Progress Reviews

Intracerebral Hemorrhage: Non-Hypertensive Causes

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SPONTANEOUS, non-traumatic intracerebral hemorrhage (ICH) in the adult is most commonly secondary to hypertensive cerebrovascular disease. In 70–90% of cases of spontaneous ICH, arterial hypertension is the presumed cause. These hypertensive hemorrhages show a predilection for certain anatomic locations: the basal ganglia (the putamen in particular), the subcortical white matter, and the thalamus account for 35%, 25%, and 20% of ICHs, respectively, whereas the posterior fossa locations, the cerebellum and pons, are responsible for only 10% and 5% of the cases. Irrespective of their anatomic locations, the common pathogenesis in these hemorrhages involves the hypertension-induced degeneration of the media of small (50–200 micra) arteries called "lypo-hyalinosis," and/or the formation of "microaneurysms", both of which occur preferentially in perforating or small sub-cortical arteries, thus resulting in the characteristic anatomic distribution of hypertensive ICH.

A significant number of cases of ICH are due to causes other than hypertension. The frequency of such cases varies from 25% to 50% among series, and depends on the anatomic type of ICH being considered: non-hypertensive mechanisms may account for as many as 55% of "lobar" ICH cases, while pontine hemorrhage is virtually always (90%) hypertensive, and the deep ganglionic (putaminal, thalamic) and cerebellar varieties occupy an intermediate position (35%, 25%, and 38% being of non-hypertensive mechanism, respectively). Among the many possible mechanisms of ICH not primarily related to hypertension, there are several that occur with high enough frequency to warrant separate discussion. These causes of ICH are related to special types of arterial pathologies, to the presence of brain tumors, or to the use of medications, and include: cerebral amyloid angiopathy, small vascular malformations, primary or metastatic brain tumors, oral anticoagulants, and amphetamines and a variety of other sympathomimetic drugs.

Cerebral Amyloid Angiopathy

This condition is a unique form of angiopathy due to deposits of amyloid in the media and adventitia of small and medium-size arteries of the cerebral hemispheres. The arteries affected are preferentially located in the superficial layers of the cerebral cortex and the leptomeninges, cerebral amyloid angiopathy (CAA) being virtually absent in the deep grey nuclei, where ICH of hypertensive origin predominates. CAA is a condition restricted to the cerebral vasculature, since it is not associated with systemic vascular amyloidosis, and it is almost always of sporadic occurrence, although familial incidence has been documented in Iceland and in the Netherlands. In these the condition is inherited as an autosomal dominant trait, and leads to ICH early in life, especially in the Icelandic families, in which the majority of the ICHs occurred in the third and fourth decades. In a group of these patients it has been recently shown that the basic abnormality appears to be in the metabolism of an alkaline microprotein called "gamma-trace", which is found in abnormally low concentrations in the CSF of these patients, as compared with controls. An abnormality in the catabolism of this microprotein is thought to cause the vascular deposition of amyloid fibrils.

