlusion. Adapted from Fisher [93]

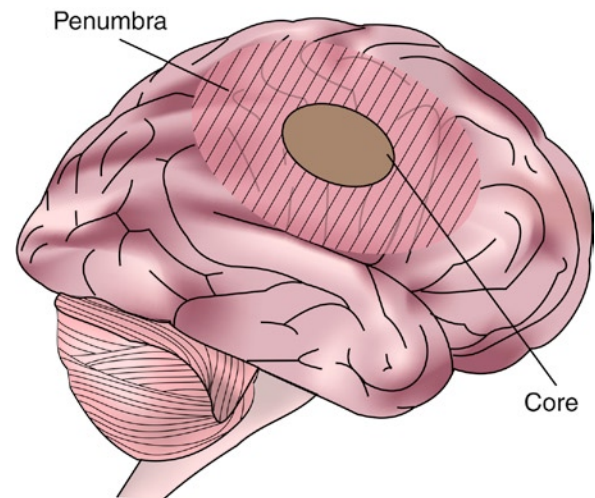


Fig. 2.6 Penumbra/core. Adapted from Fisher [93]

of hypertension, hyperlipidemia, and the institution of antiplatelet drug treatment [7, 8]. Globally, hypertension is the most significant risk factor for stroke, both ischemic and hemorrhagic. Elevation in blood pressure plays a big role in the development of vascular disease, including coronary heart disease, ventricular failure, atherosclerosis of the aorta, and cerebral arteries, as well as small vessel occlusion. Treating blood pressure considerably reduces coronary and stroke risk. A metaanalysis of randomized controlled trials of antihypertensive therapy after stroke or transient ischemic attack showed a reduction in stroke recurrence (RR 0.76; 95% CI 0.63–0.92)[9]. Stroke recurrence is

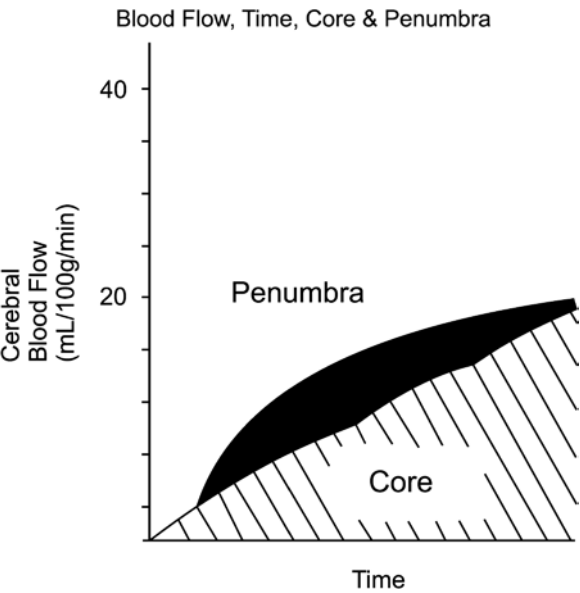


Fig. 2.7 Blood flow, time, core, and penumbra. Adapted from Fisher [93]

Table 2.1 Major risk factors for acute stroke

| |
|--|
| Previous transient ischemic attack or stroke |
| Hypertension |
| Diabetes mellitus |
| Hyperlipidemia |
| Atrial fibrillation certain other cardiac conditions |
| Obesity |
| Carotid artery stenosis |
| Exposure to cigarette smoke |
| Sickle cell disease |
| Postmenopausal hormone therapy |

decreased across a range of blood pressure and type of stroke. Diabetes mellitus ranks highly as a stroke risk factor. Rigorous control of blood pressure and lipids is recommended in patients with diabetes. Tight glucose control should be the goal among diabetics with ischemic stroke or transient ischemic attack to reduce microvascular complications [6, 7]. Hyperlipidemia is not as potent a risk factor for stroke when compared to high-risk cardiac conditions; however, stroke may be reduced by the use of statins in patients with coronary artery disease [6–8]. Because risk reductions with statins are more than what is expected exclusively through cholesterol lowering, other potential beneficial mechanisms have been considered. In the Stroke Prevention

by Aggressive Reduction in Cholesterol Levels trial (SPARCL), treatment with intensive statin therapy (e.g., atorvastatin 80 mg) reduced stroke recurrence in patients without indications for lipid lowering (HR 0.84; 95% CI 0.71–0.99), while in the Heart Protection Study simvastatin reduced vascular events in patients with prior stroke and reduced stroke in patients with other vascular disease (RR 0.76) [10, 11]. Unless it is quelled, the current epidemic of obesity is expected to fuel greater stroke risk in the near future. Although no study has directly shown that weight reduction reduces stroke risk, it does improve control of blood pressure, serum lipids, and glucose. Because obesity is a risk factor to other well-documented stroke risk factors, promoting the maintenance of a healthy weight cannot be overemphasized [6].

2.4 Primary Lesions of the Cerebrovascular System

2.4.1 Carotid Stenosis

Many stroke patients have atherosclerosis, indicating a link between cardiac and cerebrovascular disease (see Table 2.2). But it is difficult for clinicians to predict the likelihood of stroke using signs and symptoms of heart disease. For instance, carotid bruits are more reliably predictive of ischemic heart disease than of stroke. Around 23% of ischemic stroke originates from carotid atherosclerosis. The degree of stenosis alone cannot predict vulnerable lesions [12]. Cerebrovascular ischemic events also result from low-grade carotid stenosis.

2.4.2 Plaque

A carotid plaque’s variable composition may affect the associated stroke risk. The structure of the carotid artery wall, including the composition, remodeling, and

Table 2.2 Primary lesions of the cerebrovascular system that cause ischemic stroke

| |
|---|
| Extracranial carotid atherosclerosis or intimal hyperplasia |
| Intracranial atherosclerosis |
| Aortic atherosclerosis |
| Extracranial arterial dissection |

inflammation of plaques, seems to be important factors in determining the stroke risk associated with carotid artery stenosis [12]. Rupture of the plaque surface and subsequent luminal thrombus formation are probably important mechanisms underlying acute ischemic stroke. Plaque is often echo-dense and calcified and can be formed by the homogenous deposition of cholesterol. Plaque is dangerous not only because of its stenotic effects, but also because it may rupture or dissect at the atherosclerotic wall, showering debris into the bloodstream, leading to multiple embolic cerebral infarcts downstream of the plaque [12, 13]. The ruptured, ulcerated plaque can also be a source of thrombus formation in that the anticoagulant properties of the endothelial surface are locally disrupted. Using transcranial Doppler, a number of groups have shown increased frequency of microembolic signals in the ipsilateral MCA in the days after symptom onset in patients with carotid stenosis [14].

