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Spontaneous intracerebral hemorrhage: epidemiology and clinical presentation

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The advent of widespread CT availability has dramatically changed our understanding of the incidence and risk factors regarding intracerebral hemorrhage (ICH). In the pre-CT era, many patients with a small ICH were misclassified having had ischemic strokes and patients with massive ICH or subarachnoid hemorrhage (SAH) were often difficult to classify correctly. The fact that the precise mechanism of spontaneous ICH is often difficult to ascertain without pathologic evidence continues to hamper epidemiologic studies. This article reviews the incidence rates, natural history, epidemiology, and clinical presentations of nontraumatic ICH.

Epidemiology: population-based studies

ICH accounts for approximately 10% of all strokes and is defined as nontraumatic abrupt onset of severe headache, altered level of consciousness, and/or focal neurologic deficit that is associated with a focal collection of blood within the blood parenchyma on neuroimaging or autopsy and is not caused by trauma or hemorrhagic conversion of a cerebral infarction [1].

Table 1 compares the age-adjusted incidence rates of ICH throughout various population-based studies in the CT era. Such comparisons are limited by differing definitions of stroke subtype, availability of neuroimaging, and differences in study design [2,3]. If one compares the six studies performed in which incidence figures can be compared with the 1990 US population, in which CT was performed in greater than 75% of the cases, the sex/gender–adjusted incidence rate of ICH ranges from 12 to 15 per 100,000 population. According to a population-based study in Greater Cincinnati during 1988, ICH was more common with advancing age among blacks compared with whites and among men compared with women [4]. The incidence rate of ICH increased exponentially with age among whites but was found to plateau after the age of 65 years among blacks (Fig. 1). This may reflect the limited number of cases in the oldest age group among blacks, however.

Clinical presentation

Mohr et al [5] reported on The Harvard Cooperative Stroke Registry, in which ICH was defined as a presentation with gradual progression (over minutes or days) or sudden onset of focal neurologic deficit, usually accompanied by signs of increased intracranial pressure, such as vomiting or diminished consciousness. In that study, they found that 91% of patients had a systolic blood pressure greater than or equal to 160 mm Hg and/or a diastolic blood pressure greater than or equal to 100 at the onset of the stroke and that 72% had hypertension in the past (Table 2).

Vomiting was more common in ICH and SAH (51% and 47%, respectively) than in ischemic

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Table 1
Annual incidence of intracerebral hemorrhage per 100,000 population in CT era

Site	Period	Rate (%)	Number
Rochester, MN	1975–1979	13	38
Tilburg, The Netherlands	1978–1980	17	54
South Alabama	1980	23	13
Rochester, MN	1980–1984	15	42
Benghazi, Libya	1983–1984	9	48
Oxfordshire, England	1981–1986	14	66
Soderhamm, Sweden	1983–1986	22	35
Dijon, France	1985–1989	29	158
Jyvaskyla, Finland	1985–1989	29	158
Greater Cincinnati, OH	1988	13	188

From Broderick J. Natural history of primary intracerebral hemorrhage. In: Whisnant J, editor. Population-based clinical epidemiology of stroke. Oxford: Butterworth-Heinemann; 1993; with permission.

stroke (4%–10% of cases). Although SAH presented with headache at onset in 78% of cases, one third of all ICH patients also had headache at onset compared with only 3% to 12% of ischemic stroke subtype patients. Equal numbers of SAH and ICH patients (24% of cases) presented with coma compared with less than 5% of ischemic stroke subtype patients. A particular characteristic of ICH was the smooth or gradual progression of symptoms in 63% of cases. Sudden onset was seen in 34% of cases (Table 3). In comparison, smooth or gradual onset of stroke was only seen in 5% to 20% of ischemic stroke subtype patients and in 14% of SAH patients.

Morbidity and mortality

The 30-day mortality rate for ICH is 44% to 51% [6–10], with half of the deaths occurring within the first 2 days after symptom onset [11]. The most important predictors of outcome are the volume of ICH, level of consciousness of the patient at presentation, and presence/volume of intraventricular hemorrhage [12–16].

In a population-based study in Greater Cincinnati, the volume of ICH in combination with the Glasgow Coma Scale (GCS) score predicted overall 30-day mortality with 96% sensitivity and 98% specificity (Table 4) [11]. Patients with a volume of 60 cm^3 and a GCS score less than or equal to 8 had a predicted mortality rate of 91%, whereas those

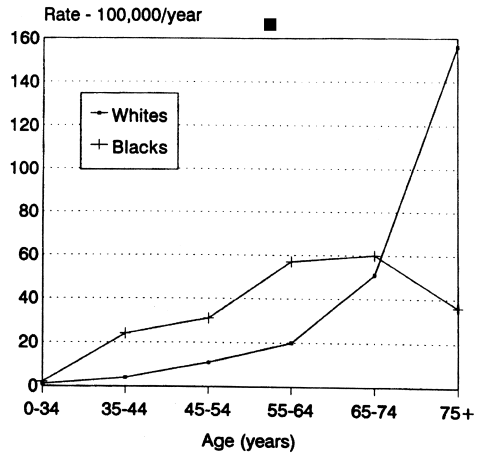

Fig. 1. Age-specific incidence rates of intracerebral hemorrhage by race in Greater Cincinnati during 1988 [4].

Table 2
Frequency of presenting signs and symptoms of intracerebral hemorrhage

Finding	Intracerebral hemorrhage (%)	Aneurysm, Arteriovenous malformation (%)
Seizure	6	7
Vomiting	51	47
Coma	24	24
Headache preceding	8	5
Headache at onset	33	78
Headache later	19	31
Bloody cerebrospinal fluid	70	94
Transient ischemic attack	8	7
Atherosclerosis	11	5
Diabetes	15	2
Past hypertension	72	19
Onset hypertension	91	34
Valvular heart disease	3	0

From Mohr JP, Caplan LR, Melski JW, et al. The Harvard Cooperative Stroke Registry: a prospective registry. Neurology 1978;28:754–62; with permission.