The common sporadic variety of CAA typically affects elderly individuals. Its incidence in autopsy series increases with age, from a mere 8% in the seventh decade, to close to 60% in individuals older than 90. An association with Alzheimer's disease has long been recognized, particularly in regards to a high frequency of some of its histopathologic features in brains of patients with CAA. In at least 50% of reported cases of CAA, neuritic plaques have been documented, with a lower frequency of detection of neurofibrillary tangles. The presence of clinical progressive dementia of the Alzheimer type has been reported with differing frequency in various series, affecting from 10% to 30% of the patients. Pathologically, CAA is characterized by deposits of Congo-red positive material in the media and adventitia of cortical and leptomeningeal arteries. These Congo-red stained vessels show characteristic bi-refringence under polarized light, and also exhibit fluorescence with thioflavin T staining. Electron microscopic studies demonstrate the typical non-ramified 90–110 A diameter amyloid fibrils within the vessel wall. These lesions often lead to thickening of the vascular wall, with stenosis or obstruction of the lumen, resulting in small foci of necrosis (infarcts), which are rarely if ever symptomatic. The only consistent clinical result of CAA is ICH following rupture of an affected artery, due to either "weakening" of the wall by the amyloid deposits, or to rupture of a secondary "microaneurysm" developed at sites of amyloid deposition.
The ICHs from CAA characteristically occur in superficial, subcortical or "lobar" locations, since the angiopathy selectively affects arteries of the cortical surface and leptomeninges. Furthermore, these subcortical ICHs have shown, in some series, a predilection for the posterior aspects of the cerebral hemispheres, reflecting a generally heavier concentration of CAA-affected arteries in the parietal and occipital lobes. In some instances, subarachnoid or subdural hemorrhages have coexisted, again reflecting the superficial location of the vascular lesions. An additional feature of ICH related to CAA has been a tendency to produce recurrent hemorrhages over periods of months or years, occasionally even leading to simultaneous acute intracerebral hematomas in two different brain locations. In a number of published reports a history of head trauma or, less commonly, a prior neurosurgical procedure has preceded the onset of CAA-related ICH. This raises the possibility that some of these hemorrhages may be related to trauma, and the potential for such complication should be recognized when a neurosurgical procedure (such as ventricular shunt insertion, brain biopsy) is indicated for elderly demented patients. Furthermore, the need for meticulous hemostasis following surgical evacuation of ICHs in the elderly cannot be overemphasized. Some authors have considered ICH from CAA a condition with poor vital prognosis, on account of a generally larger size of the hemorrhages, and their tendency to recur. It is possible that systematic search for this etiology in specimens from surgically-evacuated intracerebral hematomas will provide an accurate estimate of the true frequency of CAA in cases of spontaneous ICH. Only then will its prognosis and tendency to post-operative local recurrence be documented.

In conclusion, CAA is probably an important etiologic factor for ICH in non-hypertensive elderly individuals who present with single or recurrent hemorrhages of subcortical "lobar" location. The actual frequency of this disorder is unknown, but is probably quite high in elderly populations. It is expected that increased awareness of this condition will lead to more accurate estimates of its frequency in surgical and autopsy specimens, and this effort may eventually result in effective measures for its treatment and prevention.

Small Vascular Malformations

These correspond to previously unsuspected small intracerebral arteriovenous malformations (AVMs), cavernous angiomas, or venous angiomas, that present as spontaneous ICH in adult life. Their reported frequency in series of ICH has varied between 4 and 8% of the cases. The diagnosis is usually established by cerebral angiography or, more commonly, following histologic study of biopsy specimens taken at the time of surgical evacuation of the ICH. With the introduction of CT scanning, an increasing number of these lesions are being diagnosed by the demonstration of calcium deposits in their vicinity or, more commonly, by the post-contrast opacification of abnormal serpiginous vascular channels adjacent to an intracerebral hematoma. The histologic type of vascular malformations leading to ICH most frequently corresponds to AVMs or venous angiomas, the cavernous angioma variety being rarely associated with bleeding. AVMs usually become symptomatic at a relatively early age, most commonly in the third and fourth decades, thus representing a potential source of ICH in non-hypertensive young populations. A striking female preponderance of these small vascular malformations has been reported in several series. Their clinical presentation is that of ICH in any location, deep or superficial, without specific clinical features, other than perhaps a relatively slower course of development, as compared with the more abrupt and rapidly evolving course of hypertensive ICH. The hemorrhages produced by these lesions tend to be more often at the level of the cerebral convexity (subcortical white matter) than in the deep portions of the hemisphere, reflecting their usually more superficial location, a feature also documented for non-ruptured small cerebral vascular malformations incidentally found at autopsy. Due to their small size, the usual absence of symptoms prior to the onset of ICH, and the difficulty in diagnosing them in life, these malformations have been called "cryptic" by some authors. On occasions there is a family history of such vascular malformations and ICH, but they occur more commonly on a sporadic basis. Since their documentation can result in successful surgical therapy and prevention of recurrent ICH, angiography should be considered part of the routine evaluation of non-hypertensive patients presenting with spontaneous ICH, in particular if the hemorrhage is located in the subcortical white matter of a cerebral hemisphere. In a number of instances, preoperative angiography has failed to document a vascular malformation that was diagnosed histologically following surgical evacuation of an intracerebral hematoma. These patients have usually had small AVMs or venous angiomas. The difficulties in demonstrating the latter lesion angiographically probably stem from their small size and lack of multiple tortuous vascular channels, as well as the absence of arteriovenous shunting of blood leading to marked dilatation of venous structures. In the case of small AVMs, lack of angiographic demonstration may at times reflect compression by an adjacent hematoma, since repeat angiograms following resorption of the hematoma have occasionally disclosed them. Spontaneous thrombosis may be an additional reason for lack of angiographic visualization of malformations. Due to the potentially negative angiograms in the setting of an acute ICH due to one of these malformations, some authors have recommended surgical evacuation of intracerebral hematomas in young non-hypertensive patients, since the resection of this type of lesion will likely prevent ICH recurrence.