Inflammation in the plaque wall has been postulated to influence thrombus formation in myocardial infarction (MI) as well as stroke. Recent studies have focused on the possibility that infection in the plaque contributes to thrombus formation and subsequent stroke or MI. *Chlamydia pneumoniae* particles have been recently discovered in carotid and coronary plaques [15]. Although several studies have shown an association between elevated serum antibody titers for *Chlamydia pneumoniae* and cerebrovascular and cardiovascular events, there remains no clear evidence of stroke risk reduction associated with antibiotic therapy [6, 16]. Another condition that can produce progressive carotid narrowing not due to atherosclerosis is intimal hyperplasia, which can occur after radiation treatment to the neck or prior carotid endarterectomy.

2.4.3 Atherosclerosis Leading to Stroke: Two Pathways

An atherosclerotic lesion at the origin of the ICA can lead to stroke. The first pathway is a result of progressive narrowing of the ICA until the sluggish blood flow promotes the formation of a thrombus at the residual lumen, which results in complete occlusion. The acute occlusion may be asymptomatic if excellent collateral circulation exists along the circle of Willis and between leptomeningeal vessels; alternatively, it may cause a large hemispheric stroke if collaterals are poor. The second pathway,

termed “artery to artery” embolism, is a common pathway for MCA distribution stroke in patients with severe extracranial internal carotid stenosis. Commonly, this occurs at the time of ICA occlusion [17].

2.4.4 Collateral Pathways in the Event of Carotid Stenosis or Occlusion

In the pathway shown above (Fig. 2.5a, b), leptomeningeal collateral blood sources traveling over the surface of the brain bring blood from the distal ACA branches into the distal MCA branches. This type of leptomeningeal collateral flow can also come from the PCA branches to fill the distal MCA. Flow from the vertebrobasilar system can fill the distal ICA and its branches through the posterior communicating artery (PCoA) [5, 18]. The potential for collateral flow in the case of carotid occlusion depends on the vascular anatomy of these alternative pathways. The hemodynamic effects of the collateral circulation are important in maintaining perfusion to penumbral regions. When collateral flow is not sufficient, ischemia occurs in the border zone (sometimes called “watershed”) regions between the ACA/MCA or MCA/PCA [5, 19].

2.4.5 Transient Neurological Deficits

Recurrent transient neurological deficits also occur commonly in patients with ICA stenosis. These deficits generally last for less than 3 min and include transient monocular blindness as well as transient hemispheric neurologic deficits. Their pathologic basis is unknown, though in some cases of transient monocular blindness there is evidence of low flow (the “box car” appearance of red cell clumps separated by clear space) in the retinal arterioles. The retina may also contain highly refractile cholesterol emboli called Hollenhorst plaques. In many instances of severe carotid stenosis or occlusion, the intracranial collateral flow is sufficient to perfuse the brain and prevent ischemia [17].

2.4.6 Intracranial Atherosclerosis

Atherosclerosis can also occur intracranially to cause focal or multifocal stenosis in the siphon portion of the

ICA, the MCA stem, the branch points of the major MCA branches, the ACA, A1 and A2 branches, the P1 and P2 segment of the PCA, the distal vertebral artery, the vertebral artery origin, the vertebrobasilar junction, and the basilar artery. Microatherosclerotic plaques can occur as described above in the proximal portion of the penetrator arteries arising from the major vessels at the base of the brain. They are not seen in the leptomeningeal vessels over the cortex [20].

Patients who have had a stroke or transitory ischemic attack associated with intracranial artery stenosis ($\geq 50\%$) have a 12–14% risk of subsequent stroke in the 2-year period after the initial event, regardless of treatment with antithrombotic medications. Atherosclerosis in the intracranial portion of the ICA and the MCA is more common in the African-American, Hispanic, and Asian populations for unknown reasons. The proportion of patients hospitalized for ischemic strokes with symptomatic intracranial stenosis ranges from 1% in non-Hispanic whites to as high as 50% in Asian populations [21, 22]. Atherosclerosis in the intracranial portion of the carotid and in the MCA often causes multiple strokes in the same vascular territory. It may also cause “slow stroke” syndrome, in which there is progressive worsening of focal cortical ischemic symptoms over days or weeks. In addition, the penetrator arteries flowing to the deep white matter and striatum originate from the MCA stem (M1) and may be occluded in patients with severe MCA stenosis [20].

Additional common sites for atherosclerotic occlusion include the origin of the vertebral artery, the distal vertebral and vertebrobasilar junction, the midbasilar artery, and the proximal PCA. Unlike ICA disease, severe atherosclerotic stenosis in the distal intracranial vertebral and basilar arteries can cause stroke via thrombotic occlusion of local branches as well as artery-to-artery embolus to the top of the basilar artery or the PCA(s). Low flow in the basilar artery can lead to thrombus formation with occlusion of one brainstem penetrator vessel after another. Basilar thrombosis is not rare and is fatal because brainstem function is completely dependent on this vascular supply [20, 23].

Low flow to the basilar artery can also be caused by vertebral disease. Sometimes one vertebral artery is small and terminates as the posterior inferior cerebellar artery, never making the connection to the basilar artery. Other times, one vertebral artery is occluded. In these two circumstances, flow-limiting disease in the dominant or remaining vertebral artery may then produce

basilar ischemia. Thrombus at the site of vertebral artery stenosis can also dislodge and cause embolic stroke in the distal basilar artery or PCA territory [23].

