

Cerebrovascular Disease (Dr. Merchut) ---Clinical Aspects

Ischemic Cerebrovascular Disease

1. Definitions and terminology

Ischemia or hemorrhage are the byproducts of cerebrovascular disease, manifest as **sudden, focal neurological deficits related to specific vascular territories** of the central nervous system. Impairment or loss of consciousness is a global deficit, which rarely is caused by simultaneous, extensive or multiple hemorrhages or ischemic infarctions, and is more commonly due to other causes such as cerebral hypoperfusion, vasovagal syncope, or toximetabolic disorders. Some focal neurological deficits occur transiently from migraine or after seizures, and may mimic cerebrovascular disease (rarely migraine-related ischemic infarctions do occur). Cerebrovascular disease follows cancer and cardiovascular disease as a common cause of disability and death in the United States.

Transient ischemic attacks (TIAs) are defined as sudden, focal neurological deficits which completely resolve within 24 hours. Years of experience have shown that most TIAs only last minutes, but are a serious warning of high stroke risk. **Stroke** refers to a sudden, focal neurological deficit which does not completely resolve within 24 hours, but may variably improve over several weeks to months. Most of the time, a stroke is caused by ischemic infarction. Immediate medical attention is required for both TIAs and stroke, in order to prevent complications, limit neurological deficits if possible, and prevent future strokes. Appropriate therapy will vary and depends on the mechanism of the TIA or stroke and the localization of the vascular territory affected.

2. Pathogenesis of ischemic cerebrovascular disease

Most patients with cerebrovascular disease have significant atherosclerosis, predisposed by one or more risk factors such as hypertension, heart disease, diabetes mellitus, smoking, hyperlipidemia, and family history of vascular disease. Minor contributing factors include obesity, lack of exercise, and excessive alcohol consumption. Atherosclerotic vascular changes become more common even in older patients who lack these major risk factors. This vascular pathology may create symptoms by affecting larger arteries or smaller arterial branches, with some differences in the treatments for each condition. **Atherosclerotic changes predominate at the bifurcation points of large, major cervical and intracranial arteries**, perhaps partly due to more turbulent blood flow at these sites (Fig. 1). Gradually over months to years, intravascular **atheromas or arterial plaques** develop from subintimal lipid deposition, smooth muscle proliferation, and fibrosis. Enlarging atheromas or plaques may narrow or occlude an artery, or may ulcerate, or both. As ulceration disrupts the intima, the coagulation process is initiated, leading to local occlusion (thrombosis) or the distal propagation (embolization) of blood clot, platelets, fibrin, cholesterol, or calcified elements (emboli) which then occlude smaller caliber arteries downstream. **The two basic mechanisms of ischemic infarction are therefore local arterial thrombosis of an atheroma or embolic arterial occlusions from proximal sources** (Fig. 2).

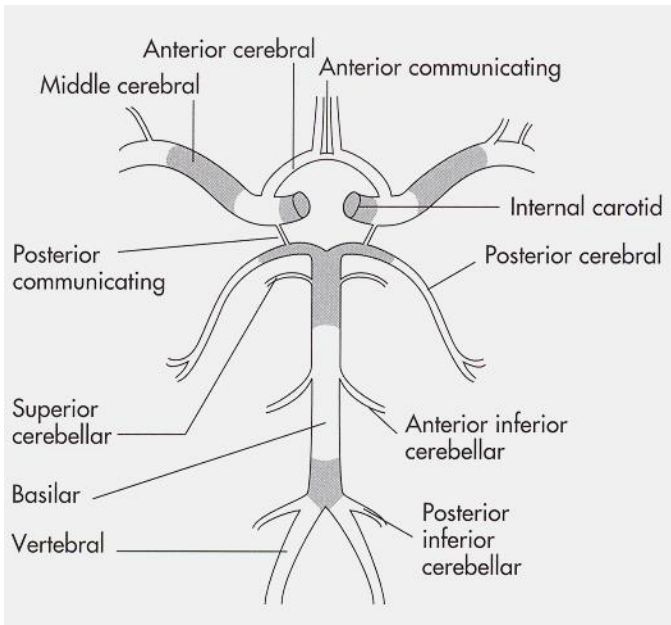


Fig. 1 Arterial anatomy at the base of the brain. Common sites for atherosclerosis are typically at bifurcation points, and appear shaded.