Brain Tumors

Hemorrhage into a brain tumor is a relatively rare, but well documented, cause of non-traumatic, non-hypertensive ICH. In series of brain tumors, ICH oc-
curs in less than 1% of these cases, whereas underlying tumors in ICH series are found in 2 to 6% of the cases.20,21 Occasionally in as many as 10% of the cases.22 These are instances of ICH in either a previously unknown cerebral neoplasm or, more commonly, as a complication of a known brain tumor. As a result, ICH produces the acute onset of either a new focal neurologic deficit, or worsening of pre-existing focal deficits, in both instances commonly associated with deterioration in the level of consciousness. The brain tumors likely to present as ICH are largely malignant, either primary astrocytoma (glioblastoma multiforme) or metastatic, most commonly bronchogenic carcinoma, melanoma, choriocarcinoma, or renal-cell carcinoma.21-24 Benign brain tumors such as meningiomas or oligodendrogliomas have rarely been reported as presenting with episodes of non-traumatic ICH. The bleeding potential of malignant tumors is thought to be related to their tendency toward spontaneous necrosis and to the richness and neoplastic character of their vasculature, as well as the biologic tendency of some tumors such as choriocarcinoma to invade the walls of blood vessels. Metastases from this tumor are noteworthy for their tendency to become hemorrhagic in at least 50% of the cases.24

The sites of ICH relate in some degree to the type of underlying tumor, since deeply-seated white matter tumors such as glioblastoma multiforme will produce deep hemispheric hemorrhages, while those resulting from metastatic tumors are more often cortico-subcortical, reflecting the predilection of secondary tumors for the superficial portions of the cerebral hemispheres. Most commonly, these hemorrhages originate at the margins of the tumor, or between the tumor and the adjacent edematous brain parenchyma.21 Instances in which an underlying tumor is suspected in a patient with ICH include: (a) History of preceding chronic headache and/or focal neurologic deficit and/or personality change for days or weeks prior to the onset of ICH, or the finding of papilledema on initial presentation with ICH; (b) The presence of multiple separated foci of ICH occurring simultaneously; (c) An area of “ring-like” hemorrhage with a low-density center in non-contrast CT scan; (d) An ICH that on CT scan appears as irregular, mottled high-density, and affecting structures that are rarely involved in hypertensive ICH, such as the corpus callosum, which on the other hand is frequently affected in glioblastoma multiforme; (e) A disproportionate degree of surrounding edema and mass effect associated with the hematoma; (f) Presence of post-contrast enhancement in the vicinities of the acute high-density ICH. An angiogram can be useful in demonstrating a mass lesion with the classical “tumor blush” characteristic of highly vascular primary or metastatic brain tumors. In many instances the diagnosis is only suspected by the finding of clinical or radiologic signs of a systemic malignancy, or it is established by biopsy of the hematoma cavity following its surgical evacuation. The prognosis in this form of ICH is poor, with short-term (days to weeks) mortality in the 90% range, mostly due to the acute effects of the ICH leading to uncal herniation and brainstem compression or, less commonly, to the progression of the underlying malignant tumor.25

**Oral Anticoagulants**

Warfarin sodium, a widely used oral anticoagulant for the prevention of venous and arterial origin embolism, is associated with bleeding complications in approximately 7-8% of patients.26,27 Intracranial hemorrhage accounts for a small fraction of these hemorrhages, amounting to only 0.5-1.5% of all bleeding events related to warfarin. However, these intracranial hemorrhages have a generally dismal prognosis, thus resulting in a significant contribution to the fatal complications of oral anticoagulant therapy.

