Saccular (Berry) Aneurysms

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ACA	anterior cerebral artery
AVM	arteriovenous malformation
BA	berry aneurysm
bFGF	basic fibroblast growth factor
CT	computerized tomography
cAMP	cyclic adenosine monophosphate
ECM	extracellular matrix
FLAIR	fluid-attenuated inversion recovery
GRE	susceptibility-weighted gradient echo
GTP	guanosine triphosphate
ICA	internal cerebral artery
MCA	middle cerebral artery
MMP	matrix metalloproteinase
MRI	magnetic resonance imaging
NF	neurofibromatosis
NO	nitric oxide
SAH	subarachnoid hemorrhage
SMA	smooth muscle actin
VEGF	vascular endothelial growth factor

SYNONYMS AND HISTORICAL ANNOTATIONS

The terms "berry" and "saccular" aneurysm are essentially synonymous. This serves to distinguish them from other, less common types of aneurysm, including "mycotic/inflammatory," fusiform, dissecting, atherosclerotic (chapter 14). The most common manifestation of a berry aneurysm (BA) is rupture into the subarachnoid space (subarachnoid hemorrhage, SAH), and conversely the most common cause of (non-traumatic) SAH is a ruptured berry aneurysm. According to Stehbens (39), they have been appreciated since ancient Egyptian times and were certainly recognized by Galen. Stehbens further defines an "aneurysm," in generic terms, as "a localized and persistent dilatation that results from the yielding of components of the wall of the heart or blood vessels" (39).

EPIDEMIOLOGY

Incidence and prevalence. The incidence and prevalence of BA in the population are not known since these lesions are usually asymptomatic and only present with intracranial (usually subarachnoid) hemorrhage. Thus, an estimated incidence of SAH resulting from rupture of BAs is a more realistically approachable statistic. The incidence of SAH with ruptured BAs has shown a wide range in various studies, from 3.9 to almost 20 per 100 000/year, while it has been estimated that 400 000 adults (within the United States) live with unruptured BAs (30, 31). In Olmsted County, Minn, the rate of detection for BA was 9 per 100 000/person-years, slightly higher for women than men, and the highest incidence of detected aneurysms was among men in the 55-64 year age group, and among women in the 65-74 year age group (29). According to statistics from large stroke registries in North America, eg, the Harvard Cooperative Stroke Registry, SAH from ruptured BAs accounts for approximately 5% to 8% of all strokes (6). BAs usually rupture to produce SAH between 50 and 60 years of age, slightly more commonly in women than men. In closely monitored populations with extensive public health surveillance (eg, Finland) the incidence of SAH has remained remarkably stable from the 1980s through the late 1990s (at about 20-25 per 100 000/year) while other forms of stroke-related mortality (eg, that caused by ischemic infarcts) has shown a significant decline (38). SAH is almost twice as common in African-Americans than in whites (26).

Accurate estimates of the prevalence of BA in the *general* population are, almost by definition, impossible to ascertain. Autopsy studies are also fraught with the risk of "overinterpretation" of data, one major problem being that patients upon whom an autopsy is performed (usually in academic medical centers with markedly selective referral patterns) represent a highly *non*-representative group of patients with respect to their community. Some studies have concluded that 4% to 5% of (unselected autopsy) patients show

Figure 1. Basilar tip BA (arrow) found as an incidental finding in an elderly individual, with no past history of SAH. Notice significant atherosclerosis of the circle of Willis, as well as in the dome/wall of the aneurysm.

a BA (31), an estimate that the authors of this chapter consider to be somewhat high. However, how often the presence of a BA is detected as an incidental finding at necropsy (Figure 1) depends upon how carefully one searches for a small lesion (by blunt dissection or use of multiple specially stained histologic sections from different regions of the circle of Willis), what size criterion is used to define an aneurysm (2 mm? 5 mm? 10 mm?), and whether the basal vasculature at the time of the autopsy dissection is stressed, eg, by the infusion of water or saline under pressure into the basal arteries, in an attempt to "bring out" a small lesion or even a potential BA that has not attained a balloon-like morphology. Other estimates based upon necropsy and angiographic studies suggest a frequency for BA of 1% to 8% in the general population, while the incidence of SAH among individuals known to have a BA is 1.0% to 1.4% per year (30, 31). SAH from BA is a devastating form of stroke because it tends to occur in relatively young, productive individuals. Though mortality rates of SAH have decreased by as much as 1% per year since 1979 and patients who suffer a SAH now have marginally better survival, mean age at death for this condition was 60 years (in 1994), whereas median age at death was 73 for intracerebral (parenchymal)

hemorrhage and 81 for ischemic stroke (21).

Risk factors. Two components of "risk" must be examined in the context of BA: the risk of developing a BA in the first instance, and the risk of developing a SAH from that aneurysm. A large international retrospective study has addressed the latter question and concluded that 2 groups of patients must be considered (17): in one group, composed of those with no history of aneurysmal SAH, the cumulative rate of rupture of BAs less than 10 mm in diameter was 0.05% per year, while in another group, defined by having a history of SAH (successfully treated) from a different aneurysm, the rate was 11 times higher. In both groups the rate of rupture of BAs of a size greater than 10 mm in diameter, was less than 1% per year. However, the rate of rupture was 6% in the first year for giant BAs, defined as being 25 mm or greater in diameter (17). The findings of this 1998 study were fiercely debated at the time of its appearance (2, 5); an editorial published simultaneously with the ISUIA article emphasized the need to individualize and customize therapeutic intervention in a patient with a known (though possibly asymptomatic) BA (10).