In some patients with long-standing hypertension there is a dramatic dilatation of the intracranial vessels called “dolichoectasia.” Basilar artery dolichoectasia can cause compression of the brainstem or cranial nerves. Thrombus can also form in these very dilated vessels leading to basilar-branch thrombotic occlusion or distal embolic stroke.

The treatment of patients with symptomatic intracranial atherosclerotic disease can be summarized into prevention of occurrence of intraluminal thrombosis, plaque stabilization, and control of risk factors for atherosclerosis. Anticoagulation (compared with aspirin) has not shown to be beneficial in patients with intracranial atherosclerotic disease [24]. Current guidelines recommend that aspirin alone, the combination of aspirin and extended release dipyridamole, and clopidogrel monotherapy (rather than oral anticoagulants) are all acceptable options [24]. In patients with hemodynamically significant intracranial stenosis who have symptoms despite medical therapies (antithrombotics, statins, and other treatments for risk factors), the usefulness of endovascular therapy (angioplasty and/or stent placement) is uncertain and is considered investigational [22, 25].

2.4.7 Aortic Atherosclerosis and Dissection

Atherosclerotic disease of the aorta is also a risk factor for ischemic stroke. Plaques larger than 4 mm are associated to a sharply increased stroke risk [26]. Ulcerations or superimposed thrombi are characteristics of the plaque that also have been shown to confer increased stroke risk, while the presence of calcification appears to decrease it. Transesophageal echocardiographic images can show plaque or thrombus on the aortic wall with dramatic flapping of a thrombus within the aortic lumen [26]. Aortic atherosclerosis is a major cause of stroke during coronary artery bypass grafting; when the aortic cross clamp is released, atherosclerotic debris fills the aorta. Atherosclerotic emboli also occur as complications after coronary and aortic angiography due to vessel-wall trauma from the catheter.

The so-called cholesterol emboli disease can cause multiple strokes as well as joint pain, livedo reticularis

skin rash, reduced renal function, and seizures. These cholesterol embolic strokes may not be amenable to thrombolysis [27].

Type I aortic dissection is one of the most difficult vascular lesions to manage in the presence of major stroke. The patient may present with chest pain and asymmetric pulses. Stroke may occur in the distribution of any major cerebral arteries because the dissection can involve both carotid and vertebral origins [28]. Since rupture into the chest or extension of dissection into the pericardium or coronary origins is fatal, thrombolysis or anticoagulation cannot be used.

2.4.8 Cervical Artery Dissection

Extracerebral artery dissection is commonly responsible for stroke in young persons, including children. In a population-based study from North America and in two large hospital-based cervical artery dissection series, 50–52% of the patients were women. A slight predominance in men was reported in the European multicentre hospital-based series [29]. Most dissections occur in the ICA more than 2 cm after the bifurcation, although they can also occur in the vertebral artery. The pathophysiology of cervical artery dissection is not completely understood. Some authors have suggested that patients with cervical artery dissection could have a constitutional weakness of the vessel wall and that environmental factors such as infections or minor trauma could act as triggers [29, 30]. In adults, dissections tear the intima and blood enters the wall of the vessel between the intima and the media. This blood causes the vessel wall to balloon outward and compresses the lumen. If stroke results from this condition, it is most often caused by embolus; a thrombus forms at the tear site and is swept up the vessel into the brain. Dissection may also cause complete occlusion of the vessel and impair cerebral perfusion [31].

Cranial nerve palsies are rare, occurring in less than 7% of cervical artery dissection cases in hospital-based series. The outwardly distended vessel wall may compress nearby structures. In carotid dissection at the base of the skull, compression palsies of cranial nerves IX, X, XI, and XII are sometimes seen due to the dissection or to the formation of a pseudoaneurysm at the site. Carotid dissection can also interrupt the sympathetic

nerve fibers that surround the carotid, causing a Horner's syndrome ptosis and miosis [29, 32]. The dissection site can be high up in the neck, often extending to the point where the ICA becomes ensheathed in the dura at the entry site into the petrous bone. Dissection also occurs in association with redundant looping of the carotid artery. Vertebral artery dissection commonly occurs where the vessel passes over the C2 lateral process to enter the dura [29].

Symptoms. Patients with carotid or vertebral dissection commonly present with pain. Pain associated with cervical artery dissections can mimic migraine or cluster headache [29]. Cervical artery dissection presenting with isolated pain is more often caused by extracranial vertebral artery dissection and might be more common than expected [33]. In a large series of patients with cervical artery dissection who presented with pain as the only symptom, the pain was frequently continuous, headaches were generally of severe intensity and throbbing in nature, and neck pain was more commonly constrictive and of moderate intensity [33]. The pain onset can range from thunderclap headache to progressive pain. In extracranial carotid dissection the pain is localized to the region above the brow in front of the ear, or over the affected carotid. In vertebral dissection the pain is usually in the C2 distribution, ipsilateral posterior neck, and occipital regions [29].

Extracranial cerebral artery dissection can occur after anything from massive trauma as well as minor neck injuries. It also occurs after seemingly trivial incidents, such as a strong cough or sneeze, chiropractic manipulation, hyperextension of the neck during hair washing, etc., [34] or in some cases, without any recognizable precipitants. Disorders of collagen such as fibromuscular dysplasia, Marfan's syndrome, and type IV Ehlers–Danlos syndrome are also associated with increased risk of dissection [35].

Infrequently, cervical artery dissection can lead to subarachnoid hemorrhage, usually when the dissection extends to the intracranial part of the vessel, with pseudoaneurysm formation and rupture (1% of cervical artery dissection cases in the large hospital-based series) [36, 37]. Rupture of dissected vertebral arteries into the subarachnoid space is more common in children. Rupture of dissected carotid artery pseudoaneurysms into the neck or nasal sinuses is generally rare. Dissection can occur intracranially and, on rare occasions, can spread intracranially from a primary extracranial origin.