The common intracranial sites of bleeding in orally anticoagulated patients are, in decreasing order of frequency, the subdural space, brain parenchyma, and subarachnoid space. ICH in this setting represents a condition with some distinct clinical characteristics and course, as well as high mortality and serious long-term sequelae in survivors. Oral anticoagulation has been estimated to increase between 8-fold28 and 11-fold29 the risk of ICH, as compared with non-anticoagulated individuals with similar risk factors for intracranial hemorrhage. A number of possibly contributing factors to ICH have been suggested in this patient population: A) Age. Several studies have indicated a low frequency of ICH in patients younger than 50, and an increased risk for ICH as a function of increasing age,29 some suggesting age 65 as a point of sharp rise in the risk.29 Although other series have failed to show a clear relationship between increasing age and higher risk of bleeding in anticoagulated patients,26 we believe that this form of therapy should be given to patients who are older than 70 years of age only after close scrutiny of its indications and the subject’s ability to comply with its proper use and monitoring. B) Hypertension. The contribution of this factor to warfarin-related ICH has also been controversial, some series strongly suggesting a relationship,20 while others have failed to document it.28 As a result, there are no defined guidelines for the indications or contraindications for oral anticoagulants in hypertensives. It is our policy to exclude from chronic warfarin therapy patients who continue to have severe and labile hypertension in the face of full compliance with maximal anti-hypertensive therapy. C) Preceding cerebral infarction has been considered by some to be important in the pathogenesis of anticoagulant-related ICH.30 However, recent large series29,31 have failed to support such an association: in a group of 24 patients with ICH in the course of warfarin therapy,31 only 1 bled into the area of the brain that had 3 weeks before been affected by an embolic infarct; all others with prior embolic infarcts (8 patients) had ICH in a vascular territory different from that involved previously. Although an embolic infarct can acutely become complicated by the formation of a hematoma in the setting of heparrin or warfarin anticoagulation, this phenomenon is uncom-

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mon, and appears to be limited to large size embolic infarcts. D) Excessive prolongation of the prothrombin time. With very few exceptions, this factor is considered to be a consistent feature in most hemorrhagic complications in orally anticoagulated patients. ICH is no exception to this rule: fully 80% of patients with ICH have excessively prolonged prothrombin times (PT) at the onset of hemorrhage. One major difficulty in clearly establishing this fact from the literature is the lack of agreement on what the "therapeutic" PT range is: some authors recommend a prolongation of the PT to 1½ to 2½ times control, while others use strictly 1½ times control. 23,34

In studies of warfarin therapy for prevention of venous thromboembolism, there is evidence that a "low-dose" schedule of warfarin (enough to prolong the PT to 1½ times control) is associated with equal protection, but significantly fewer bleeding complications, than a "conventional" schedule with PT prolonged to 1½ to 2 times control. Similar comparisons of different schedules of oral anticoagulation are not available for the prevention of arterial thromboembolism. However, extrapolation from the venous thromboembolism data suggest that it is prudent to recommend adherence to "conservative" levels of warfarin anticoagulation, in the range of 1½ times control, for the prevention of bleeding complications. E) Duration of anticoagulant treatment. This factor has not shown a clear association with risk of ICH, since in some series the duration of therapy has most often (in 65% of the cases) exceeded 1 year, while in others as many as 70% of the events occurred within the first year of treatment. In a group of 12 cases gathered from several reports, the cases were evenly distributed below and above 1 year of therapy when the ICH occurred. 30,37-39

F) Head trauma does not appear to play a role in ICH in the setting of oral anticoagulation: only 4 of 24 patients (16%) had a preceding history of trauma in a series of anticoagulant-related ICH. In all 4 instances the traumatic episode was considered mild in nature, and was not associated with loss of consciousness.