An update from this group that incorporated both retrospective and prospective components, taking into consideration the results on over 4000 study patients, concluded that risk of SAH correlated closely with size of BAs in common locations (ie, ICA, ACA, MCA artery branch points): the 5-year cumulative rupture rates were estimated to be 0% when a BA was less than 7 mm in diameter, 2.6% when 7 to 12 mm, 14.5% when 13 to 24 mm, and a (frightening) 40% when the aneurysm was of giant proportions (18). Other studies (eg, from Finland) have suggested that risk factors for aneurysm rupture include cigarette smoking and patient age (inversely), while long term hypertension predicted fatal aneurysmal rupture (23). The same investigator concluded that cigarette smoking, possibly age and female sex, as well as hypertension seemed to be risk factors for multiple intracranial BAs in "patients of working age who have suffered a SAH" (22). Hypertension is a significant risk factor for SAH in the elderly (41).

The mechanisms by which smoking increases SAH risk are not clear, but may be the result of toxins found in smoke causing an imbalance between antiproteases and proteases, resulting in damage to connective tissue elements of arterial walls and extracellular matrix, further allowing for any inherent weaknesses in a susceptible arterial segment to evolve into a BA (24). Furthermore, disruption of normal arterial homeostasis, which results from the interaction of endothelial-derived nitric oxide (NO) and prostacyclin impacting upon smooth muscle cell cyclic adenosine monophosphate (cAMP) and activation of ATP-dependent postassium channels, may be influenced by hypertension; the precise ways in which these complex pathways and interactions may be deranged to result in BAs and SAH, however, are poorly understood. One meta-analysis has also suggested that oral contraceptive use produces a small increase in the risk of SAH (20). Heavy ethanol use is associated with BA-related SAH in a dose-dependent fashion, but whether the overindulgence in alcohol is simply a surrogate marker for concurrent heavy cigarette smoking is unclear (24). Some investigators suggest that BAs, especially when small (less than 10 mm in diameter) appear to have a low probability of rupture (45). Operative morbidity and mortality for unruptured BAs is quite low (2.5% and 6% respectively), whereas it is much higher after an aneurysm has ruptured. Detailed guidelines for the management of individuals with unruptured intracranial BAs have been published (4).

BIOMARKERS, GENETIC AND PATHOGENETIC CONSIDERATIONS

As in all fields of medicine, intense effort is aimed at identifying biomarkers for BAs—ie, ideally a simple, relatively noninvasive diagnostic test that would predict a given individual's likelihood of developing a BA, or having it rupture with dire consequences. A search for these biomarkers has been hampered by a relatively rudimentary understanding of the pathogenesis of BAs (24). BAs clearly have a tendency to occur in families; among kindreds of individuals with SAH, siblings are at high risk for having both SAH and unruptured BAs (25). In a Finnish study that utilized magnetic resonance imaging (MRA) to screen 400 individuals with at least 2 first-degree relatives with a documented BA, this test revealed aneurysms in 37 asymptomatic individuals, ie, the yield was 9.25%. MRA appears, however, to be a suboptimal screening modality to detect BAs, in part because conventional angiography fails to confirm existence of a BA in many individuals who are "detected" by MRA. Guidelines for screening individuals with even a fairly weak family history of BA (one first degree relative) using these very expensive tools remain elusive (24). Unfortunately, none of the risk factors for BA/SAH established by epidemiologic studies provides sufficient predictive power to make expensive screening techniques cost effective.

BAs or focal arterial weakening that may predispose to BA are known to have a high incidence in certain well-characterized genetic conditions, especially Ehlers-Danlos syndrome, Marfan syndrome, neurofibromatosis type 1 (NF1) and polycystic kidney disease, the latter associated with mutations in 2 separate genes, *PKD1* and *PKD2* (24). These strong associations have suggested novel mechanistic approaches to understanding vascular weakening. Arterial thinning in NF1 may result from a defect in the protein neurofibrin, one that contains a GTP-activating protein domain crucial for the maintenance of cytoplasmic microtubules. In Marfan syndrome, there is a defect in the glycoprotein fibrillin-1, a significant component of the extracellular matrix present in many vascular tissues. In Ehlers-Danlos syndrome (type IV) there is a molecular lesion in type III collagen, a major component of elastic tissues, including blood vessels. One obvious inference to be drawn from these rare diseases is that a fruitful search for genetic or biomarkers of BAs might be in the area of extracellular matrix (ECM), elastica or collagen components (24). Studies focusing on relative proportions of Type III and Type I collagen in BAs, or mutations in collagen-encoding genes carried by affected patients, have yielded mixed and somewhat inconsistent results (9, 24). Recently, a large Japanese study has suggest-

ed that collagen type I alpha2 (*COL1A2*) on chromosome 7q22.1 is a susceptibility gene for intracranial BAs (46). Other putative biomarkers or molecules of importance in BA/SAH pathogenesis include matrix metalloproteinases (MMPs), endopeptidases with activity against the ECM of arterial basement membranes, growth factors that impact development, evolution and repair of the vasculature (vascular endothelial growth factor, VEGF, and basic fibroblast growth factor, bFGF), and flow-responsive molecules (34). While studies of BA pathogenesis and rupture have clearly entered the realm of molecular genetics, with an emphasis on the interplay of genetic and environmental risk factors, earlier painstaking and elegant studies emphasizing the role of physical stresses in the initiation, enlargement and rupture of human intracranial BAs in various models contributed immensely to our understanding of their natural history and complications (13).

CLINICAL FEATURES

Signs and symptoms. The most feared, and frequently fatal, complication of a BA is SAH. In the vast majority of affected individuals, this manifests as severe sudden onset headache; less common clinical manifestations include neck pain, eye or back pain, and (much less often) chest and abdominal pain which may even mimic a myocardial infarct or ruptured abdominal aortic aneurysm (1). Some patients receive warning of an impending larger SAH in the form of a small "leak" causing a small SAH, which usually manifests as a severe sudden onset headache, or "sentinel headache"—estimates of how often these occur vary in individuals who eventually experience a larger symptomatic SAH, from 10% to 43% (35). Such sentinel bleeds occur in close temporal proximity to a larger bleed—over 60% occur within one month, and over 90% within 3 months of a catastrophic hemorrhage (44). Giant aneurysms may present as compressive mass lesions, rather than with hemorrhage (7). Childhood BAs are rare, accounting for only 0.6% to 4.6% of all BAs (19).