2.5 Primary Cardiac Abnormalities

2.5.1 Atrial Fibrillation

Persistent and paroxysmal atrial fibrillation (AF) are potent risk factors for first and recurrent stroke. It has been estimated that AF affects more than 2,000,000 Americans and becomes more frequent with age, being the most frequent cardiac arrhythmia in the elderly [6, 38]. The prevalence of AF peaks at 8.8% among people over the age of 80 years. In the Framingham Stroke Study, 14% of strokes occurred because of AF. The absolute risk of stroke in patients with AF varies 20-fold, according to age and the presence of vascular risk factors [6, 7]. Several stroke risk stratification schemes have been developed and validated. Overall, patients with prior stroke or transient ischemic attack carry the highest stroke risk [6, 39].

These emboli often originate as a mural thrombus, usually harbored by the fibrillating atrium, and more specifically the atrial appendage, because of its potential for regions of stagnant blood flow. Anticoagulation with warfarin has been shown to decrease stroke risk in patients with AF, with a risk ratio reduction of 68% (95% CI, 50–79) and an absolute reduction based on several studies in annual stroke rate from 4.5% for the control patients to 1.4% in patients treated with adjusted-dose warfarin [6, 7, 40]. The risk of warfarin-associated major hemorrhage, mostly intracranial, is approximately 0.5% per year. A hemorrhagic stroke, however, can still occur with a well-controlled prothrombin time [40].

2.5.2 Myocardial Infarction

Myocardial infarction (MI) commonly causes intraventricular thrombus to form on the damaged surface of the endocardium. Stroke or systemic embolism can occur in up to 12% of patients with acute MI and a left ventricular thrombus. Stroke rate is even higher in those with anterior infarcts, reaching 20% of those with large anteroapical [41] infarcts. Poor left ventricular function and ventricular aneurysm is also associated with increased risk of embolic stroke. Embolism is more frequent during the first 1–3 months, although the embolic risk remains substantial even beyond the acute phase in patients with AF, persistent myocardial dysfunction, or congestive heart failure [7, 41].

2.5.3 Valvular Heart Disease

Atrial fibrillation with mitral valve disease has long been considered a stroke risk factor. Recurrent embolism occurs in 30–65% of patients with rheumatic mitral valve disease who have a history of a previous embolic event. Most of these recurrences (around 60%) develop within the first year. Mechanical prosthetic valves are a prime site for thrombus formation and patients with these valves require anticoagulation [7, 38]. Bacterial endocarditis can cause stroke as well as intracerebral mycotic aneurysms. Because mycotic aneurysms are inflammatory defects in the vessel wall, treatment with systemic thrombolysis or anticoagulation can lead to rupture with subsequent lobar hemorrhage. Nonbacterial, or “marantic,” endocarditis is also associated with multiple embolic strokes. This condition is most common in patients with mucinous carcinoma and may be associated with a low-grade disseminated intravascular coagulation. A nonbacterial endocarditis, called Libman–Sacks endocarditis, occurs in patients with systemic lupus erythematosus (SLE) [42].

The role of mitral valve prolapse in stroke remains controversial. It is the most common form of valve disease in adults. Although generally innocuous, it can become symptomatic, and serious complications can occur. Strands of filamentous material attached to the mitral valve seen by echocardiography have recently been reported as a risk factor for embolic stroke [38].

2.5.4 Patent Foramen Ovale

Patent foramen ovale (PFO) occurs in approximately 27% of the population. Atrial septal aneurysms (>10-mm excursions of the interatrial septum) are less common, affecting approximately 2% of the population [43]. Though the left-sided pressures are usually higher than those on the right, the flow of venous blood toward the foramen ovale can direct some blood to the left side of the heart. Increases in right-sided pressures, which can occur with pulmonary embolism or Valsalva maneuver, increase blood flow from right to left atrium. Studies have found an association between PFO and cryptogenic stroke. It is thought that venous thromboembolism from leg or pelvic vein clots enter the right atrium, and then cross to the left side of the heart and enter the cerebrovascular arterial circulation causing embolic stroke [7, 44]. This conclusion

is supported when stroke occurs in the context of deep vein thrombosis (DVT) or pulmonary embolus (PE) in a patient with PFO. Echocardiography has shown these paradoxical emboli crossing the foramen ovale. The diagnosis of PFO can be made by echocardiography when bubble contrast is seen to cross to the left side of the heart after intravenous injection, or bubble contrast is seen on transcranial Doppler examination of the intracranial vessels [43]. Without concurrent DVT or PE, it is never clear whether the PFO was causal. In the Patent Foramen Ovale in Cryptogenic Stroke Study (PICSS), a substudy of WARSS (Warfarin Aspirin Recurrent stroke study), no difference in recurrent stroke risk was attributable to the presence of PFO, neither was there a difference in recurrent stroke in patients treated with aspirin compared to warfarin [45]. However, these subjects were neither randomized based on PFO status, nor were most otherwise cryptogenic, so the generalizability of this study for PFO management is limited. Insufficient data exist to recommend PFO closure in patients with a first stroke and a PFO. PFO closure, however, may be considered for patients with recurrent cryptogenic stroke despite optimal medical therapy [7].

2.5.5 Cardiac Masses

Atrial myxoma is a rare atrial tumor that causes multiple emboli of either thrombus or myxomatous tissue. When myxomatous material is embolized from the left atrium into the brain arteries, they may cause the formation of multiple distal cerebral aneurysms with risk of hemorrhage [46]. Papillary fibroelastomas are rare benign cardiac tumors usually involving a heart valve. They are small vascular growths with marked papillary projections. They usually grow on the aortic or mitral valves. The tumor consists of fibrous tissue surrounded by an elastic membrane, which in turn is covered by endothelium. One of the most common clinical presentations is of transient ischemic attack or stroke [47, 48].