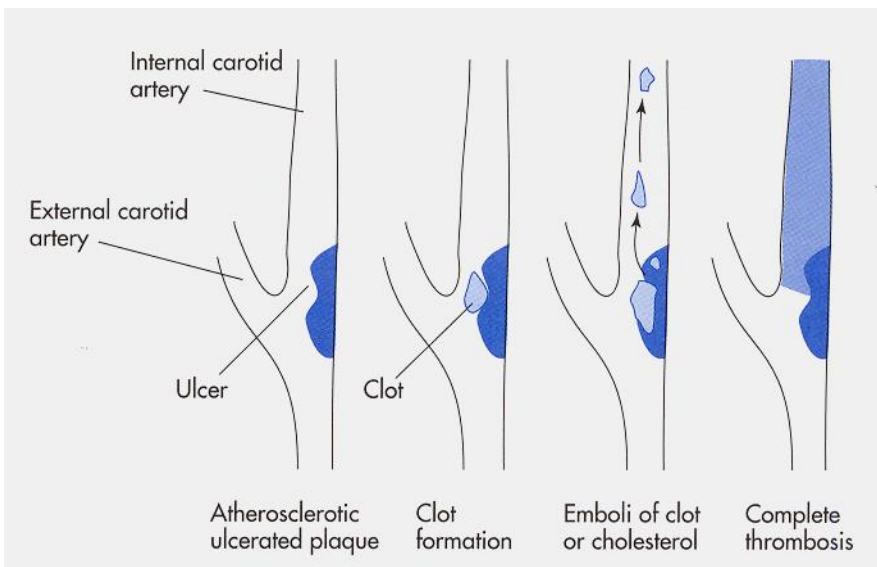


Fig. 2 Atherosclerosis at the cervical internal carotid artery.

For some fortunate patients having the gradual thrombosis of a cerebral artery, other arteries may detour blood flow to the potentially ischemic area of brain or brain stem, and an infarction and consequent neurological deficit is avoided. In that situation, the chance of having such valuable **collateral blood flow** is enhanced by a congenitally "complete" circle of Willis at the base of the brain. Those patients with an asymptomatic occlusion of a cervical internal carotid artery have benefited by collaterals from the external carotid artery, the vertebrobasilar arteries, or both. Branches of the external carotid artery may supply blood in reverse direction (retrograde flow) through the ophthalmic artery to the circle of Willis. Vertebrobasilar flow ending in the posterior cerebral arteries may continue through patent posterior communicating branches of the circle of Willis and supply the middle and anterior cerebral arteries. Such effective collateral flow is less common when arterial branches are suddenly occluded by emboli. The neurological deficit produced by an ischemic infarction, whether from a thrombotic or embolic mechanism, may improve within hours to days if partially ischemic areas of brain recover, or may improve more slowly over the subsequent weeks or months as different areas of the brain compensate for the impairment.

Pathologically, a large artery infarction causes the affected cerebral cortex to appear soft and swollen, with less distinction of the gray-white matter junction, and some spotty hyperemia from extravasated blood. Atrophy of this area subsequently occurs. Microscopically, within 12 to 36 hours of the clinical stroke, ischemic neurons shrink and appear eosinophilic ("pink neurons"). Days later, macrophages scavenge necrotic debris and cyst formation occurs with astrocytes at the periphery of the infarction.