The clinical outcome to be expected in an individual who experiences an aneurysmal SAH is poor—8% to 60% of patients expire before reaching hospital, often secondary to cardiorespiratory arrest, while after hospital admission the mortality rate is 37%, severe disability follows in 17% and outcome is good in only 45% to 47% of patients evaluated 3 months postoperatively (30, 32, 33, 36). Clinical grading schema used to evaluate patients with BA include the "Modified Botterell" and "Hunt and Hess" approaches to evaluation, as well as assessment of the Glasgow Coma Scale. As might be predicted, the best, Grade 0 (in both Botterell and Hunt/Hess schema) is assigned to someone with an unruptured BA or one that has not bled within 30 days, while the worst, Grade 4 or 5 in the 2 different schema respectively, is given to a SAH patient deeply comatose with decerebrate rigidity, with or without major lateralizing signs (16, 30). Focal neurologic signs can be used to predict the site of a BA, even prior to angiography, especially if a component of the SAH has been into brain parenchyma; an anterior communicating a. BA may be associated with akinetic mutism or paresis of the lower limbs, middle cerebral a. aneurysm is suggested by hemiparesis, internal carotid, carotid-ophthalmic or anterior communicating a. aneurysm by unilateral blindness, and a posterior communicating a. aneurysm by a CN III palsy (32). As many as 30% of individuals with a BA-related SAH may have multiple aneurysms, while 9% to 19% have "mirror image" aneurysms situated at identical sites bilaterally on the circle of Willis (44).

Assuming a patient survives a major SAH, major medical complications may involve the lungs (infection, aspiration, atelectasis, edema and pulmonary emboli), cardiac arrhythmias (in as many as 20%-40% of patients), electrolyte disturbances, gastrointstinal complications—especially stress ulcers (in up to 3%-4% of patients), systemic infections and deep vein thrombosis (16). Neurologic complications include rebleeding, vasospasm (with evolution of post-SAH infarcts in as many as 15%-20% of patients), hydrocephalus and seizures (16, 30, 32, 44).

Imaging. Computerized tomography (CT scanning) is quite effective in detecting SAH, using 3- to 5-mm thick images, whereas subtle evidence of bleeding may be overlooked if routine 8- to 10-mm thick slices are used (3). Within the first day of its occurrence, unenhanced CT scanning is said to have 92% to 98% sensitivity for detecting SAH; however, this falls to below 50% one week following the initial event. Hemorrhage shows up as a bright signal (increased attenuation coefficient) in the CSF spaces, apparently related to the presence of hemoglobin in the fluid. Unfortunately, blood with a fairly low hemoglobin value (less than 10 g/dl) in the CSF may be isodense with the cortical mantle on CT scanning. Neuroimaging studies also reveal that SAH secondary to a ruptured BA is associated with intraparenchymal, intraventricular and subdural hematoma in 19.0, 20.0 and 1.8% of cases, respectively (3). Magnetic resonance imaging (MRI) has become more sensitive in detecting acute SAH with its latest hardware modifications, ie, fluid-attenuated inversion recovery (FLAIR), and susceptibility-weighted gradient echo (GRE). MRI appears to be more effective than CT in detecting subacute or chronic SAH.

CT angiography may demonstrate aneurysms as small as 2 to 3 mm, with sensitivity of 77% to 97% and specificity of 87% to 100%, while MR angiography is useful as a screening modality, with sensitivity of 69% to 93%, and is especially useful for detecting BAs of 3 to 5 mm in size (4). BAs themselves must usually be conclusively detected by the "gold standard," invasive high resolution cerebral angiography (Figure 2), which has the added benefit of showing a coincident AVM in the event that one is present (recall that the 2 lesions may occur in one and the same patient) or other smaller aneurysms in addition to the one that has caused a SAH. Large aneurysms, eg, of the basilar tip, may show up as a flow void on a FLAIR sequence of the MRI of an afflicted patient. Giant aneurysms may appear on CT and/or MRI scans, where they may mimic a neoplasm—reason enough to move forward with angiography on any patient in whom there is concern that such a lesion may indeed be aneurysmal in origin.

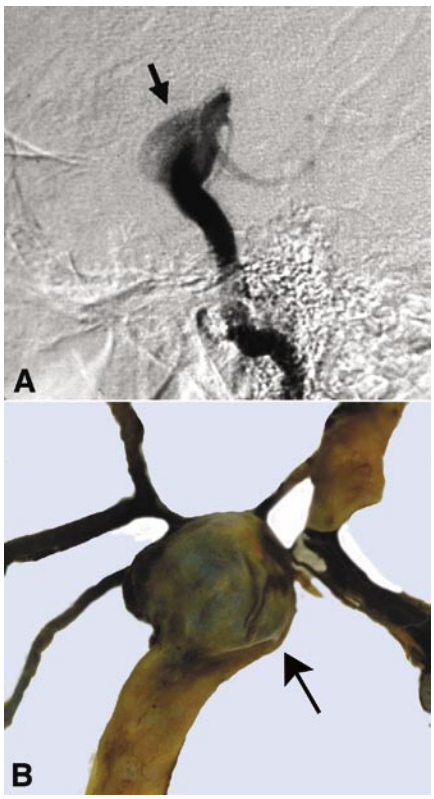


Figure 2. **A**. Cerebral angiogram (vertebro-basilar injection) demonstrates a large BA tip aneurysm (arrow). **B**. At autopsy, a large partly thrombosed BA tip aneurysm (arrow) is seen.

Laboratory findings. Routine laboratory work-up of a patient in whom the clinical diagnosis of SAH has been made should include evaluation of hematologic parameters (platelets, coagulation factors) to ensure that no systemic factor increased the risk of hemorrhage. Lumbar puncture, assuming it is deemed safe in a patient with possibly raised intracranial pressure, will show elevated opening pressure, CSF that is bloody (but often with residual xanthochromia after the blood has been centrifuged), with or without an increase in white blood cell concentration and a moderate to pronounced elevation of CSF protein. CSF glucose is usually normal or minimally decreased (16). Xanthochromia may not be visible to the naked eye, but still detectable by spectrophotometric techniques in the Biochemistry/Hematology laboratory.