Table 3
Clinical presentation of symptoms by subtype of stroke

	Thrombosis	Lacune	Embolus	Intracerebral hemorrhage	Subarachnoid hemorrhage
Maximal at onset	40%	38%	79%	34%	80%
Stepwise	34%	32%	11%	3%	3%
Gradual	13%	20%	5%	63%	14%
Fluctuating	13%	10%	5%	0%	3%

From Mohr JP, Caplan LR, Melski JW, et al. The Harvard Cooperative Stroke Registry: a prospective registry. Neurology 1978;28:754–62; with permission.

with a volume of less than or 30 cm^3 and a GCS score greater than or equal to 9 had a predicted mortality rate of 19%. Only 1 of the 71 patients in Broderick et al's study [11] with a volume of ICH greater than or equal to 30 cm^3 could function independently at 30 days. For ICH with a volume of greater than or equal to 60 cm^3, the 30-day mortality rate for deep hemorrhages was 93%, and it was 71% for lobar hemorrhages (see Table 4).

Radiographic presentation

ICH is also known to be the subtype most likely to worsen significantly in severity as well as in volume in the first 24 hours. In a prospective study of CT scans of ICH performed at baseline, 1 hour after presentation, and 20 hours after presentation, Brott et al [17] demonstrated that 26% of cases had substantial growth in hemorrhage volume between the baseline and 1-hour scans. An additional 12% of patients had substantial growth between the 1- and 20-hour CT scans. This growth in hemorrhage volume was associated with clinical deterioration as measured by the GCS and the National Institutes of Health Stroke Scale (Fig. 2).

In a retrospective study of 627 cases of ICH by Fujii et al [18], the overall rate of hemorrhage growth or rebleeding was 14%. Subsequent reports found that of cases with clinical deterioration, more than 50% had hematoma enlargement and that hemorrhage growth occurred in more than one third of cases that underwent initial CT scanning within 3 hours of symptom onset [19]. By comparison, only 6% of cases that had an initial scan between 12 and 24 hours after stroke onset and 0% of cases that had an initial scan 24 hours after onset had hematoma enlargement by subsequent imaging.

Perihematoma edema

Perihematoma edema, the low-density rim surrounding ICH on a CT scan, and its importance to subsequent morbidity and mortality have drawn more attention as a target for future therapies. Edema formation after ICH may lead to increased intracranial pressure, brain herniation, and possibly death. The nature of the perihematoma edema and the causes of it have been elusive, however. Wagner et al [20] infused whole blood into the cerebral lobes of a pig and found that the perihematoma edema developed within 1 hour after infusion. When red blood cells were injected without serum, however, edema did not develop for nearly 72 hours. This suggests that early edema was caused by factors within serum and not from red blood cells or leakage of fluid through an injured blood–brain barrier. Subsequent edema after 72 hours may be secondary to lysis of red blood cells or breakdown of the blood–brain barrier [20,21].

Further studies have discovered that perihematoma edema can occur by using clotting factors

Table 4
Mortality of intracerebral hemorrhage based on volume and location of hematoma

	Overall 30-day mortality (n = 188)	≤30 cm^3 ICH	30–60 cm^3 ICH	≥60 cm^3 ICH
Lobar (n = 66)	39%	23%	60%	71%
Deep (n = 76)	48%	7%	64%	93%
Pontine (n = 9)	44%	43%	100%	N/A
Cerebellum (n = 11)	64%	57%	75%	N/A

ICH = intracerebral hemorrhage.

From Broderick J, Brott T, Duldner J, et al. Volume of intracerebral hemorrhage: a powerful and easy-to-use predictor of 30-day mortality. Stroke 1993;24:987–93; with permission.

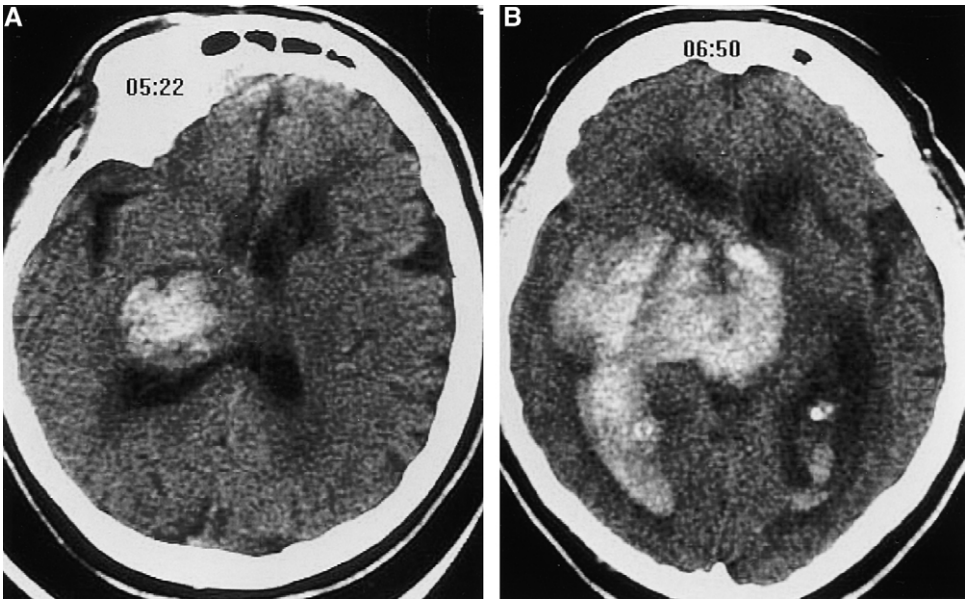

Fig. 2. Increase in hemorrhage size. (A) Thalamic intracerebral hemorrhage is seen in this patient with a history of hypertension at 5:22 PM. (B) The patient's condition continues to deteriorate over the next hour, and repeat imaging at 6:50 PM demonstrates enlargement of the hematoma and rupture into the ventricles.