Several important smaller arteries arise abruptly from the basilar artery and proximal anterior and middle cerebral arteries. This is somewhat unusual anatomy, lacking the typical, gradually progressive decrease in arterial caliber. These **perforator or lenticulostriate arteries supply deeper structures with significant functions, such as the basal ganglia, internal capsule, thalamus, and corona radiata**. Although occlusion of such a small artery may produce an ischemic infarction only millimeters in size, such a lesion in the internal capsule may cause a disabling hemiparesis. These small lesions have been called **lacunar infarcts**. Thrombosis, not emboli, causes these small artery occlusions.

3. Diagnosis of TIA and ischemic infarction

Generally in a **transient ischemic attack (TIA)**, an embolus from an arterial or cardiac source obstructs a branch of an internal carotid or vertebrobasilar artery. The clinical deficit produced depends upon the location of the ischemic area, but resolves quickly as the embolus fragments or disintegrates, re-establishing blood flow before any permanent damage occurs. A detailed history of the patient's transient symptoms is critical to determine which vascular system or territory was involved, to best determine therapy to prevent any future ischemic infarction. **Amaurosis fugax (monocular blindness)** is one type of **carotid territory TIA** involving the ophthalmic artery or its retinal branches. The patient often describes a "lowered dark shade" in one eye which gradually lightens up. Other carotid TIAs may cause hemispherical ischemia leading to **hemiparesis or aphasia**. **Vertebrobasilar territory TIAs** cause ischemia of the brain stem, cerebellum, or visual (occipital) cortex, producing symptoms of **ataxia**,

homonymous hemianopsia, or hemiparesis associated with "crossed" brain stem syndromes.

In the patient with a completed **ischemic infarction**, the neurological findings in conjunction with the history help localize the lesion and the arterial territory involved. A subsequent brain scan confirms or refutes the clinical impression, and excludes a hemorrhage, tumor or infection mimicking an ischemic infarction (Fig. 3). **Certain stroke syndromes suggest occlusion of larger arteries or branches.** A hemiparesis with greater weakness of the face and upper limb suggests an infarct in the precentral middle cerebral artery (MCA) territory. A hemiparesis with greater weakness of the lower limb suggests an infarct in the precentral anterior cerebral artery (ACA) territory. Sensory deficits limited to the face and upper limb likewise suggest an infarct in the postcentral MCA, while sensory deficits limited to the lower limb suggest an infarct in the postcentral ACA. Infarctions involving other MCA branches may produce aphasia or homonymous visual field deficits. Cerebellar hemispherical syndromes or "crossed" brain stem syndromes (Weber syndrome, Wallenberg syndrome) occur with occlusion of large vertebrobasilar arterial branches. **Infarcts from small artery occlusions may cause one of the "classic" lacunar syndromes or no symptoms at all** if the lesion involves a more "silent" part of the brain. **Pure motor hemiplegia, ataxic-hemiparesis, and clumsy hand-dysarthria** are lacunar syndromes from tiny infarcts in the internal capsule, corona radiata, or basilar pons. A **pure sensory stroke** is a lacunar syndrome from a small vessel occlusion involving the thalamus.