MACROSCOPIC FINDINGS

BAs are most commonly located on major branch points on the circle of Willis; most commonly (estimated as 70%-90%) on the "anterior circulation," where favored locations are the anterior cerebral-

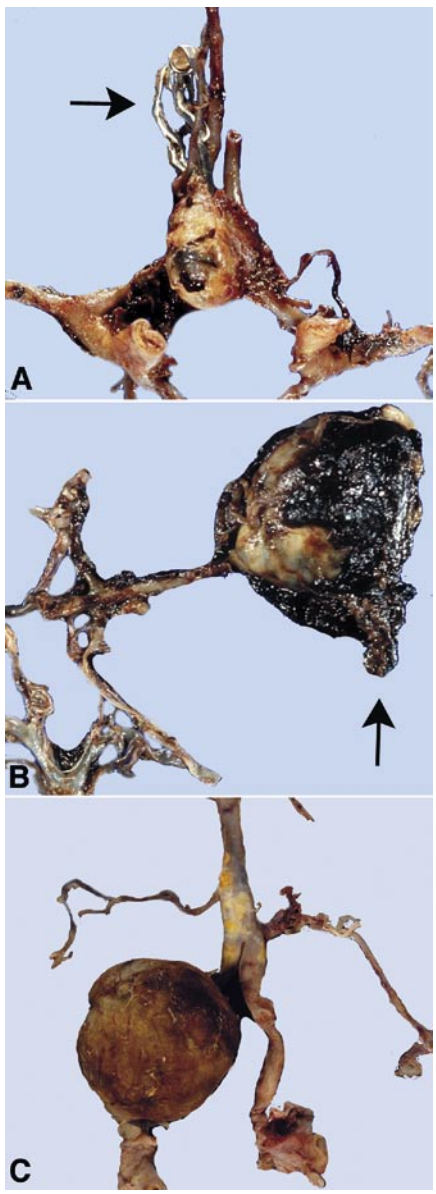


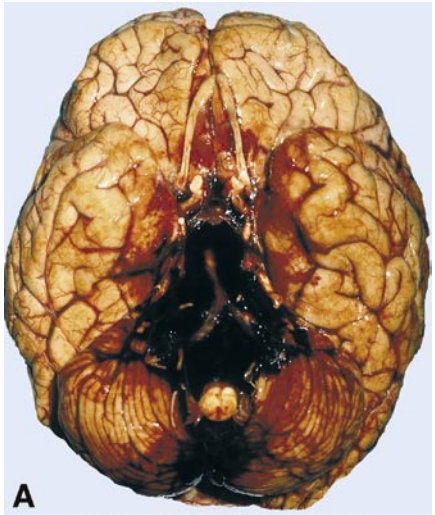
Figure 3. **A**. Large BA at the ACA/anterior communicating artery junction; this aneurysm underwent surgical clipping—clip is identified on the aneurysm (arrow)—though unfortunately the patient expired. Note significant acute (subarachnoid) hemorrhage immediately adjacent to the aneurysm. **B**. A large BA (of near "giant" proportions) at the left MCA bifurcation (arrow). Note extensive acute hemorrhage at the dome (presumed rupture site) of the aneurysm. **C**. Large right vertebral artery aneurysm; this is an unusual location for BA.

anterior communicating a. junction, the ICA-posterior communicating a. junction, and the bi- or trifurcation of the middle cerebral artery in the Sylvian fissure (Figure 3). BAs on the posterior circulation may occur at any branch point, but are most common at the basilar a. tip (Figure 4); the resultant BA is often

Figure 4. A large basilar artery tip BA (arrow), which has *collapsed*. *In situ*, this BA was buried in the interpeduncular cistern. This is the most common location for BAs on the vertebro-basilar circulation.

"buried" in the interpeduncular cistern (12, 43).

In a patient who comes to necropsy with a diagnosis of SAH, BA must be suspected as the etiology, but other possible causes must be ruled out—indeed, a patient with a BA may also have an arteriovenous malformation (AVM), the BA having developed at a vulnerable branch point secondary to high blood flow through an artery feeding the AVM. In such a case, an attempt to precisely identify the lesion causing the SAH must be made—and is sometimes futile. Especially if an affected individual dies rapidly after the SAH—a common occurrence—the existence or location of the aneurysm is best and most accurately ascertained at the time of the autopsy, by gently washing away blood simultaneously with blunt dissection at the time of the necropsy. A fear that this procedure will destroy the causative BA or create an artefactual tear in an artery or small aneurysm, that will then appear to be a rupture site, is rarely justified. The temptation for the prosector to defer a "search for the BA" until after the brain has been fixed is best avoided, because dissecting fixed caked blood away from the base of the brain to locate a vascular lesion (or lesions) that has bled is far more difficult than doing this in the fresh state (Figure 5). Once a "candidate" aneurysm has been ascertained as the cause of SAH, a rupture site or tear needs to be identified,



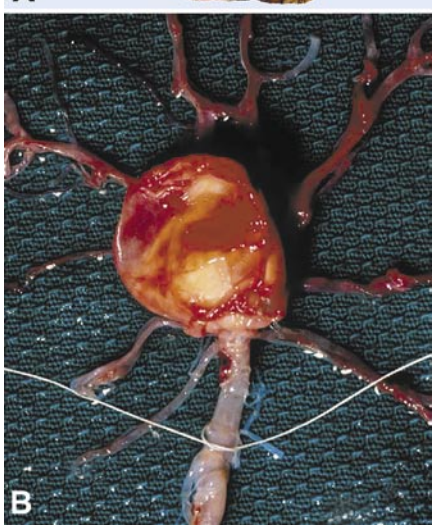


Figure 5. **A**. Freshly removed, edematous brain taken from an individual who experienced fatal SAH. Note obliteration of the basal cisterns, major branches of the circle of Willis and cranial nerves by abundant fresh blood. During an autopsy, the extent of hemorrhage should be documented photographically, and the blood then carefully dissected away to find the 'guilty' BA(s). **B**. Massive basilar tip BA on a circle of Willis, dissected in the fresh state at the time of necropsy. To show true size of the BA approximating its dimensions during life, it has been injected with water.