alone. In particular, thrombin and fibrinogen cascade elements have been implicated in edema formation [22]. This was subsequently confirmed by a separate group of investigators who reported that when heparinized blood was injected into the brain, minimal perihematoma edema occurred compared with injection with unheparinized blood, where perihematoma edema developed rapidly [23].

In human studies, Gebel et al [24] reported that most hemorrhages caused by thrombolysis were large and had little perihematoma edema. This would be consistent with the finding that the activity of clotting factors may be related to formation of early perihematoma edema. In comparison to spontaneous ICH, thrombolysis-related ICH had visible perihematoma less than half as often as the cases with spontaneous ICH and also had lower amounts of absolute and relative volumes of edema [25]. Figure 3 compares a case of spontaneous ICH with a case of coagulopathy-associated ICH. Both cases had CT scans performed less than 3 hours after onset of symptoms.

To summarize, activation of the coagulation cascade seems to be important to the development of early perihematoma edema. ICH related to thrombolysis or coagulopathy may have less perihematoma edema than spontaneous ICH. In the future, therapies directed at reducing perihematoma edema may help to prevent the associated mass effect and potential herniation after ICH.

Gradient-echo MRI

MRI of the brain has greatly enhanced our ability to detect previous, small, or recurrent hemorrhages. Gradient-echo MRI is a technique that increases the amount of signal dropout from deposits of iron representing residual blood products as a result of past hemorrhage. This increases the potential for detecting small micro- or petechial hemorrhages. Initial reports suggested that as many as 60% of lobar hemorrhage cases may have evidence of petechial hemorrhage on gradient-echo MRI (Fig. 4) [26]. In addition, the technique has been demonstrated to find new hemorrhages in 47% of cases of probable cerebral amyloid angiopathy (CAA) [27]. Roob et al [28] reported that evidence of previous petechial hemorrhage could be found in 6.4% of otherwise healthy elderly individuals and may therefore be a means of detecting early disease. A study by Offenbacher et al [29] suggests that the rate of previous microhemorrhages may not be different among cases of lobar ICH compared with cases of nonlobar ICH, however. This study found that

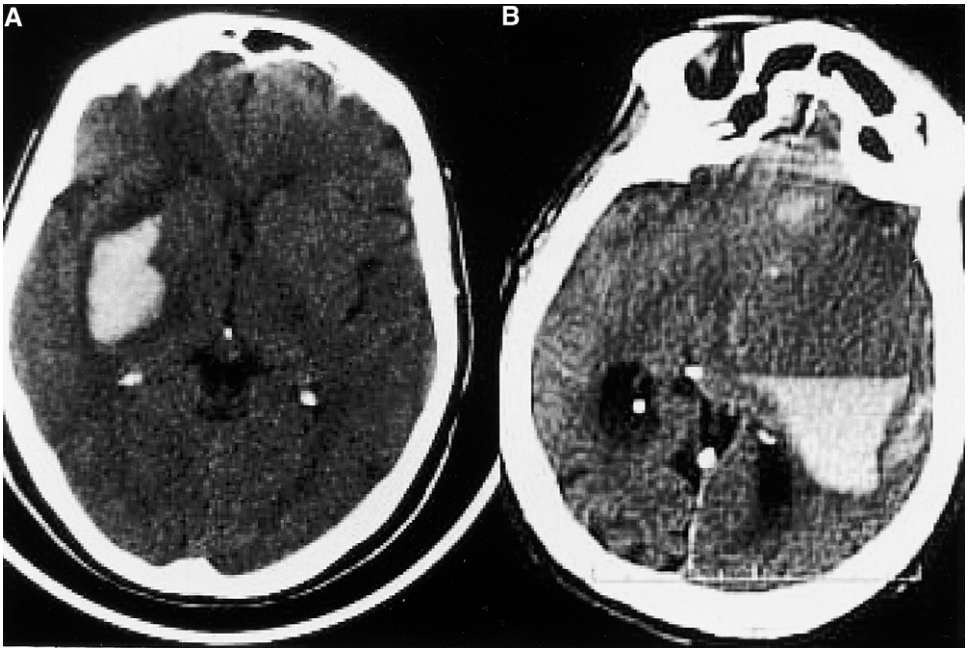

Fig. 3. (A) Spontaneous intracerebral hemorrhage (ICH) with perihematoma edema seen. (B) Coagulopathy-associated ICH with minimal perihematoma edema despite greater size than hemorrhage in (A).

one third of cases of ICH had previous hemorrhages consisting of microbleeds or old hematomas and that the presence of these previous hemorrhages was not associated with the location of the index hemorrhage. Nevertheless, the use of gradient-echo MRI is an important tool in the identification of patients with previous hemorrhage.