2.6 Embolic Stroke

2.6.1 The Local Vascular Lesion

The occlusion of an intracerebral vessel causes local changes in the affected vessel and its tributaries. There

is also a vascular change in the microcirculation supplied by these vessels. As an embolus travels toward the brain, it is forced into progressively narrower vessels before it lodges into a vessel too small for it to pass [49]. The initial shape of emboli and their course are not well known. Because the major vessels of the Circle of Willis have lumen diameters of <4 mm, dangerous clots need not to be very large. Some clots that have a string shape and curl, like those from a deep vein, become temporarily stuck at turns in the vessel, eventually becoming compacted into a plug when they finally lodge. The vessel is often distended [49, 50]. For example, symptoms localized to basilar branches sometimes occur in the moments before a top of the basilar ischemic syndrome occurs. Called the “basilar scrape,” this is thought to result from temporary ischemia caused by the embolus as it travels up the vertebral and basilar vessels to the bifurcation at the top of the basilar artery. Emboli lodge at branch points, such as the T-like bifurcation of the basilar into two posterior cerebral arteries and the T-like bifurcation of the carotid into the ACA and MCA. The fork of the MCA stem into the two or three divisions of the MCA is another common lodging site for emboli. Small branches coming off the large vessel at these sites will be occluded [51]. There are a number of thin penetrator vessels that supply the midbrain and the overlying thalamus that are occluded when there is an embolus to the top of the basilar artery. Penetrators to the striatum and internal capsule arise from the MCA stem, and the anterior choroidal artery arises from the distal internal carotid. Ischemia in these vascular territories that have little collateral flow can quickly lead to infarction as compared to ischemia in the cerebral cortex, which can receive blood flow via leptomeningeal collaterals.

2.6.2 Microvascular Changes in Ischemic Brain

In contrast to what happens when small vessels without collateral circulation are occluded, the vascular tree distal to an occlusion in a main cerebral vessel has many potential collateral channels to keep it patent distally. In order to keep blood flow at normal levels, the distal vascular tree undergoes maximal vasodilatation which is in part regulated by the action of nitric oxide on the vascular wall. Ischemic vasodilatation can recruit collateral

flow to the cortex from other vascular channels through leptomeningeal vessels [5]. In the fully dilated bed, the cerebral blood flow will be driven by the blood pressure. As blood flow falls in the microvessels, there is potential for microvascular thrombus formation. The endothelial surface of the microvascular circulation normally has an anticoagulant coating. Under ischemic conditions, it becomes activated to express white blood cell adhesion molecules. White blood cells attach to the vessel wall and may mediate microvascular injury and microthrombosis [49]. Therefore, sometimes despite the recanalization of the main feeder vessel, there is “no reflow” of blood to the tissue. This loss of accessibility of the microvasculature to the blood pool and decreased cerebral blood volume are closely linked to infarction [52]. In animal studies, stroke size is decreased if white blood cell counts are reduced or drugs are given to block white cell adhesion. Free radical production by the white blood cells is considered an important mediator of vessel-wall injury in stroke [53].

Damage to the vessel wall is manifested as hemorrhage into the infarct. Hemorrhagic conversion of embolic stroke is very common when examined by magnetic resonance imaging (MRI) sequences sensitive to magnetic susceptibility of the iron. In hemorrhagic conversion there are multiple small hemorrhages in the infarct that may not be apparent on CT scan or may be seen as a hazy or stippled increase in signal intensity. Large hemorrhages can also occur in the infarcted tissue. The latter are more common in large strokes that include the deep white matter and basal ganglia. As opposed to hemorrhagic conversion, which is usually not accompanied by clinical change, the large hematoma in the infarcted zone is often associated with worsened neurologic deficit [54, 55]. These hematomas frequently exert considerable mass effect on adjacent brain tissue and can increase intracranial pressure (ICP) and distort mid-brain and diencephalic structures. Since these hemorrhages more commonly occur in the larger strokes, they often compound the mass effect due to ischemic edema. Hematoma formation is the major risk of thrombolytic therapy. Hemorrhagic transformation after thrombolytic therapy in ischemic stroke may be related to dysregulated extracellular proteolysis within the neurovascular matrix. Possible mediators of this process are matrix metalloproteinases, a large family of zinc endopeptidases responsible for remodeling almost all matrix substrates in brain [54, 56]. The use of drugs that impair hemostasis (anticoagulants) may also increase the probability of

bleeding into a vascular territory with an injured vascular wall. Hemorrhage occurs when the blood flow and blood pressure are restored in a previously ischemic zone. The injured vascular wall is incompetent to withstand the hydrostatic pressure and the return of oxygen and white blood cells may also intensify the reperfusion injury at the vascular wall [54].

The vascular wall also regulates the flow of large molecules from the vascular space to the intercellular space (the so-called blood–brain barrier). In ischemia, there is net movement of water into the brain tissue. This is the basis of the increased T2 signal on MRI and the low density on CT in the first few days after stroke [57, 58]. At variable times after stroke, contrast imaging studies show that large molecules also cross into the brain tissue. The net water movement into brain, ischemic edema, can lead to secondary brain injury as a result of increased ICP and the distortion of surrounding tissues by the edematous mass effect [58]. Mass effect, causing clinical worsening and classical herniation syndromes, is not uncommon in patients with large MCA strokes.

2.6.3 MCA Embolus

An embolus to the MCA is common and can cause a catastrophic stroke. It is also amenable to rapid therapy. For these reasons, special emphasis is placed here on this stroke subtype. As discussed above, carotid stenosis and occlusion can cause stroke by artery-to-artery embolus to the MCA territory or by causing a low-flow state [17]. Distinguishing features of carotid stenosis include the common occurrence of multiple stereotypic spells of transient ipsilateral hemispheric or monocular dysfunction. In addition, in carotid stenosis multiple emboli may occur over a short period of time. In some cases of embolus to the MCA from a severely stenotic carotid, the embolus may be less well tolerated and the stroke more severe due to the lower perfusion pressure above the carotid lesion [17]. Embolus from the carotid to the MCA can also occur from the stump of a completely occluded carotid [59]. If the occlusion is hyperacute, often the absence of flow in the region from the carotid bulb to the distal ICA reflects collapse of the lumen due to low pressure rather than occlusion of the entire carotid with thrombus. In these cases, it is sometimes possible to dissolve the fresh clot in the extracerebral portion of the carotid and advance a catheter to treat the intracerebral clot. This can be

followed by angioplasty of the carotid stenosis. However, if the carotid occlusion is chronic, the organized clot might extend up from the occlusion in the neck intracranially and prevent passage of the catheter. This will preclude intra-arterial thrombolysis of the MCA clot [60, 61].