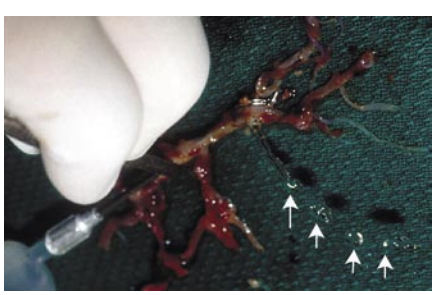


Figure 6. Rupture site of a BA can be highlighted by gently injecting the circle of Willis with water; the rupture site is visualized by droplets of fluid escaping through the tear in the BA wall, as in this case.

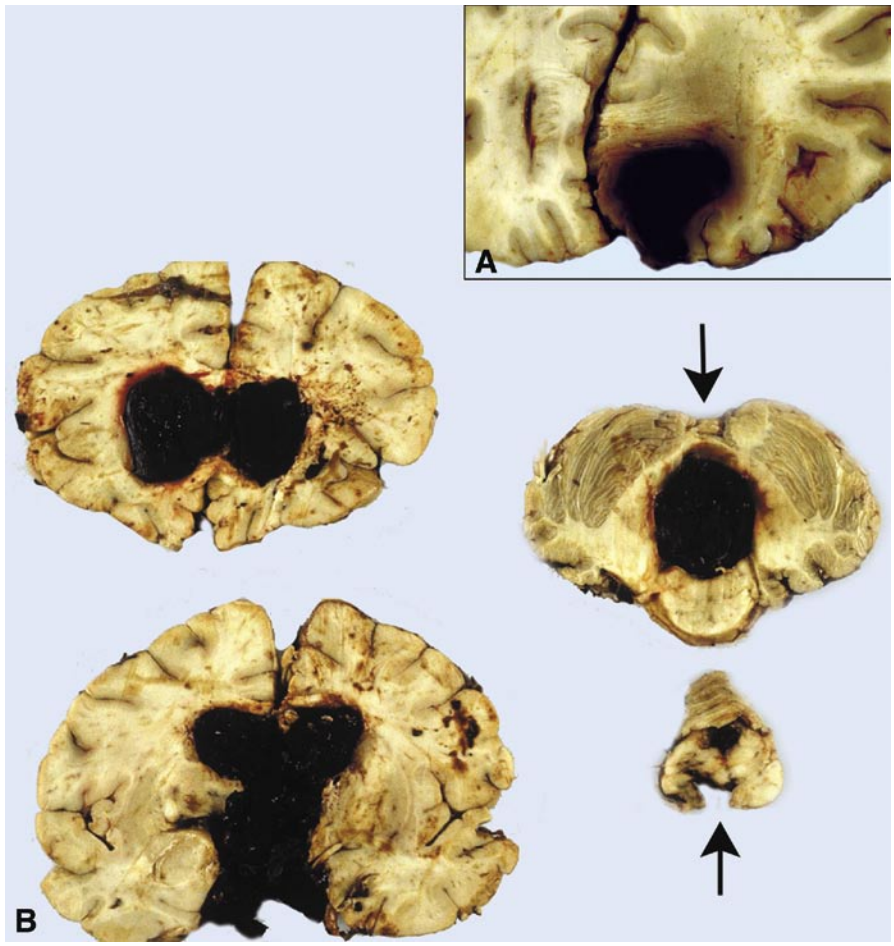


Figure 7. **A**. Right frontal intraparenchymal hematoma from a ruptured carotid-ophthalmic aneurysm. MCA and ACA aneurysms commonly produce intraparenchymal hemorrhage when the ruptured dome of the BA is embedded within adjacent brain parenchyma. **B**. Massive intraventricular hemorrhage from a ruptured BA. Secondary Duret hemorrhages in the midbrain (arrows) may be difficult to distinguish from aqueductal or IV ventricular blood that has dissected, under immense pressure, into brain parenchyma.

and can usually be done by simple inspection—it is often present in the dome of an aneurysm. A procedure used in some laboratories to confirm the rupture site is to inject water (through a syringe) into an artery feeding the BA, with the result that a stream of the injected liquid will "squirt" through the rupture site (Figure 6).

Because the dome of an aneurysm may be buried within brain parenchyma, BA must be considered in the differential diagnosis of any intraparenchymal hemorrhage (Figure 7A), especially if such occurs suddenly, affecting frontal/temporal lobes and/or basal ganglia, in a previously healthy young or middle-aged individual (12). The circle of Willis in such cases is best dissected away from the base of the brain prior to the brain being further sectioned after fixation. In the case of giant aneurysms (defined as being greater than 2.5 cm in greatest dimension), the BA often behaves as a mass lesion, and its lumen may show considerable organization, mural or even occlusive thrombosis (Figure 8). A large SAH may extend over the base of the brain, its convexities, around the spinal cord, and fill the ventricular system with blood (Figure 7B).