Mechanisms and risk factors

Hypertension

Hypertension is the most important and prevalent risk factor for primary ICH. In the biracial population of Greater Cincinnati during 1988, the presence of hypertension among patients with a primary ICH was remarkably similar for whites

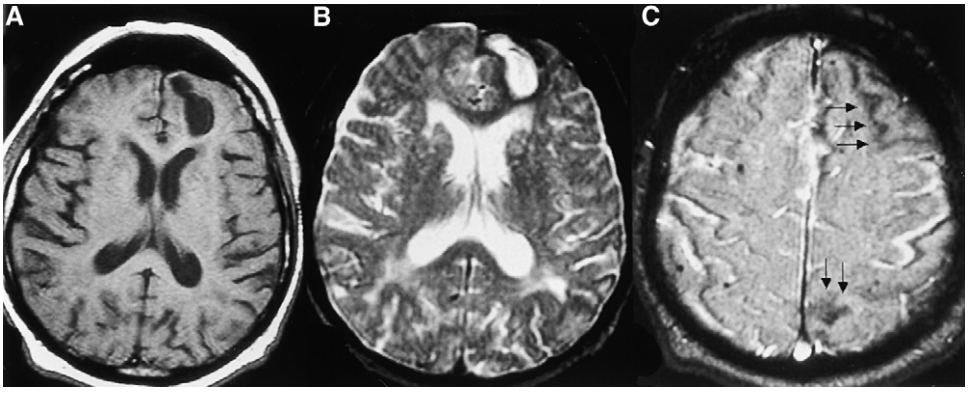

Fig. 4. Gradient-echo MRI of a patient with previous microhemorrhages in multifocal regions typical of cerebral amyloid angiopathy. (A) T1-weighted image demonstrates an old lesion in the left frontal lobe. (B) T2-weighted image demonstrates a hemosiderin ring around the left frontal lesion. (C) Gradient-echo imaging demonstrates chronic microhemorrhages in the left frontal and left medial parietal region (*arrows*).

(73%), blacks (71%), men (72%), and women (73%) [7].

Hemorrhage originating in the thalamus, basal ganglia, deep periventricular white matter, pons, or cerebellum has been linked to a vasculopathy of the small penetrating arteries and arterioles that is strongly associated with hypertension. The vasculopathy primarily involves arteries that are 100 to 600 μm in diameter and is characterized by severe degeneration of medial smooth muscle cells, miliary aneurysms associated with thrombus and microhemorrhages, accumulation of nonfatty debris, and hyalinization of the intima [30–33]. Extensive degeneration of the tunica media seems to be the most important and consistent finding and appears to be separate from the frequently associated intimal changes in larger arterioles thought to be caused by atherosclerosis [31,33].

In a population-based study of ICH, Woo et al [34] reported that 34% of all ICHs and particularly 54% of nonlobar ICHs could be attributed to the effects of hypertension. Hemorrhage caused by vascular malformations was not included in their study.

Amyloid angiography

Although once considered to be a rare cause of lobar hemorrhage, CAA is now considered to be an important cause of lobar hemorrhage in the elderly [35–37]. Its principal pathologic feature is the deposition of amyloid protein in the media and adventitia of leptomeningeal arteries, arterioles, capillaries, and, less often, veins [35–39]. The suspected cause of ICH as a result of CAA involves destruction of the normal vascular elements by deposition of amyloid in the media and adventitia. These brittle blood vessels may be more prone to rupture in response to minor trauma or sudden changes in blood pressure [40]. CAA may also be responsible for transient neurologic symptoms and dementia with leukoencephalopathy [41].

CAA occurs almost exclusively in lobar regions of the brain. In addition, deposition of amyloid within cortical blood vessels has been found to increase with advancing age. Of persons 60 to 69 years of age, only 5% to 8% were found to have amyloid angiopathy compared with 57% to 58% of those older than 90 years [42,43]. This deposition is most prominent in the parietal and occipital regions but rarely can be found in the basal ganglia, brain stem, or cerebellum [35–38].

Okazaki and Whisnant [35] reported that amyloid angiopathy was present in 5 of 17 persons aged 65 years or older who suffered from a fatal ICH, and Drury and colleagues [44] reported that half of all ICHs occurring in those aged 65 years or older had a lobar hemorrhage. On the basis of these findings, Drury et al [44] suggested that amyloid angiopathy might be the predominant cause of ICH in the elderly. The recurrent and multifocal nature of CAA is a distinguishing feature from hypertensive hemorrhage, which rarely recurs. Hill et al [45] reported that patients with a lobar hemorrhage were nearly four times more likely to suffer from a recurrent hemorrhage and that lobar location was the single most important predictor of a recurrent hemorrhage.

Apolipoprotein E and cerebral amyloid angiopathy

Several studies have now found that the presence of an apolipoprotein E ε2 (ApoE2) genotype (at least one ApoE2 allele) and apolipoprotein E ε4 (ApoE4) genotype (at least one ApoE4 allele) is associated with CAA-associated ICH [46–49]. Greenberg et al [46] reported that among 45 cases of lobar hemorrhage from Massachusetts compared with 1899 population-based controls from Iowa, the cases of lobar hemorrhage had twice the prevalence of ApoE4 compared with the population-based sample. The carriers of the ApoE4 allele tended to have their first hemorrhage 5 years earlier than noncarriers. Nicoll et al [49] reported that among 36 patients with pathologically confirmed or probable cases of CAA, ApoE4 was a risk factor for concomitant Alzheimer's disease but was not an independent risk factor for CAA-related hemorrhage. These investigators did report that 42% of CAA cases had an ApoE2 allele. They studied 61 patients with dementia and 43 healthy elderly individuals as controls. A limitation of these studies was the comparison of cases with controls from different populations and the lack of a multivariate analysis that controlled for the presence of numerous other risk factors associated with ICH.