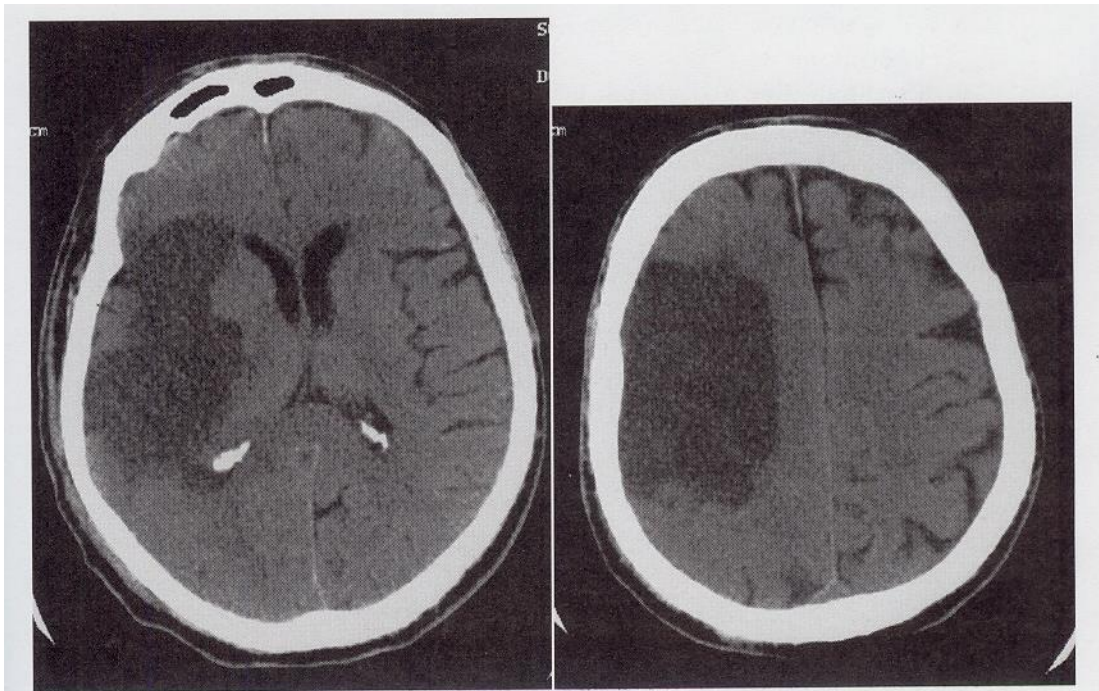


Fig. 3 CT scan of an acute infarct in the middle cerebral artery territory, appearing as a lucent area. The associated edema is shifting the lateral ventricles to the other side and obscuring the cortical sulci ipsilaterally.

All ischemic events can be considered problems with the "plumbing system" of the "pump" (heart), "pipes" (blood vessels), or "fluid" (blood). **The heart can be a source of emboli causing TIAs or ischemic infarction in large artery territories.** Emboli can arise from the endocardial clot associated with an acute myocardial infarction or poorly contracting left ventricle, or from left atrial clot created during atrial fibrillation. Infected or septic emboli may occur from endocarditis, an infection of heart valves. Venous clots in adults with a patent foramen-ovale can pass from the right to left atrium, and then into the cerebral circulation. **Arterial lesions usually consist of atherosclerotic plaques or stenoses which locally thrombose or embolize distally.** If a TIA or ischemic infarction occurs in an internal carotid artery territory, specific surgical or neuro-interventional procedures may be available, but are not applicable for vertebrobasilar lesions. **Lacunar infarctions from small vessel atherosclerotic occlusions are thrombotic in nature, and a diagnostic search for a cardiac or large artery source of emboli is not critical.** Non-atherosclerotic arterial lesions may also rarely occur, such as traumatic or spontaneous arterial dissections, inflammation (vasculitis), or degenerative occlusive disease such as fibromuscular dysplasia, where different treatment is indicated. **Hypercoagulable states, hereditary or acquired, can cause occlusions not only of large and small arteries but cortical veins as well.** Examples include sickle cell anemia, polycythemia vera, and the antiphospholipid antibody syndrome.

4. Treatment of transient ischemic attack (TIA)

A patient with TIAs typically has a normal neurological examination, but should be evaluated and treated urgently due to an increased risk of future stroke. In younger patients or those lacking stroke risk factors, a work-up for coagulopathy or non-atherosclerotic causes of ischemia should be done. In the more typical stroke-prone patient, **echocardiography** helps to determine any cardiac sources of emboli. Carotid TIAs can be evaluated with **ultrasound imaging** of the cervical internal carotid artery. Other arterial imaging techniques are useful for carotid or vertebrobasilar TIAs, such as **magnetic resonance angiography (MRA), computed tomography angiography (CTA)** or more invasive **catheter angiography** methods.