2.6.4 Borderzone vs. Embolic Infarctions

Carotid stenosis can also cause low-flow stroke when the collateral flow from the anterior communicating artery (ACoA), PCoA, and retrograde through the ophthalmic artery is insufficient to perfuse the ipsilateral hemisphere. Low flow causes symptoms and infarction in the distal cortical borderzone territory between the distal branches of the ACA, MCA, and PCA [17]. The actual boundaries between these territories may shift due to increased flow through the ACA or PCA to supply the MCA. The classic presentation is called the “man in the barrel syndrome.” The borderzone ischemia causes dysfunction in the regions for motor control of the proximal arm and leg [19, 62]. There may be an aphasia known as “transcortical aphasia” due to disconnection of the laterally placed language areas and medial cortex. In transcortical aphasia, repetition is relatively preserved. In transcortical motor aphasia there is hesitant speech but preserved comprehension. In transcortical sensory aphasia, comprehension is more severely impaired than speech. Cortical borderzone stroke is seen on imaging as a thin strip of infarction that runs from the posterior confluence of the MCA, ACA, and PCA branches in the posterior parietal cortex extending forward on the upper lateral surface of the cerebrum. On axial scans there is a small region of stroke on each of the upper cuts; only by mentally stacking the images does the examiner appreciate that the lesions are contiguous and form an anterior to posterior strip of infarction. The strip overlies the motor areas for control of proximal leg and arm. A cortical borderzone infarction is not entirely specific for low flow, because it can also be caused by showers of microemboli that lodge in the region of neutral hydrostatic pressure [19, 62, 63].

In addition to the cortical borderzone, there is also an internal borderzone formed by the junction of the penetrator arteries from the MCA and the leptomeningeal cortical vessels that enter the cortex and extend into the white matter. These lesions lie in the corona radiata and centrum semiovale. This borderzone again forms a strip that

lies in the white matter just above and lateral to the lateral ventricle. Instead of a strip of contiguous stroke, the internal borderzone region usually undergoes multiple discrete circular or oval-shaped strokes that line up in an anterior to posterior strip. Partial internal borderzone infarctions often have indistinct margins and are distinguished from lacunae, which are smaller (<1.5 cm in diameter) and occur at a lower axial plane. It is also important to distinguish internal watershed from striato-capsular infarctions, which often are comma-shaped lesions and occur at a lower plane with involvement of the internal capsule and striatum. Internal borderzone infarction may be more specific for low-flow stroke [19, 64].

2.7 Lacunar Strokes

Lacunar infarcts are small infarcts in the deeper parts of the cerebrum and brainstem and result from occlusion of penetrating branches of the large cerebral arteries—MCA, PCA, basilar, and less commonly, ACA and vertebral arteries. Penetrator vessels come off the basilar artery, the MCA stem, and the PCA at right angles to the parent vessel. Small-vessel occlusive disease is almost entirely related to hypertension and is characterized pathologically by lipohyalinosis and fibrinoid necrosis of small 80–800 µm penetrator vessels. Occlusion of these penetrators causes small infarcts, termed lacunars, in their respective vascular territories, most commonly in the caudate, putamen, external capsule, internal capsule, corona radiata, pontine tegmentum, and thalamus [65]. Hypertensive hemorrhage occurs in these same regions and is due to the same hypertensive changes in the penetrator vessels. Small deep infarcts are not classified as lacunes if they are part of larger infarcts involving the cortex or are due to occlusion of large arteries. Lacunar infarcts can vary in size from large (1.5–2.0 cm) to very small (3–4 mm). The deficits caused by these small strokes are a function of their location. Because the penetrator vessels supply deep white matter tracts as they converge in the internal capsule or brainstem, the consequence of lacunar stroke is often related to disconnection of neural circuits [1, 65, 66].

Lacunar strokes are especially common in patients who have diabetes in addition to hypertension. Lacunar strokes can cause immediate motor and sensory deficits, though many patients recover considerable function in the weeks or months following lacunar-stroke onset [66]. In the National Institute of Neurological

Disorders and Stroke Recombinant Tissue Plasminogen Activator Stroke Study (NINDS rt-PA Study), 50% of patients returned to a normal functional level within 3 months without rt-PA treatment. In the group receiving rt-PA, the probability of good recovery increased to 70% [67].

A number of clinical syndromes commonly occur due to lacunar strokes (see Table 2.3). Pure sensory stroke or transient ischemic attack is the most common lacunar manifestation. It takes the form of numbness of the face, arm, and leg on one side in the absence of other symptoms. Pure motor hemiparesis is the second most frequent syndrome and refers to a pure motor stroke involving face, arm, and leg. However, the clinical symptoms may not be specific for the chronic occlusive disease of the small penetrator vessels described above. Of special importance is the infarct in a penetrator territory caused by disease of the parent vessel. In some cases, the penetrator stroke is only one, sometimes the first, of many regions to undergo infarction due to major vessel occlusion [65, 66]. In basilar artery occlusive disease, ischemia in the distribution of a single penetrator may occur as the “opening shot.” On succeeding days, the origin of multiple penetrators becomes occluded due to the propagation of mural thrombus in the vessel. In addition, atherosclerosis in the parent vessel may narrow the lumen at the origin of the penetrators [68].

Table 2.3 Clinical lacunar syndrome and corresponding infarct locations

| Clinical syndrome | Location of lacunar stroke |
|--|--|
| Pure motor hemiparesis involving face, arm, and leg | Contralateral posterior limb internal capsule or overlying corona radiata Contralateral pontine tegmentum |
| Pure unilateral sensory loss involving face, arm, and leg | Contralateral thalamus |
| Hemiparesis with homolateral ataxia | Contralateral thalamocapsular region Contralateral upper third of the medial pons |
| Dysarthria, clumsy hand | Contralateral lower third of the medial pons |
| Hemisensory loss and homolateral hemiparesis | Genu of the internal capsule |
| Sensory loss around corner of mouth and homolateral weakness of hand | Thalamocapsular region |

Atherosclerosis may also occur in some of the larger penetrators. Large strokes, or giant lacunes, occur as a result of the occlusion of multiple penetrators with occlusive disease in the parent vessel. This is particularly common in the MCA territory where leptomeningeal collateral flow preserves the cortex, but absence of collateral flow to the penetrator territory results in infarction [65, 66].