Woo et al [34] recently reported that in a population-based case–control study of hemorrhagic stroke in Greater Cincinnati/Northern Kentucky in which cases of ICH were matched by age, race, and gender to population-based controls, the presence of possessing either an ApoE2 or ApoE4 allele conferred a significant risk of having a lobar ICH (odds ratio [OR] = 2.2) after controlling for all other significant risk factors. These investigators also reported that nearly 30% of lobar ICH cases may be attributed to the effects of ApoE2 or ApoE4.

Finally, ApoE genotype may influence the risk of recurrent hemorrhage. As described previously, recurrent hemorrhage is associated with CAA. O'Donnell et al [50] reported that carriers of ApoE2 or ApoE4 alleles had a 2-year recurrence rate of 28% compared with a rate of 10% for those possessing an ApoE3/E3 genotype. In particular, patients with a history of hemorrhagic stroke that had an ApoE2 or ApoE4 genotype before enrolling in the study had a 2-year recurrence rate of 61%.

Although lobar hemorrhage and CAA are not synonymous terms, most cases in the population do not undergo pathologic confirmation of the mechanism of stroke. These studies provide evidence of the impact of ApoE genotype on the incidence of ICH, but the relation is still one of association rather than an established cause of CAA or lobar hemorrhage.

Structural lesions

Intracranial vascular malformations consist of aneurysms, arteriovenous malformations (AVMs), cavernous angiomas, venous angiomas, and telangiectasias. An AVM is composed of a mass of abnormal blood vessels in which arterial and venous channels are connected without a capillary bed. Typically, abnormal and normal brain tissue is found between these vessels. By contrast, cavernous angiomas consist of large sinusoidal channels without intervening brain tissue. Hemosiderin-laden macrophages may frequently be seen within and surrounding the channels, reflecting previous hemorrhages.

Venous angiomas consist of numerous dilated channels (with normal brain between the channels) emptying into a larger venous channel that is connected to one of the dural sinuses. Telangiectasias consist of capillary vessels or vessel walls that lack muscular or elastic elements and are separated by normal brain parenchyma. Reports suggest that vascular malformations are particularly important as a cause of ICH among young people [51–53]. In a prospective study of 206 cases of spontaneous ICH that underwent angiography, Zhu et al [54] found that 65% of lobar ICH cases in those aged 45 years or younger had an underlying structural lesion compared with 0% in older patients with nonlobar ICH. Other studies have reported that vascular malformations were predominately lobar (63%–71%) in location.

In a prospective autopsy series, 4% of all brains were found to have vascular malformations, of which 63% were venous angiomas [55]. This contrasts with lesions that cause hemorrhage as reported by autopsy (Table 5) [56]. These data demonstrate that although venous angiomas represent the most common lesion in the general population, they are associated with only a small percentage of cases with ICH. Similarly, cerebral telangiectasias are more common at autopsy than either AVMs or cavernous angiomas but are a rare cause of ICH. A limitation of this comparison is the inclusion of "mixed types" in the symptomatic ICH study; these mixed types were not included in the original population-based study.

Arteriovenous malformation

Clinical presentations of AVMs include intracranial hemorrhage, headache, and seizures. They are composed of a mass of abnormal blood vessels, of which some are arterial or venous and are connected by abnormally dilated channels without an intervening capillary bed. Typically, abnormal as well as normal brain tissue is found between the vessels. Patients with an AVM may present with intracranial hemorrhage, seizures, focal neurologic deficits, and headache. Intracranial hemorrhage is the presenting symptom in 65% of cases of intracranial AVMs [57]. Of these, parenchymal ICH occurred in 45%, SAH in 20%, both ICH and SAH in 10%, intraventricular hemorrhage in 10%, and both intraventricular hemorrhage and ICH in 15%.

Although AVMs are considered to be congenital in origin, only 18% to 20% of cerebral AVMs are diagnosed in individuals less than 15 years old, suggesting that growth is a part of the natural history of the AVMs. Brown et al [58] report that 75% of hemorrhages caused by AVMs occurred before patients reached their fiftieth birthday and that the peak occurrence of hemorrhage was during

Table 5
Comparison of the frequency of vascular malformations in autopsy series versus symptomatic intracerebral hemorrage patients series

	Population-based autopsy [55]	Intracerebral hemorrhage patients autopsy [56]
Venous angioma	105 (63%)	2 (1.3%)
Telangiectasia	28 (17%)	1 (0.6%)
Arteriovenous	24 (14%)	159 (88%)
Cavernous	16 (10%)	6 (3%)
Mixed type	N/A	11 (6%)

N/A = not applicable.

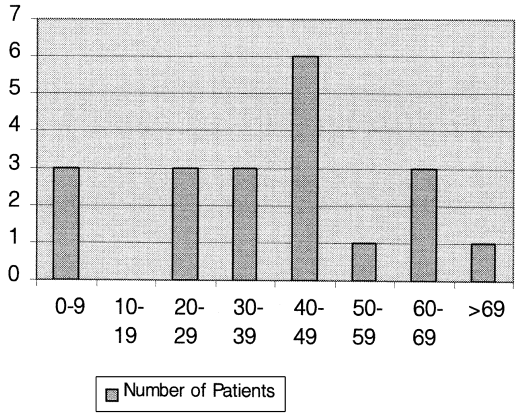

Fig. 5. Bar graph depicting the age of first intracranial hemorrhage by intracranial vascular malformations (*Adapted from* Brown RDJ, Wiebers DO, Torner JC, et al. Frequency of intracranial hemorrhage as a presenting symptom and subtype analysis: a population-based study of intracranial vascular malformations in Olmsted County, Minnesota. J Neurosurg 1996;85:30; with permission.)

the fifth decade of life. Another peak was seen at the age of 0 to 9 years (Fig. 5). Therefore, a vascular malformation should be a strong consideration in a young patient with ICH. Surprisingly, smaller AVMs present with hemorrhage more often than larger AVMs [58–62]. Spetzler et al [63] reported that 82% of AVMs less than 3 cm in size presented with hemorrhage compared with only 21% of AVMs larger than 6 cm. In addition, smaller AVMs tended to have a larger sized hemorrhage when they ruptured compared with larger AVMs. The proposed mechanism for this finding is that a greater difference in intravascular pressure between the feeding artery and draining vein may exist in smaller AVMs that are symptomatic. If the difference is not great, however, these AVMs may increase in size to become larger AVMs. Whereas the risk of hemorrhage is lower with larger AVMS (Fig. 6), they have a higher surgical risk. The Spetzler scale of surgical risk is based on AVM size, eloquence of adjacent brain, and pattern of venous drainage (Table 6) [64].