Patients with **symptomatic atheromatous lesions of 70 to 99 % stenosis at the origin of the internal carotid artery, benefit from carotid endarterectomy**, the surgical removal of this lesion, unless other life-limiting health conditions exist. A smaller risk reduction in future stroke exists when endarterectomy is done for symptomatic lesions of 50 to 69% stenosis, and even for **asymptomatic** lesions of 60 to 99% stenosis. These benefits depend on an experienced surgical team with a low complication rate. A complete or 100% stenotic lesion precludes any surgery since its thrombotic occlusion extends from the neck to the base of the skull. Other neuro-interventional procedures offer alternative ways of treating cervical internal carotid stenotic disease in those unable to tolerate or wishing to avoid surgery, including arterial **stenting and angioplasty** by means of intravascular catheters.

Warfarin therapy helps reduce the stroke risk in patients with chronic atrial fibrillation (target INR 2.5) if no contraindications for anticoagulation exist. In all other TIA patients, stroke reduction is achieved with **antiplatelet drugs such as aspirin 50 to**

325 mg daily, **clopidogrel** 75 mg daily, or **aspirin 25 mg/dipyridamole 200 mg** twice daily. **Statin drugs** reduce the risk of stroke even in the absence of hyperlipidemia. Medical control of blood pressure and diabetes, cessation of smoking, and other stroke preventative measures are indicated in all patients.

5. Treatment of ischemic infarction

Patients with an acute ischemic infarction and a moderate neurological deficit may have improved functional recovery if **intravenous tPA (tissue plasminogen activator), a thrombolytic drug, is administered within 3 hours of stroke onset** (or even up to 4.5 hours for milder deficits in patients under 80 years of age). Conditions prohibiting tPA include the presence of hemorrhage on a brain CT scan, uncontrollable hypertension, extreme hypo- or hyperglycemia, concurrent use of warfarin, or increased bleeding risk from recent surgical or invasive procedures. Obviously, the greatest risk of using tPA is intracranial hemorrhage, which can be fatal. In special stroke centers, tPA may also be given via arterial catheter during angiography. In ischemic stroke patients who cannot receive tPA, endovascular thrombectomy may be an alternative acute therapy. In any patient, **brain CT or MRI scans help indicate whether a large artery occlusion occurred, in which case embolic sources must be investigated for the possible need for warfarin, carotid endarterectomy or interventional procedures, versus a small artery occlusion, where antiplatelet drugs and medical therapy are used.** Regardless of the selected therapy, patient survival is improved by hospitalization in a specialized stroke unit.

Hyperglycemia during an acute ischemic infarction is associated with a poorer prognosis, so saline without dextrose is the preferred initial intravenous fluid, and insulin may be needed to **ensure normal glucose levels.** **Blood pressure (BP)** must be carefully monitored but not "over treated" since further reduction in cerebral perfusion may further worsen an area of focal ischemia. In the absence of symptoms from hypertensive encephalopathy, mild to moderate blood pressure elevations can be observed without treatment. BP maintenance below 185/110 mm Hg is required when using thrombolytic therapy, while intravenous antihypertensive drugs like labetalol may be needed for BP > 220/120 mm Hg. **Warfarin** anticoagulation clearly reduces future stroke risk in patients with atrial fibrillation, but may need to be temporarily withheld to avoid early complications of cerebral hemorrhage in patients with large acute ischemic infarctions. Warfarin therapy appears indicated also for ischemic infarction related to antiphospholipid syndrome and cerebral venous thrombosis. Newer direct thrombin inhibitors provide an alternative to warfarin. **Antiplatelet medication** is used in patients where warfarin is not indicated. All patients must be prevented from complications that may accompany the neurological deficits of stroke, such as seizures, aspiration or choking, and pulmonary emboli from deep venous thrombosis.