HISTOPATHOLOGY

The diagnosis of BA is not a particularly challenging one in tissue sections; light microscopy is confirmatory of gross inspection of the lesion. A BA is best examined after "bivalving" it through the putative rupture site and embedding both halves of the lesion. Though the diagnosis is easily made on routine (H&E-stained) sections, the focal deficiency of internal elastic lamina characteristic of a BA is highlighted using the elastica van Gieson

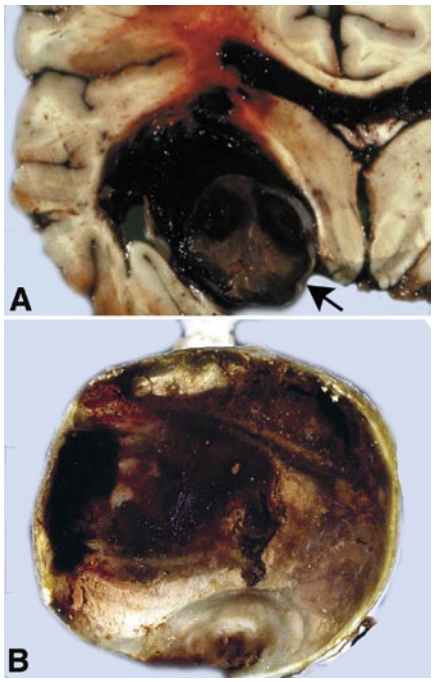


Figure 8. **A**. Giant aneurysm in left temporal lobe, which has ruptured, resulting in predominantly intraparenchymal and intraventricular hemorrhage. Note extensive organized thrombus within the aneurysm. **B**. Giant BA (from another patient), cut in cross section, may show extensive organized thrombus in its lumen; in this case, there is nearly complete thrombosis of the aneurysm lumen.

(EVG) stain or the Movat pentachrome technique (43) (Figure 9). It is particularly dramatic to show, in an appropriately (fortuitously) sampled section, the "mouth" of the BA on the parent artery, and then to track the normal elastica as it goes from the healthy arterial segment, tapers and then disappears near the ruptured dome of an aneurysm (Figure 9), though this is not always possible. Masson trichrome stain effectively highlights focal or diffuse fibrosis of the aneurysmal vessel wall, which (especially in elderly individuals) may show significant atherosclerotic change, sometimes with punctate dystrophic calcification. Periodic acid-Schiff (PAS) stain may be valuable in demonstrating glycosaminoglycans within an aneurysm wall. Deposits of hemosiderin around the rupture site of a BA may suggest previous small hemorrhage(s), which may correlate with a history of sentinel leaks from the aneurysm. Giant aneurysms often show extensive organizing mural thrombi, probably as a result of turbulence within their lumina (40).

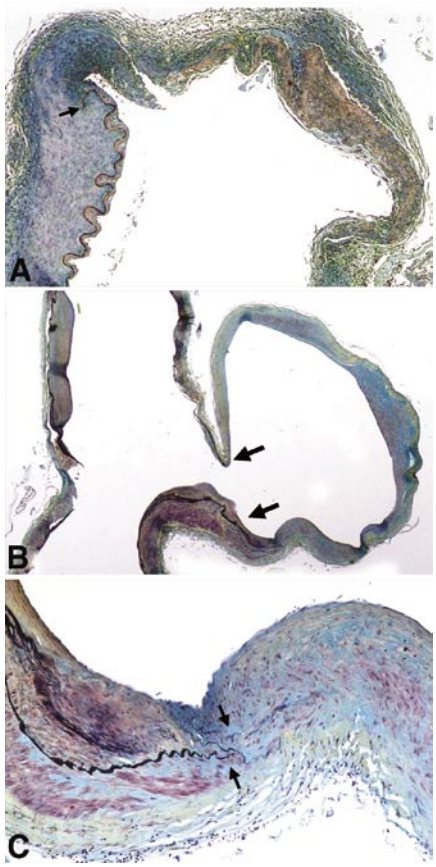


Figure 9. Microscopic features of a BA are best demonstrated using either an elastica van Gieson or Movat pentachrome stain. **A**. "Dome" of a small BA. Note medial thickening of the aneurysm wall (at left), as well as loss of the elastica (arrow), which is absent from most of the aneurysm wall (top and right). **B**. A small unruptured aneurysm shows attenuation and loss of the elastica at "mouth" of the BA (arrows), and its absence throughout the aneurysm itself. **C**. Detail from wall of an aneurysm highlights (arrows) thinning and loss of the elastica.

IMMUNOHISTOCHEMISTRY AND ULTRASTRUCTURAL FINDINGS

While ultrastructural examination of a BA is almost never required to confirm or "illuminate" the diagnosis, immunohistochemistry may be helpful though is not necessary for definitive diagnosis. Antibodies to macrophages (CD68 or others) are useful in showing atherosclerotic change in the BA wall. Anti-smooth muscle actin (SMA) draws attention to attenuation of the media that may accompany deficiencies of the elastica.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of SAH is fairly broad and includes lesions (eg, AVM) discussed in this and other chapters, including non-saccular aneurysms.

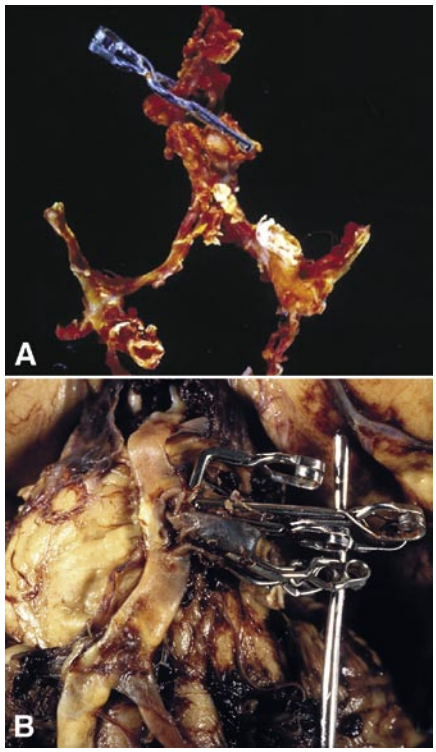


Figure 10. Clipping of (ruptured) BAs remains a mainstay of treatment for these lesions. **A**. Large clip has been placed across mouth of an ACA/anterior communicating artery aneursym. **B**. Several clips on a large basilary artery branch aneurysm.