Cavernous angioma

Cavernous angiomas, also known as cavernomas, cavernous hemangiomas, or cavernous malformations, are usually solitary. There are patients with inherited cavernous angiomas in whom multiple angiomas are often present. The slow flow of blood through these lesions often makes them difficult to identify on routine angiograms. On CT scans, they may appear calcified, whereas on MRI, they are typified by various ages of hemorrhage seen in the region of the cavernous angioma. In addition to hemoglobin and transformation to methemoglobin in the acute and subacute phases, residual hemosiderin from a previous hemorrhage may be deposited on the periphery of the lesion (Fig. 7).

MRI and autopsy studies report a prevalence of 0.5% for cavernous malformations in the general population (Table 7) [65]. Porter et al [66] reported

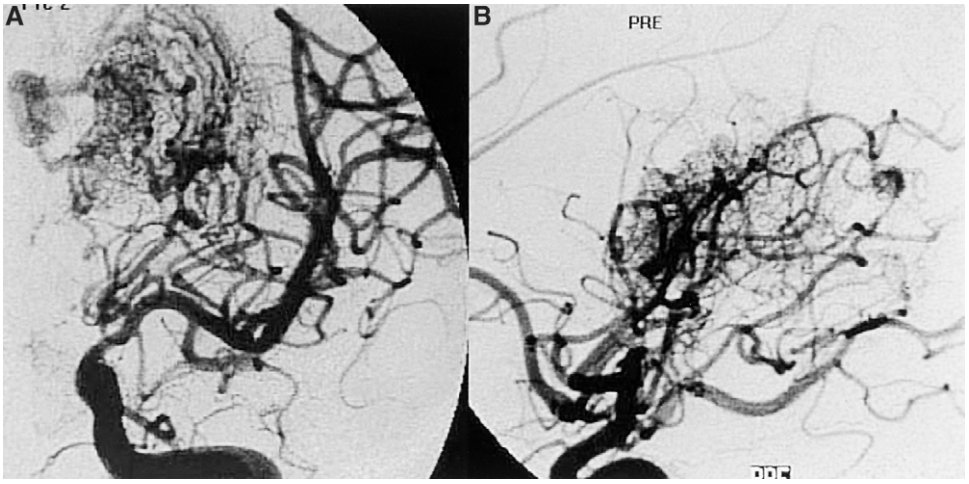

Fig. 6. High-grade arteriovenous malformation with a nidus greater than 6 cm and a deep draining vein, which is located in an eloquent area of the brain. Internal carotid angiogram: anteroposterior view (A), lateral view (B).

Table 6
Determination of arteriovenous malformation grade; Spetzler scale

Graded feature	Points assigned
Size of arteriovenous malformation	
Small (<3 cm)	1
Medium (3–6 cm)	2
Large (>6 cm)	3
Eloquence of adjacent brain	
Noneloquent	0
Eloquent	1
Pattern of venous drainage	
Superficial only	0
Deep	1

From Spetzler RF, Martin NA. A proposed grading system for arteriovenous malformations. J Neurosurg 1986;65:476–83; with permission.

their experience with 173 cases of cavernous malformations. The mean age at presentation was 37.5 years, and 18% of their patients had multiple lesions. Seizure was the presentation in 36%, hemorrhage in 25%, and focal neurologic deficit in 20%. Isolated headache was the presentation in 6%, and 12% were discovered incidentally. After 427 patient-years of review, only 18 of the patients had a subsequent event, for an overall event rate of 4.2% per year. Deep cavernous angiomas had a higher annual event rate (10.6% per year) than superficial lesions (<1% per year), and 63% of lesions were superficial.

Of the vascular malformations, cavernous angiomas have the strongest evidence of familial aggregation, particularly among Hispanic Americans. Rigamonti et al [67] studied 24 cases with cavernous angiomas and found that 13 of these patients were members of Mexican-American families. On interview of the first- and second-degree members of these families, these investigators reported that 11% of first- and second-degree relatives (7 of 64) had a history of seizures. MRI had been performed on 16 relatives, of whom 5 were asymptomatic, and it was discovered that 14 had cavernous angiomas and 11 had multiple angiomas. Subsequently, Mason et al [68] reported the discovery of a Hispanic family with 10 of 22 members having cavernous angiomas. Ultimately, genetic linkage studies have mapped a gene associated with cavernous malformations to a segment of the long arm of chromosome 7 (7q) [69–73].