The clinical presentation of anticoagulant-related ICH has some distinctive features. A gradual and slow progression of the focal signs was recorded in 58% of the cases in one series, and one-half of these progressed over exceedingly long periods of time, of 24, 48, and even 72 hours. In some instances, this slowly progressive course could be correlated with CT-detected increase in size of the ICH. This feature contrasts with the usual course of hypertensive ICH, in which such a protracted initial course is rarely observed, and occasionally enlargement of the hematoma by CT occurs exceptionally following admission (observed in only 2 of a personal consecutive series of 100 cases of ICH). This extended initial course suggests a process of slow bleeding into the parenchyma, different from the usually catastrophic course in patients with hypertensive ICH. An additional feature in anticoagulant-related hemorrhages has been an apparent difference in their topographic distribution, as compared with hypertensive ICH: a relative predilection for the cerebellum was noted in one series, and that location was also overrepresented in a group of 13 cases gathered from the literature. This anatomical feature of warfarin-related hemorrhages has no clear explanation, as it is also unclear what the actual pathogenesis of these hemorrhages is, in terms of the size and type of the ruptured vessels leading to the hemorrhage. It is possible that these hemorrhages are related to bleeding from vessels different from those responsible for hypertensive ICH. Serial microscopic sections of pathologic specimens will be required to clarify these points.

The overall prognosis in these ICHs is poor, with mortalities in the range of 65% of the cases. This high mortality correlates with generally large size hematomas, probably reflecting the slow but eventually massive extravasation of blood into the parenchyma as a result of the drug-induced coagulation defect. Despite the routine use of vitamin K and fresh frozen plasma for the rapid reversal of the coagulation defect, neurologic deterioration and fatal outcome is the expected course in two-thirds of the cases.

Use of Amphetamines and Other Sympathomimetic Drugs

A number of examples of ICH secondary to the use and abuse of amphetamines and related drugs have been documented. The most commonly implicated preparation has been methamphetamine by the intravenous route, but examples of ICH following its intranasal and oral use are also in record. Less frequently, the responsible substances have been amphetamine and pseudoephedrine. ICH has generally occurred shortly after use of the drug, within minutes to a few hours after exposure, and the affected individuals have been in general chronic users, although occasional examples have followed alleged first-time use. The majority of the hematomas have been located in the subcortical white matter of the cerebral hemispheres, only occasional ones occurring at the level of the basal ganglia.

An association with transiently elevated blood pressure has been noted in approximately 50% of the cases, and this represents a likely etiologic mechanism. However, angiographic changes suggestive of vasculitis ("arteritis") have also been documented, raising the possibility of a drug-induced angiopathy as the etiologic factor. This view is further supported by the reported disappearance of such angiographic changes following drug discontinuation or the use of steroids. This angiopathy, also called "speed arteritis", is characterized angiographically by multiple focal areas of stenosis or constriction of medium-size intracranial arteries. Pathologic examination of these vessels has shown a necrotizing angiitis similar to periarteritis nodosa characterized by fibrinoid degeneration and necrosis of the media and intima of medium-size and small arteries and arterioles, associated with variable degrees of inflammatory leukocytic infiltration of the vessel walls. At a later, reparative phase of the angiopathy, collagen replacement of muscular and elastic tissue can follow, at times resulting in the formation of
aneurysmal dilatations of the arterial wall. These vascular changes are considered to be secondary to either a direct “toxic” effect of the drug or a hypersensitivity reaction to the drug or its vehicle. In a few isolated instances, angiography has revealed a coincidental AVM or aneurysm as the source of hemorrhage, which has been parenchymatous or subarachnoid, respectively. In these instances, the apparent role of the drug has been that of the precipitant rather than the actual cause of the hemorrhage.