Intracranial hematomas resulting from a ruptured AVM usually have both parenchymal and meningeal components, but this is not always helpful in distinguishing between hemorrhage from an AVM and aneurysm. Highly vascular primary or secondary neoplasms may produce intraparenchymal and subarachnoid hemorrhage, even when the tumor itself appears relatively inconspicuous on initial imaging studies. Systemic factors (coagulopathy, platelet abnormalities) must always be considered as either a primary cause of SAH, or as contributing to a bleed from an aneurismal lesion.

FUTURE DIRECTIONS AND THERAPY

While "clipping" of a ruptured BA (Figure 10) was considered for decades the "standard of care" for this lesion (8, 11, 11a, 44), innovative alternate therapies have emerged in recent years (27) (chapter 16). These include endovascular treatment of BAs with electrothrombosis and detachable devices (Figure 11), especially the Guglielmi coil (14, 15, 28). Therapeutic/iatrogenic embolization of aneurysms using various agents, aimed at

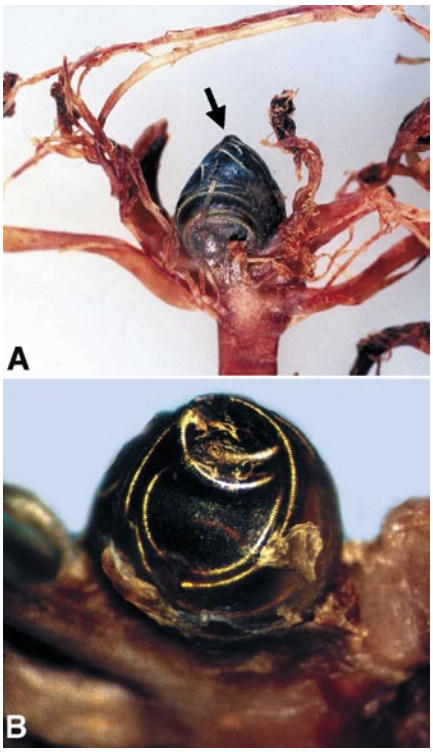


Figure 11. "Coils" are increasingly used to cause thrombosis of large BAs. **A**. Basilar tip BA (arrow) that has undergone therapeutic coiling. **B.** Dome of a BA has been removed to show intraluminal coil, surrounded by extensive thrombus.

decreasing or eliminating their likelihood of subsequent rupture, is currently under investigation in experimental BA models. As the molecular events crucial to BA growth, rupture and repair become better known based upon work in these models, individualized therapy for these lesions is likely to become the norm. This may include a combination of endovascular and gene therapy approaches, whereby genes that promote vessel wall repair after BA rupture are inserted into component cells of the aneurysm wall (37).

REFERENCES

1. Adams HP Jr, Kassell NF, Boarini DJ, Kongable G (1991) The clinical spectrum of aneurysmal subarachnoid hemorrhage. *J Stroke Cerebrovasc Dis* 1:3-8.

2. Ausman JI (1999) The New England Journal of Medicine report on unruptured intracranial aneurysms: A critique. *Surg Neurol* 51:227-229.

3. Aygun N, Perl J II (2003) Subarachnoid hemorrhage. In: *Imaging Cerebrovascular Disease*, VL Babikian, LR Wechsler, RT Higashida (eds). Butterworth-Heinemann: Philadelphia. pp. 241-269.

4. Bederson JB, Awad IA, Wiebers DO, Piepgras D, Haley EC, Brott T, et al (2000) Recommendations for the management of patients with unruptured intracranial aneurysms. A statement for healthcare professionals from the Stroke Council of the American Heart Association. *Stroke* 31:2742-2750.

5. Berenstein A, Flamm ES, Kupersmith MJ (1999) Unruptured intracranial aneurysms (letter to the editor). *N Engl J Med* 340:1439-1440.

6. Biller J, Godersky JC, Adams HP Jr (1988) Management of aneurysmal subarachnoid hemorrhage. *Stroke* 23:13-18.

7. Bokemeyer C, Frank B, Brandis A, Weinrich W (1990) Giant aneurysm causing frontal lobe syndrome. *J Neurol* 237:47-50.

8. Bonita R, Thomson S (1985) Subarachnoid hemorrhage: Epidemiology, diagnosis, management, and outcome. *Stroke* 16:591-594.

9. Brega KE, Seltzer WK, Munro LG, Breeze RE (1996) Genotypic variations of type III collagen in patients with cerebral aneurysms. *Surg Neurol* 46:253-257.

10. Caplan LR (1998) Should intracranial aneurysms be treated before they rupture? *N Engl J Med* 339:1774-1775.

11. Drake CG (1968) Further experience with surgical treatment of aneurysms of the basilar artery. *J Neurosurg* 29:372-392.

11a. Drake CG (1981) Management of cerebral aneurysm. *Stroke* 12:273-283.

12. Ellison D, Love S, Chimelli L, Harding BN, Lowe J, Vinters HV (2004) *Neuropathology. A Reference Text of CNS Pathology*. 2nd ed Edinburgh-London: Mosby, pp. 209-237.

13. Ferguson GG (1972) Physical factors in the initiation, growth, and rupture of human intracranial saccular aneurysms. *J Neurosurg* 37:666-677.

14. Guglielmi G, Vinuela F, Sepetka I, Macellari V (1991) Electrothrombosis of saccular aneurysms via endovascular approach. Part 1: Electrochemical basis, technique, and experimental results. *J Neurosurg* 75:1-7.

15. Guglielmi G, Vinuela F, Dion J, Duckwiler G (1991) Electrothrombosis of saccular aneurysms via endovascular approach. Part 2: Preliminary clinical experience. *J Neurosurg* 75:8-14.

16. Ho HW, Batjer HH. Aneurysmal subarachnoid hemorrhage: Pathophysiology and sequelae (1997) In: *Cerebrovascular Disease*. HH Batjer (ed). Lippincott-Raven: Philadelphia-New York. pp. 889-899.