Venous angioma

Whereas cavernous malformations are a precapillary lesion without a venous component, venous angiomas are a postcapillary malformation. On neuroimaging, the large draining vein or varix is

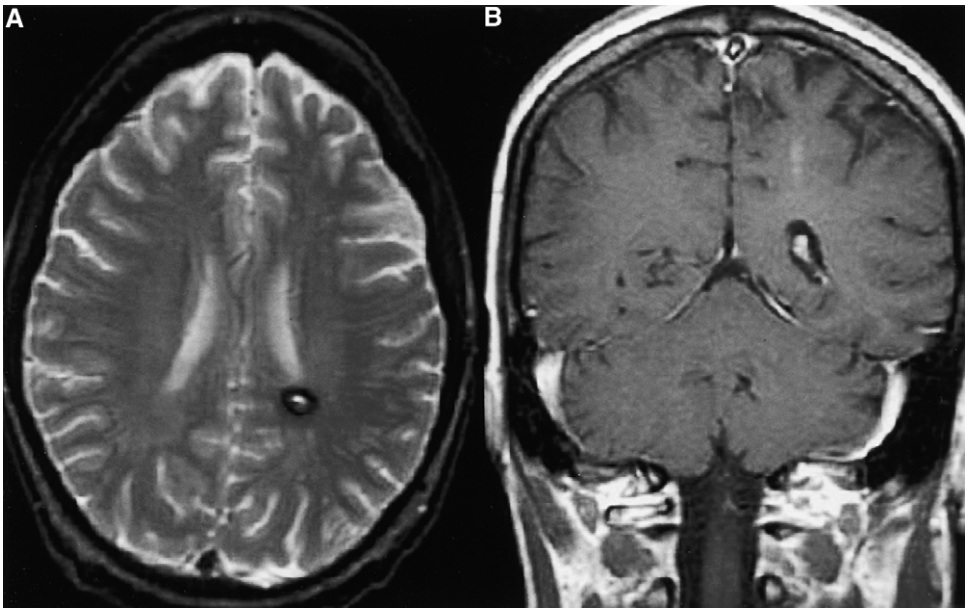

Fig. 7. Cavernous angioma. (A) T2-weighted image of a cavernous angioma with a dark rim of hemosiderin surrounding a region of increased intensity. (B) T1-weighted image with contrast demonstrating modest enhancement of the angioma.

Table 7
Distribution of cavernous and venous angiomas

Location	Cavernous angioma (%) [66]	Venous angioma (%) [74]
Frontal	28	42
Parietal	7	24
Temporal	17	2
Occipital	4	4
Basal ganglia/thalamus	7	11
Corpus callosum	0.6	
Brain stem/cerebellum	6	3

often oriented toward the cortical surface and to the nearest dural sinus and should enhance after contrast infusion (Fig. 8). On angiography, venous angiomas have a characteristic ''medusa head'' appearance.

As described previously, autopsy studies have found that venous angiomas count for 63% of all vascular malformations but are the least likely to present with hemorrhage (see Table 5). In fact, numerous studies have found that the natural history of venous angiomas is generally benign [74,75]. Yet, these studies as well as others frequently describe cases that may be ''symptomatic'' from a venous angioma [76–81]. Presentation varies considerably, with headaches, seizures, and occasionally hemorrhage having been attributed to venous angiomas.

Telangiectasia/hereditary hemorrhagic telangiectasia/Rendu-Osler-Weber syndrome

Most telangiectasia changes (Fig. 9) in the central nervous system are benign structures and rarely lead to hemorrhage. Hereditary hemorrhagic telangiectasia (HHT) or Rendu-Osler-Weber syndrome is a disease in which numerous telangiectasias and other vascular malformations may occur, however. This disorder is typified by the classic triad of telangiectasia, recurrent hemorrhage, and a family history of disease. In particular, a lack of cerebral telangiectasia does not rule out HHT.

Although neurologic complications occur in approximately 10% of cases of HHT, less than one third of these are caused by cerebrovascular malformations [82]. The most frequent cause (~60%) is septic microemboli from pulmonary arteriovenous fistulas, which subsequently lead to brain abscesses and hemorrhage [82–84]. In addition, patients with HHT have a propensity for aneurysms, AVMs, and carotid-cavernous fistulae [85–88].

HHT is inherited by an autosomal dominant mode of inheritance with 97% penetrance [89]. HHT occurs in all races [90] and occurs equally in both sexes [91]. Reports of incidence rates vary, but Bideau et al [92,93] reported that HHT affects 1 in every 8345 persons. The gene for HHT is on the q33-q34 region of chromosome 9, which codes for endoglin or transforming growth factor-β

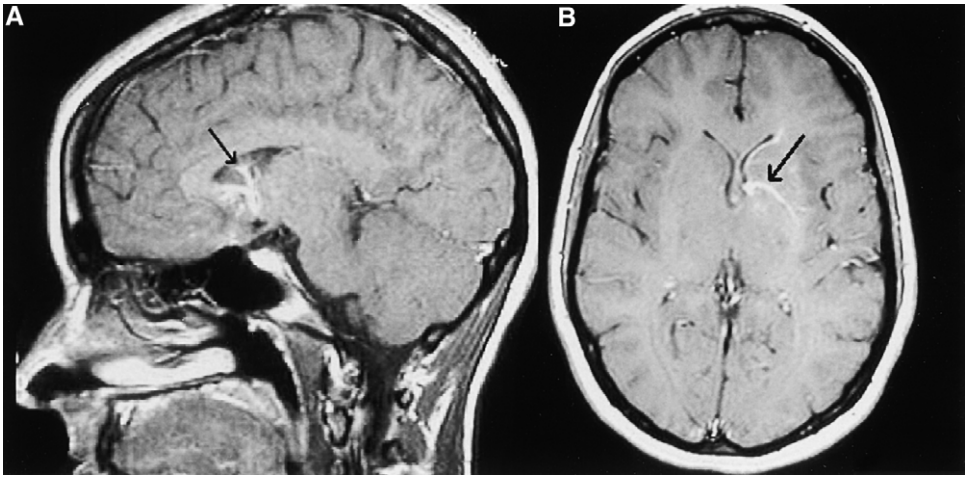

Fig. 8. Venous angioma. (A) Sagittal view: T1-weighted postcontrast image. Venous angioma is seen (*arrow*). (B) Axial view: T1-weighted postcontrast image. Venous angioma is seen (*arrow*).