In some cases, showers of small emboli cause penetrator strokes as well as cortical strokes. Small emboli may also reach these vessels. Chronic meningitis due to tuberculosis or syphilis commonly causes stroke in the penetrator territory due to inflammation around the parent vessel at the base of the brain with occlusion of the thin penetrators exiting through the inflammatory reaction (Table 2.4 lists the causes of lacunar infarcts) [69].

Table 2.4 Causes of small vessel infarction

| Vascular lesion underlying penetrator vessel stroke | Clue to diagnosis |
|---|--|
| Hyalinization and fibrinoid necrosis | History of hypertension, especially with diabetes. Small lesion <1 cm diameter in the distal territory of the penetrator. Often multiple, bilateral, and even symmetrically placed lesions |
| Atherosclerosis of the parent vessel occluding the lumen of the penetrator by atherosclerotic plaque or superimposed thrombus | Stenosis in the parent vessel on MRA, CTA, transcranial ultrasound, or direct angiography Large infarct that extends to the origin of the penetrator from the parent vessel. Multiple strokes in the distribution of the same parent vessel |
| Atherosclerosis in the penetrator vessel | Large infarct in penetrator territory with normal parent vessel lumen on CTA/MRA/direct angiography |
| Chronic meningitis | Large infarct in the penetrator territory. Rapidly progressive stroke course, presence of fever, chronic headache, elevated ESR, abnormal RPR, inflammatory CSF Narrowing of the lumen with gadolinium enhancement of the parent vessel on MRI |
| Embolism to the penetrating artery | Evidence of other small emboli. No history of hypertension or atherosclerosis |

CSF Cerebrospinal fluid; CTA CT angiography; ESR erythrocyte sedimentation rate; MRA magnetic resonance angiography; MRI magnetic resonance imaging; RPR rapid plasma reagent

2.8 Other Causes of Stroke

2.8.1 Inflammatory Conditions

Primary angiitis of the central nervous system is a rare form of vasculitis of unknown cause. Blood vessels of various sizes are affected by inflammation and, on occasion, hemorrhage occurs in addition to ischemic stroke. The mean age of onset is 50 years, and men are affected twice as often as women. Headache and encephalopathy are the most frequent initial symptoms. Stroke or focal symptoms develop in less than 20% of patients at the onset of disease and are uncommon in the absence of headache or encephalopathy. The cerebrospinal fluid (CSF) often shows signs of inflammation. Diagnosis is commonly made after a biopsy of the leptomeningeal vessels demonstrates the granulomatous inflammation [70]. Foreign body and Langerhan-type giant cells may be seen, with associated lymphocytes, plasma cells, and histiocytes, a reactive pleomorphic infiltrate. When caught in its early stages, treatment with cyclophosphamide and/or steroids can reverse the process. Left untreated, the disease is usually fatal and causes severe diffuse or multifocal brain injury [70, 71].

Systemic lupus erythematosus (SLE) has a variety of presentations in the nervous system. SLE is a relatively rare etiology of stroke, even in young persons, being found in 3.5% of patients presenting with stroke before the age of 45. The risk of recurrence of stroke in patients with SLE is much higher than in other stroke patients (more than 50% of SLE patients who have a stroke will have multiple infarcts if secondary prophylaxis is not instituted). The major causes of stroke in SLE patients are cardiogenic emboli and hypercoagulable states [72–74]. Lupus anticoagulant includes a heterogeneous group of antibodies that interfere with phospholipid coagulation tests in vitro (increases the partial thrombin time). Lupus anticoagulant and anticardiolipin antibodies are partially overlapping autoantibodies associated with venous thrombosis, spontaneous abortion, and stroke. Patients with SLE can have multiple cardiac abnormalities, and based on autopsy material, cardiogenic sources of emboli appear to be the most common etiology of stroke in patients with stroke. Liebman-Sacks is a verrucous endocarditis with deposition on the heart valves of platelet thrombus and hyalinized blood, not covered by endothelium. The idea that stroke in patients with SLE is caused by

vasculitis and should be treated with steroids or immunosuppression was not validated by autopsy studies or biopsy data [72, 74].

Temporal arteritis is a giant cell arteritis involving various medium-sized and larger arteries seen in older adults with an elevated erythrocyte sedimentation rate and elevated fibrinogen level. Temporal arteritis can cause headache, tenderness over the temporal artery, jaw claudication, and transient visual loss. It is sometimes associated with polymyalgia rheumatica. Blindness due to ischemic optic neuropathy is probably the most feared manifestation of the disease, but stroke is the leading cause of death in temporal arteritis [75, 76]. At microscopic level, there is an inflammatory infiltrate of the vessel wall that is usually focal and segmental. Cranial branches of the aorta are the main vessels involved, with a preference for vessels with a high elastic component like the ophthalmic and posterior ciliary arteries. It occasionally affects the vertebral artery [76].

Takayasu's arteritis is a giant cell arteritis of the large vessels off the arch of the aorta that occurs predominantly in young women. Inflammatory narrowing or obstruction of the proximal portion of the aortic arch major branches is characteristic [77]. It can cause occlusive disease in the carotid and vertebral arteries, leading to stroke. The etiology of Takayasu's arteritis is still unknown, although an autoimmune pathogenesis is often suggested [77, 78].