If a patient with a recent cerebral infarction develops impaired consciousness in the absence of hypoglycemia, **increased intracranial pressure** must be considered. Within 3-5 days of an extensive cerebral infarction brain edema can develop, or even earlier, hemorrhagic transformation of an initially ischemic infarct can occur. If an obtunded patient requires tracheal intubation for airway protection, **mechanical hyperventilation** to a pCO₂ of 30-35 mm Hg helps reduce increased intracranial pressure

(ICP). The hypocapnia induces cerebral vasoconstriction which reduces cerebral blood volume. Elevated ICP can also be lowered with intermittent intravenous boluses of **mannitol or hypertonic saline**. Emergent surgical removal of herniating ischemic or hemorrhagic brain is a more aggressive approach which may be best used for cerebellar lesions. Corticosteroids do not reduce the increased ICP from ischemic infarction or hemorrhage, but do counteract the elevated ICP from tumor or infection.

After any acute stroke treatment and management of complications, future stroke risk prevention is planned where indicated, including various procedures for cervical carotid stenotic lesions, use of warfarin or antiplatelet medication, statin drugs, and medical management of stroke risk factors. Conservative, supportive care may be the rational choice for patients surviving with severe neurological deficits and disability. Other patients expected of some recovery are sent to rehabilitation programs for physical, occupational, and speech therapy.

Intracranial Hemorrhage

1. Pathogenesis of cerebral hemorrhage

Cerebrovascular disease from hemorrhage is less common than that from ischemic infarction. Although several causes of cerebral hemorrhage may occur, the clinical symptoms are often similar. Since arterial blood pressure normally exceeds intracranial pressure (ICP), the sudden rupture of arterial blood into the brain parenchyma abruptly increases ICP, causing **severe headache, impairment or loss of consciousness, and a focal neurological deficit** dependent on the location of the bleeding. The edema around the hematoma worsens, leading to potentially fatal shifting or herniation of the brain. Although perfusion around the area of the hematoma is impaired, this focal ischemia may resolve with improvement of the clinical deficit if the patient survives the increased ICP. Rarely a small hemorrhage will not affect consciousness and will be clinically mistaken for an ischemic infarction until brain imaging is performed. **A deeply located hemorrhage suggests hypertension as the cause, while more superficial hemorrhages at the poles of the frontal, temporal, or occipital lobes often occur from head trauma.**

Pathologically cerebral hemorrhage appears as a dark red clot with surrounding edema and occasional dissection into the ventricular system if the bleeding is deep and extensive. The clot gradually liquefies, edema resolves, and the remaining cyst or slit appears to be peripherally stained brown from hemosiderin.

Bleeding from venous sources becomes a problem in elderly patients who normally have some degree of brain atrophy. Mild or trivial head trauma may tear taut bridging cortical veins, which empty into larger venous sinuses. Such venous bleeding usually accumulates in the subdural space, not within the brain parenchyma. Progressive expansion of the **subdural hematoma** may also impair cognition and consciousness, and even create some focal neurological deficits, treated by timely surgical removal of the clot.

2. Etiology and treatment of cerebral hemorrhage

Patients with an acute cerebral hemorrhage should be observed in the intensive care or stroke unit. Most cerebral hemorrhages are readily seen with a noncontrasted CT brain scan (Fig. 4). **Traumatic** hemorrhage is usually obvious from the history and other signs on the physical examination. The prothrombin time (INR) should be checked if the patient takes **warfarin** for another medical condition, and other blood tests for a **bleeding disorder** warrant checking if the cause of hemorrhage is unclear or non-traumatic bleeding is also occurring elsewhere in the body. Infusions of platelets or plasma clotting factors are urgently given where indicated. **Cocaine** or other sympathomimetic drugs which abruptly increase blood pressure may also cause cerebral hemorrhage, so screening the urine for these illicit drugs may be indicated in some cases. **Hypertension is the most common cause of cerebral hemorrhage.** The weakened walls of small, lenticulostriate arteries rupture, **bleeding most often into the striatum** (putamen and caudate) **and thalamus**, and less often into the subcortical white matter, pons, and cerebellum. Treatment involves control of blood pressure and increased intracranial pressure. Surgical evacuation of the hematoma is warranted generally only for worsening cerebellar hemorrhages, where brain stem herniation is prevented often with minimal residual neurological deficits.