The usual therapy for this variety of ICH has been the use of high-dose steroids, occasionally accompanied by immunosuppressant drugs (cyclophosphamide). The clinical picture has followed the expected course of slow resolution of the intracerebral hematoma, and follow-up angiograms have often shown an improvement or disappearance of the signs of vasculitis, attesting to its reversible character.

Phenytoin-propanolamine, a structural analog of amphetamine contained in over-the-counter appetite control and decongestant preparations, has been associated with ICH in previously healthy individuals. The hematomas have occasionally been multiple and simultaneous, and a “vasculitic” picture like that seen in amphetamine-related hemorrhages has also been documented.

Illicit drugs have occasionally been associated with episodes of ICH closely following their use. These include cocaine and the combination Tylan-pyrimethamine (“T’s and blues”). These drugs have at times resulted in the production of cerebral infarction instead of ICH, and both lesions are thought to be the result of an angiopathy due to the drug or some of its vehicles.

In conclusion, this review of non-hypertensive causes of ICH suggests that these various pathological entities account for a significant number of cases of ICH. It is possible that their relative contribution to the total group of ICH cases will even increase in the future, as the frequency of the hypertensive form of ICH is likely to continue to decline, reflecting improved control of hypertension in the population at risk. It is hoped that increased awareness, as well as improved diagnostic methods, will result in the clinical diagnosis of these conditions, which are currently for the most part diagnosed only pathologically. This improvement in diagnosis is likely to provide a better estimate of their true frequency in the ICH population.

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Thrombolytic Therapy in Stroke: Possibilities and Hazards

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AGENTS WHICH MEDIATE THE dissolution of thrombi are receiving increasingly wide therapeutic application. Urokinase or streptokinase have been employed in the treatment of acute thrombosis of coronary123 and selected peripheral arteries,15 23-34 traumatic inter carotid artery occlusion,35 as well as of pulmonary embolism66-70 and peripheral deep venous thrombosis.15 40-49

The demonstration that acute stroke is typically an atherothrombotic or thromboembolic process60-76 provides a theoretical basis for the use of thrombolytic therapy in the treatment of acute stroke. However, because of the possibility that intracerebral hemorrhage may develop during thrombolytic therapy, use of such agents in stroke treatment has generally been contraindicated. Nevertheless, limited recent experience indicates that careful infusion of thrombolytic agents may lead to thrombus dissolution and clinical improvement in selected patients presenting with acute stroke.77-79

It is the purpose of this discussion to review the molecular basis for the thrombolytic state, clinical experience with systemic and local treatment of stroke patients with various thrombolytic agents, and to weigh the relative risk of intracerebral hemorrhage in patients treated with fibrinolytic agents for stroke and for other thrombotic disorders.

Mechanism of Thrombolysis

Arterial thrombosis and thrombus extension involve to varying degrees the processes of endothelial injury, platelet aggregation and release, and thrombin generation. Thrombin-mediated fibrinogen cleavage results in fibrin formation which is required for thrombus stabilization.80 Thrombin-mediated fibrin formation occurs in direct relation to platelet activation by several mechanisms. Platelets promote activation of the early stages of intrinsic coagulation by a process that involves a factor XI receptor and high molecular weight kininogen.81 Also, factors V and VIII interact with platelet membrane phospholipids to facilitate the activation of factor X to Xa and the conversion of prothrombin to thrombin.82 Platelet-bound thrombin-modified factor V (factor Va) serves as a high affinity platelet receptor for factor Xa.83 Consequently, the rate of thrombin generation is accelerated 10 fold, providing a potent positive feedback mechanism for initiation of thrombin formation on the platelet surface, fibrin network formation in the thrombus, and indirectly, fibrinolysis.

Thrombus dissolution is, in large part, mediated by fibrinolysis localized within the thrombus.84-86 Fibrin (and fibrinogen) degradation is catalyzed by plasmin, the product of plasminogen activation.87 In the consolidating thrombus plasminogen binds to fibrin and to platelets, allowing local release of plasmin within the thrombus. The circulating plasminogen activators, tissue plasminogen activator (tPA) and single chain urokinase plasminogen activator (scuPA), catalyze pla-
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