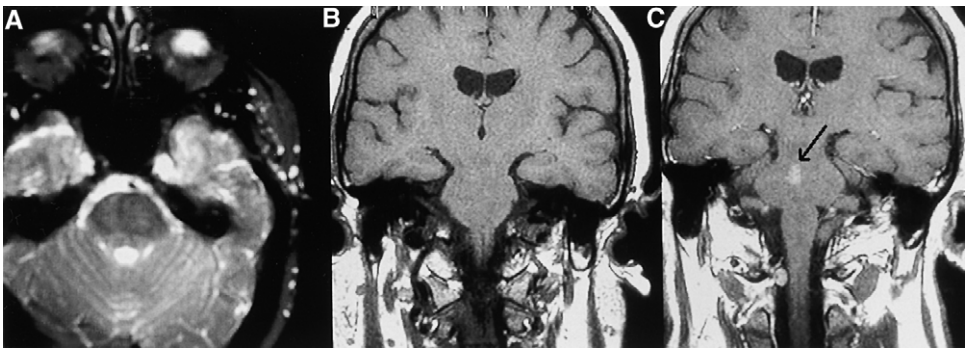

Fig. 9. Telangiectasis. (A) T2-weighted image of the midbrain. (B) T1-weighted image did not reveal any abnormalities. (C) Contrast-enhanced T1-weighted image demonstrates an enhancing lesion in the midbrain (*arrow*).

binding protein [94–96]. With few exceptions, patients manifest the disease by 40 years of age [97,98], and cutaneous lesions are rarely detected before the second or third decade of life [99].

Coagulopathy and thrombolysis-associated intracerebral hemorrhage

Coagulopathy, whether a result of congenital or medically induced causes, is associated with ICH (see Fig. 4). The oral anticoagulant coumadin has been associated with a 6- to 11-fold increased risk of ICH [100,101]. Petty et al [102] reported that the risk of ICH increased over time from 1% at 6 months to 7% at 2 and 3 years of treatment. Although higher levels of anticoagulation were associated with an increased risk of ICH, most cases occur with therapeutic degrees of anticoagulation [103,104]. In addition, previous stroke or head trauma has not been clearly associated with coagulopathy-related ICH [105,106], which suggests that other mechanisms, such as hypertension or amyloid angiopathy, may be a predisposing factor. In fact, thrombolysis studies have found that as many as 20% of hemorrhages related to thrombolytic use occur outside the vascular distribution of the presenting ischemic stroke [107].

Woo et al [34] reported that in a population-based case–control study in Cincinnati, 12% of all patients with ICH were on blood thinners at the time of their hemorrhage compared with only 4% of age-, race-, and gender-matched controls (OR = 3.6; 95% confidence interval [CI]: 1.8–7.2) and that the risk of hemorrhage was particularly high for nonlobar ICH (OR = 5.6; CI: 2.2–14.0).

Gebel et al [24] reported that 77% of cases of thrombolytic-associated ICH occurred in lobar regions of the brain. Thrombolytic-associated hemorrhage was solitary in 66% of cases, confluent in 80%, and had a blood–fluid level in 82%. Pfelger et al [108] reported that the blood–fluid level is 98% specific for an abnormal prothrombin or partial thromboplastin time.

Prior cerebral infarction

Prior cerebral infarction has been associated with a 5- to 22-fold increased risk of ICH [34, 109,110]. This close relation between ICH and cerebral infarction is not surprising, because hemorrhage and infarction share similar risk factors, such as hypertension. In a population-based study in Greater Cincinnati, 15% of patients with ICH had a history of previous stroke and the odds ratio for ICH in patients with prior stroke was 7.0 (CI: 2.7–186.0) [34]. Woo et al [34] also reported that 13% of all ICH can be attributed to prior ischemic stroke as a risk factor.

Hypocholesterolemia

Several studies have demonstrated that hypocholesterolemia is a risk factor for ICH compared with normal cholesterol levels. In a population-based study in Dijon, France, Giroud et al [10] reported that in multivariate analysis, the only significant risk factors for cerebral hemorrhage were hypertension and low cholesterol. The importance of this factor may vary by gender and location of hemorrhage. Okumura et al [111] reported that low cholesterol was found to be a significant risk factor for ICH in men but that this relation was not statistically significant in women (in that study, low cholesterol was defined as a total cholesterol level of 167 mg/dL or less). Segal et al [112] reported that the nearly 47% of cases of deep ICH had low cholesterol compared with only 27% of cases of

lobar hemorrhage. In their study, the overall rate of low cholesterol was 42% in patients compared with 20% in age- and gender-matched controls. These studies seem to support the initial report of an increased risk of ICH with hypocholesterolemia by Okada et al [110] in 1976.

Frequent alcohol use

Several population-based case–control studies have reported that frequent alcohol use was a significant risk factor for ICH. Caicoya et al [113] reported that drinking more than 140 g/d of alcohol yielded an OR of 6.2 (CI: 1.3–24.0) for ICH. Monforte et al [114] reported that this relation was most significant for lobar ICH. In the Greater Cincinnati study, the multivariate OR for frequent alcohol consumption (>two drinks per day) for lobar ICH was 5.3 (CI: 1.4–20). Woo et al [34] reported that 8% of all lobar ICH can be attributed to frequent alcohol use. No relation to nonlobar ICH was identified in either the Greater Cincinnati study [34] or the study by Monforte et al [114,115].

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