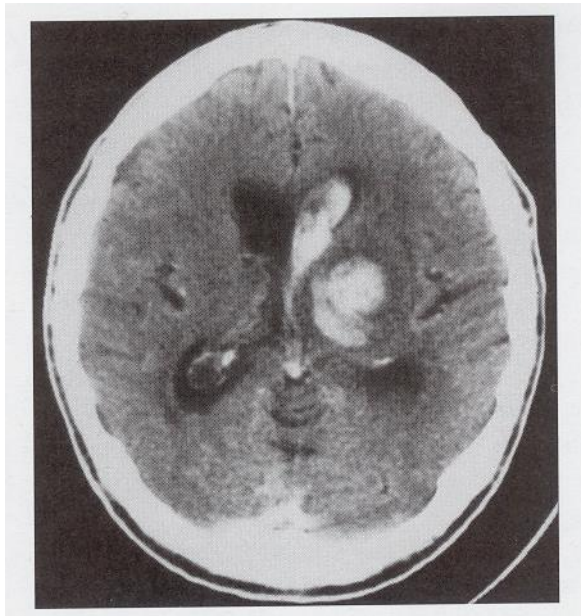


Fig. 4 CT scan of an acute hypertensive hemorrhage, originating in the thalamus and rupturing into the lateral ventricle. Acute blood appears dense or “white” on CT, as do calcified structures such as the skull.

Cerebral amyloid angiopathy leads to recurrent lobar hemorrhages usually in the posterior cerebral hemispheres. It is a hereditary condition whereby arterial walls are weakened by amyloid deposits. Some **congenital vascular abnormalities** also carry a risk of rupture and hemorrhage, especially **arteriovenous malformations (AVMs)**. AVMs are an abnormal connection of cerebral artery to vein, without intervening capillary bed, which enlarge slowly over time. Computed tomography or catheter angiography may be needed if an AVM is not already visualized on a brain MRI scan. Small AVMs may be successfully resected surgically, or occluded by intravascular procedures, to prevent future bleeding. Cerebral hemorrhages may also occur **within brain tumors or ischemic infarcts**. Damaged, ischemic endothelium may leak or ooze blood if reperfusion occurs in an ischemic infarction.

3. Etiology and treatment of subarachnoid hemorrhage

Trauma is the most common cause of bleeding into the subarachnoid space. In the absence of trauma, a **ruptured congenital berry aneurysm** is the most common cause of subarachnoid hemorrhage (SAH). Some subarachnoid bleeding may also accompany cerebral hemorrhage or multiple hemorrhages from a systemic bleeding disorder.

Congenital berry or saccular aneurysms arise in the circle of Willis at the base of the brain, especially anteriorly, beginning as bulges or thinned out-pouchings at arterial bifurcations (Fig. 5). Berry aneurysms progressively enlarge over time, with a greater risk of rupture beyond 7 to 10 mm in size. Some patients have a **sentinel headache or "warning leak"** from a mild to moderate amount of bleeding. It is critical to make the diagnosis here, since a recurrent SAH carries a high mortality rate. The severe pain from SAH is described as "the worst headache of my life" due to the increased intracranial pressure and meningeal irritation by the blood. **Nuchal rigidity and meningeal signs** are usually present, often with nausea and vomiting and impaired consciousness. Localizing neurological signs are often absent, since the hemorrhage does not involve the brain parenchyma itself. However, the presence of a **third cranial (oculomotor) nerve palsy** suggests that the berry aneurysm is near the posterior communicating artery. Some unfortunate patients have a massive SAH at the onset and never survive.