2.8.2 Venous Sinus Thrombosis

Venous sinus thrombosis can cause focal neurologic deficits, often with seizures, headache, and other signs of raised intracranial pressure. Venous strokes are frequently hemorrhagic and located in the proximity of the occluded sinus—parasagittal in superior sagittal sinus thrombosis, temporal lobe in transverse sinus thrombosis, and thalamus in straight sinus thrombosis. The annual incidence of cerebral venous thrombosis is 3–4 cases per million [79]. According to autopsy studies, cerebral venous thrombosis causes 1–9% of all deaths because of stroke and cerebrovascular diseases. Venous sinus thrombosis is seen in patients with hypercoagulable state or as a consequence of infiltration of the major sinus by tumor or infection [7, 79]. A hypercoagulable risk factor is found in approximately 85% of patients with cerebral venous thrombosis. An environmental risk

factor like pregnancy or puerperium generally contributes to cerebral venous thrombosis in a genetically prone individual. Cerebral venous thrombosis can also follow lumbar puncture or spontaneous CSF leaks, probably due to a downward shift of the brain with increased pressure on the cerebral veins and sinuses [80].

2.8.3 Vasospasm in the Setting of Subarachnoid Hemorrhage

Subarachnoid hemorrhage (SAH) is most commonly caused by rupture of an intracranial aneurysm. It can produce vasospasm that may cause ischemia and infarction. Currently, vasospasm has surpassed rebleeding as the most important complication after rupture of an aneurysm. Vasospasm due to SAH is thought to occur in the majority of cases of SAH (angiographic vasospasm is detectable in perhaps as many as 60–70% of patients after subarachnoid hemorrhage), but is symptomatic only in about a third of this population [81]. Symptomatic vasospasm carries a 15% to 20% risk of stroke or death. Vasospasm peaks around 1 week after SAH, but it can be seen as early as 3 days or as late as 3 weeks after the initial event [82]. The underlying mechanisms are not understood, but vasospasm is clearly related to the amount of blood and its location in the subarachnoid space. Clinical symptoms generally develop slowly over a period of several hours to 1 or 2 days; however, clinical evolution can be rapid in the onset with a stroke-like presentation [81, 82].

2.8.4 Migraine

Epidemiological studies have demonstrated that migraine is associated with ischemic stroke independent of other risk factors. A meta-analysis of several observational studies showed a twofold increase in the risk of ischemic stroke in patients with migraine and threefold risk in patients with migraine with aura. The mechanism is unknown, but potential factors include vascular hyperreactivity and sensitivity to or increased amount of vasoactive substances [83]. During the aura phase of a migraine attack, spreading depression causes vasoconstriction leading to a decline in cerebral

blood flow to a level that may cause ischemic injury. Vasoconstriction can persist and cause changes in the vascular endothelium that lead to activation of platelets and coagulation cascade leading to thrombosis within the constricted artery [84]. An increased prevalence of silent infarcts has also been described in patient with migraine [84, 85].

2.8.5 Reversible Cerebral Vasoconstriction Syndrome

Reversible cerebral vasoconstriction syndrome comprises diverse conditions characterized by abrupt-onset severe headaches, focal neurological deficits, and segmental constriction-dilatation of cerebral arteries. Reversible cerebral vasoconstriction syndrome (sometimes called “Call-Fleming syndrome”) is usually benign and self-limited, with clinical-angiographic resolution occurring over days to weeks. The differential diagnosis of reversible cerebral vasoconstriction syndrome includes conditions associated with thunderclap headache and conditions that cause irreversible or progressive cerebral artery narrowing, such as intracranial atherosclerosis and cerebral vasculitis [86, 87].

2.8.6 Primary Hematologic Abnormalities

Several hematologic disorders and hemostatic defects increase risk of ischemic stroke. Inherited thrombophilias (such as factor V Leiden; protein S, protein C, or antithrombin III deficiency; or the prothrombin G20210A mutation) rarely contribute to stroke in adults, but may play a larger role in pediatric stroke. Antiphospholipid antibody syndrome consists of venous and arterial occlusive disease in multiple organs, miscarriages, and livedo reticularis [7]. The association between antiphospholipid antibodies and stroke in the absence of antiphospholipid antibody syndrome is strongest for young adults. In the Antiphospholipid Antibodies in Stroke substudy of WARSS (WARSS/APASS), antiphospholipid antibodies were detected in 40.7% of stroke patients, but they had no effect on the risk of stroke recurrence (see Table 2.5) [88]. Thrombotic thrombocytopenic purpura (TTP) has

Table 2.5 Other causes of stroke

| | |
|---|---|
| Inflammatory conditions | Primary angitis Systemic lupus erythematosus Temporal arteritis Takayasu's arteritis |
| Venous sinus thrombosis | |
| Vasospasm in the setting of subarachnoid hemorrhage | |
| Migraine Reversible cerebral vasoconstriction syndrome | |
| Primary hematologic abnormalities | Thrombotic thrombocytopenic purpura Protein C or S deficiency Antithrombin III deficiency Prothrombin G20210A mutation Factor V Leiden mutation Antiphospholipid syndrome Sickle cell disease |

been recognized by the pentad of microangiopathic hemolytic anemia, thrombocytopenia, neurological symptoms, fever and renal involvement. Only 20–40% of patients manifest the classic pentad. Neurological involvement may be noticeable as a broad spectrum of generalized and focal symptoms including headache, dizziness, and decreased level of consciousness. Thrombosis mainly affects the microvessels of gray or white matter, and cortical or small subcortical infarcts can occur. TTP remains a life-threatening disease if left untreated. Emergency plasma exchange is the first line of treatment in adults with TTP [89].

Stroke occurs in 11% of children with sickle cell disease before the age of 20 years [90]. Cerebrovascular disease is also common in adults with sickle cell disease, with an incidence ten times greater than that of stroke in African Americans without sickle cell disease. Ischemic strokes in sickle cell disease are usually the result of fibrous proliferation of the intima, leading to intracranial artery stenoses. Prophylactic blood transfusion in children with sickle cell disease and abnormal transcranial Doppler exams can reduce the incidence of stroke among such children from 10% per year to less than 1% per year [91].

2.9 Conclusion

There are many causes of ischemic stroke. In the past, the absence of advanced imaging and diagnostic tools meant that the specific stroke etiology in a given patient often remained unknown. In the present day medicine, specialists can frequently identify the stroke etiology by carefully analyzing the results of the patient's history, clinical evaluation, and imaging. Identifying the cause of a stroke in each case is critical for treating the acute phase of the stroke, minimizing its progression and acute complications, and preventing its recurrence.

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