17. The International Study of Unruptured Intracranial Aneurysms Investigators (1998) Unruptured intracranial aneurysms--risk of rupture and risks of surgical intervention. *N Engl J Med* 339:1725-1733.

18. The International Study of Unruptured Intracranial Aneurysms Investigators (2003) Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. *Lancet* 362:103-110.

19. Ito M, Yoshihara M, Ishii M, Wachi A, Sato K (1992) Cerebral aneurysms in children. *Brain & Development* 14:263-268.

20. Johnston SC, Colford JM Jr, Gress DR (1998) Oral contraceptives and the risk of subarachnoid hemorrhage. A meta-analysis. *Neurology* 51:411-418.

21. Johnston SC, Selvin S, Gress DR (1998) The burden, trends, and demographics of mortality from subarachnoid hemorrhage. *Neurology* 50:1413-1418.

22. Juvela S (2000) Risk factors for multiple intracranial aneurysms. *Stroke* 31:392-397.

23. Juvela S (2004) Treatment options of unruptured intracranial aneurysms. *Stroke* 35:372-374.

24. Kassam A, Horowitz M, Chang Y-F, Peters D (2004) Altered arterial homeostasis and cerebral aneurysms: A review of the literature and justification for a search of molecular biomarkers. *Neurosurgery* 54:1199-1212.

25. Kasuya H, Onda H, Takeshita M, Hori T, Takakura K (2000) Clinical features of intracranial aneurysms in siblings. *Neurosurgery* 46:1301-1306.

26. Kissela B, Schneider A, Kleindorfer D, Khoury J, Miller R, Alwell K, et al (2004) Stroke in a biracial population. The excess burden of stroke among Blacks. *Stroke* 35:426-431.

27. Macdonald RL (2004) Advances in vascular surgery. *Stroke* 35:375-380.

28. Maruyama Y, Vinuela F, Suzuki Y, Akiba Y, Ulihoa A, Duckwiler GR, Gobin YP, Vinters HV, Iwaki M, Abe T (1999) Development of the biologically active Guglielmi detachable coil for the treatment of cerebral aneurysms. Part II: An experimental study in a swine aneurysm model. *AJNR Am J Neuroradiol* 20:1992-1999.

29. Menghini VV, Brown RD Jr, Sicks JD, O'Fallon WM, Wiebers DO (1998) Incidence and prevalence of intracranial aneurysms and hemorrhage in Olmsted County, Minnesota, 1965 to 1995. *Neurology* 51:405-411.

30. Meyer FB, Morita A, Puumala MR, Nichols DA (1995) Medical and surgical management of intracranial aneurysms. *Mayo Clin Proc* 70:153-172.

31. Mohr JP, Kistler JP (1998) Intracranial aneurysms. In: *Stroke. Pathophysiology, Diagnosis, and Management,* 3d ed. HJM Barnett, JP Mohr, BM Stein, FM Yatsu (eds). Churchill Livingstone: New York-Edinburgh. pp. 701-723.

32. Noseworthy TW (1986) Subarachnoid hemorrhage from ruptured saccular aneurysm. *Annals Royal Coll Phys Surg Canada* 19:193-196.

33. Olafsson E, Hauser WA, Gudmundsson G (1997) A population-based study of prognosis of ruptured cerebral aneurysm: Mortality and recurrence of subarachnoid hemorrhage. *Neurology* 48:1191-1195.

34. Peters DG, Kassam A, St. Jean PL, Yonas H, Ferrell RE (1999) Functional polymorphism in the matrix metalloproteinase-9 promoter as a potential risk factor for intracranial aneurysm. *Stroke* 30:2612-2616.

35. Polmear A (2003) Sentinel headaches in aneurysmal subarachnoid hemorrhage: what is the true incidence? A systematic review. *Cephalalgia* 23:935-941.

36. Ramirez-Lassepas M, Ahmed A (1991) Cardiorespiratory arrest in aneurysmal subarachnoid hemorrhage. *J Stroke Cerebrovasc Dis* 1:49-56.

37. Ribourtout E, Raymond J (2004) Gene therapy and endovascular treatment of intracranial aneurysms. *Stroke* 35:786-793.

38. Sivenius J, Tuomilehto J, Immonen-Raiha P, Kaarisalo M, Sarti C, Torppa J, et al (2004) Continuous 15-year decrease in incidence and mortality of stroke in Finland. The FINSTROKE Study. *Stroke* 35:420-425.

39. Stehbens WE (1972 Pathology of the Cerebral Blood Vessels. CV Mosby : Saint Louis: pp. 252-470.

40. Sutherland GR, Drake CG, Kaufmann JCE (1985) Extensive organization in a thrombosed giant intracranial aneurysm: case report. *Clin Neuropathol* 4:19-22.

41. Taylor CL, Yuan Z, Selman WR, Ratcheson RA, Rimm AA (1995) Cerebral arterial aneurysm formation and rupture in 20,767 elderly patients: hypertension and other risk factors. *J Neurosurg* 83:812-819.

42. Teunissen LL, Rinkel GJE, Algra A, van Gijn J (1996) Risk factors for subarachnoid hemorrhage. *Stroke* 27:544-549.

43. Vinters HV (2001) Cerebrovascular disease--Practical issues in surgical and autopsy pathology. *Curr Top Pathol* 95:51-99.

44. Weaver JP, Fisher M (1994) Subarachnoid hemorrhage: an update of pathogenesis, diagnosis and management. *J Neurol Sci* 125:119-131.

45. Wiebers DO, Whisnant JP, Sundt TM Jr, O'Fallon WM (1987) The significance of unruptured intracranial saccular aneurysms. *J Neurosurg* 66:23-29.

46. Yoneyama T, Kasuya H, Onda H, Akagawa H, Hashiguchi K, Nakajima T, Hori T, Inoue I (2004) Collagen type I alpha2 (COL1A2) is the susceptible gene for intracranial aneurysms. *Stroke* 35: 443-448.