Patients suspected of having SAH from aneurysmal rupture should have a **noncontrasted CT brain scan**, which often shows blood in the cisterns and sulci around the base of the brain. **If the CT brain scan appears normal, lumbar puncture (LP) is necessary** to exclude a small volume of subarachnoid blood. Bleeding from a traumatic LP procedure itself makes the diagnosis of SAH difficult, but a yellow coloration (xanthochromia) of the cerebrospinal fluid (CSF) indicates the breakdown of blood within the CSF prior to the LP. With a traumatic LP, the amount of blood typically decreases as the CSF is collected in serial tubes, but the blood from a SAH is fairly constant from tube to tube. **Emergent angiography**, preferably conventional catheter angiography for optimal imaging, should be done to locate the aneurysm. To prevent any future bleeding, the aneurysm ideally should be occluded with intravascular coils or surgical clipping. Even after successful occlusion of the ruptured aneurysm, the patient

may over the next few days develop the complication of **cerebral vasospasm**. The reduced blood flow from cerebral vasospasm creates ischemic infarctions, and is more likely to occur after a large volume SAH. After the aneurysm is occluded, cerebral vasospasm may be treated with **hypertensive therapy**, using vasopressor medications to preserve cerebral blood flow. Oral nimodipine also improves patient outcome, but perhaps more from a neuroprotective effect than any vasoactive property as a calcium-channel blocker.

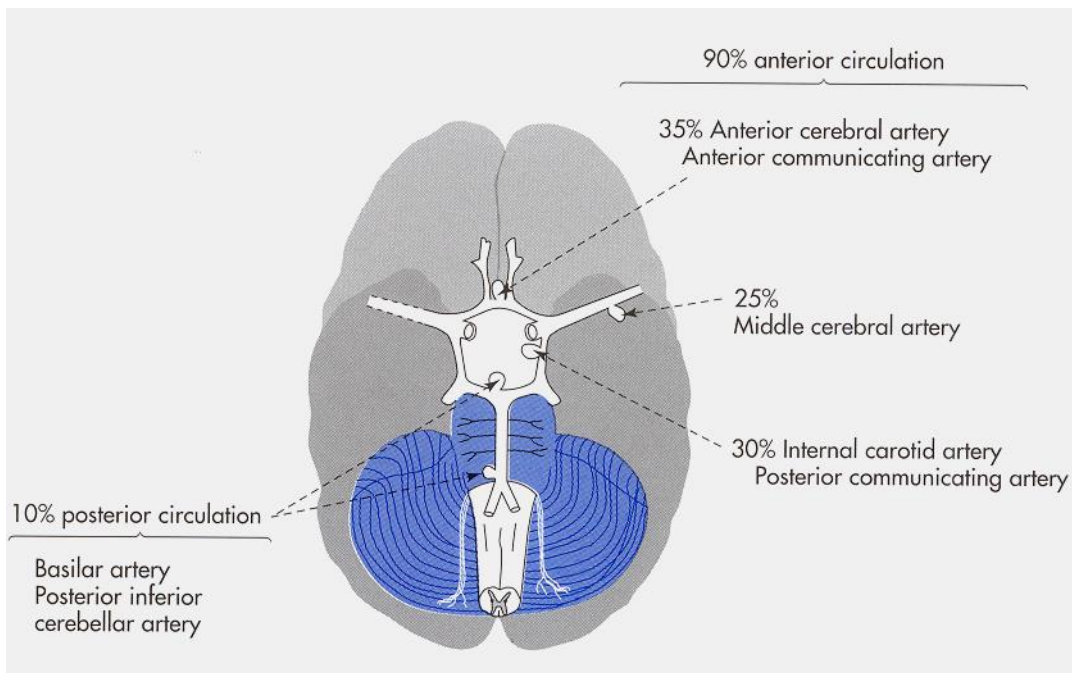


Fig. 5 Sites and incidence of congenital berry aneurysms around the circle of Willis.