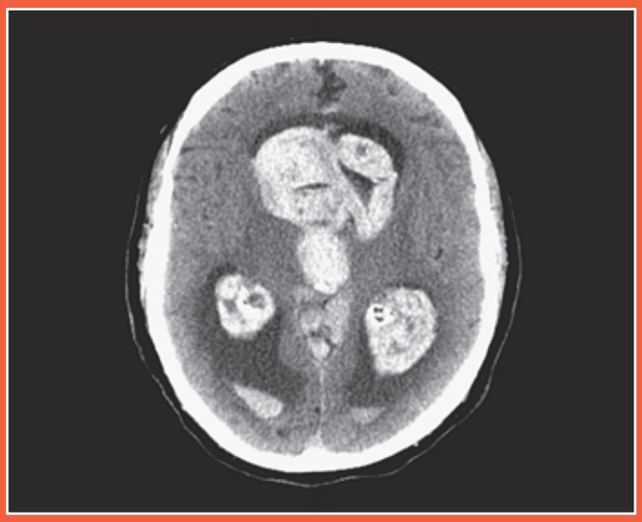
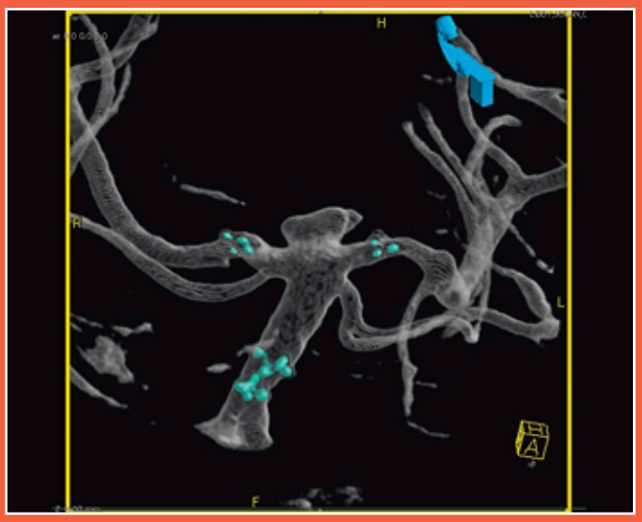
An Atlas of Investigation and Treatment

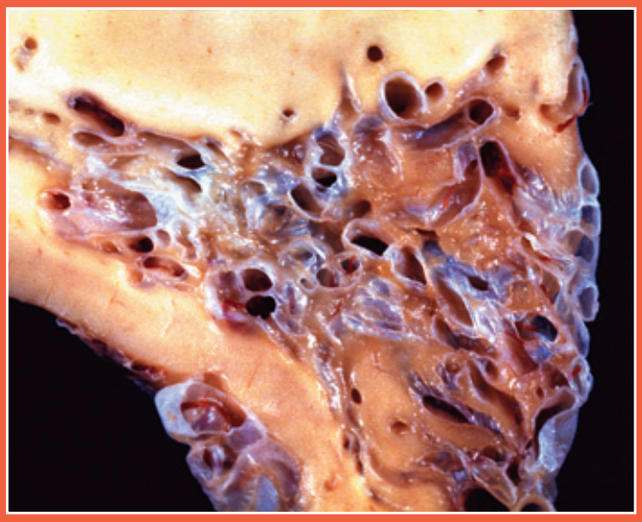
HEMORRHAGIC STROKE

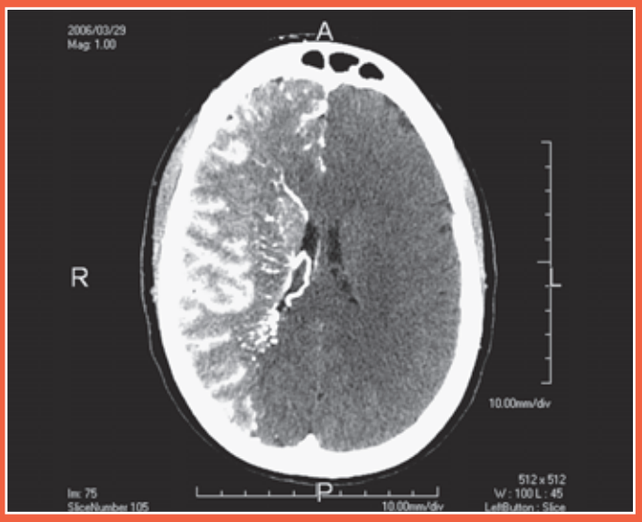
IE Silverman • MM Rymer

Foreword by JP Broderick









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An Atlas of Investigation and Treatment

HEMORRHAGIC STROKE

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Contents

Foreword

A picture is worth a thousand words but in a stroke patient, a picture also provides the definitive answer as to whether there is bleeding in or around the brain. The introduction of CT imaging of the brain in 1972 revolutionized the field of the epidemiology, pathophysiology, and treatment of stroke – particularly that of intracerebral and subarachnoid hemorrhage. For example, prior to CT and MR brain imaging, intracerebral hemorrhage (ICH) was thought to be uncommon, mostly fatal, and due to hypertension in most instances. We know now that intracerebral hemorrhage is a common cause of stroke and in many instances cannot be differentiated from ischemic stroke by clinical features alone. We have also learned that imaging of the location of bleeding, as well as associated structural changes, provides critical clues as to the probable cause.

Thus, an atlas that uses pictures to teach the epidemiology, pathophysiology and treatment of hemorrhagic stroke is a marvelous way to teach and to learn about these devastating stroke subtypes which have much higher mortality and morbidity than ischemic stroke. For example, the pattern of multiple cortical old microhemorrhages on gradient echo imaging, combined with a new lobar ICH, speaks very strongly to the likely diagnosis of amyloid-associated ICH whereas a pattern of old microhemorrhages in the deep basal ganglia and white matter structures with a new subcortical hemorrhage speaks very strongly to the likelihood of hypertensive hemorrhage. Only brain imaging can make this probable diagnosis without autopsy, and only a pictorial atlas showing the appropriate brain imaging, illustrations and pathology can allow physicians to recognize this pattern and make the likely diagnosis in their patients with hemorrhagic stroke. Imaging of ongoing bleeding in patients with intracerebral hemorrhage during the first hours after onset conveys better than any words the urgency required to slow and halt the process. Brain imaging in patients continues to evolve, with radiopharmaceutical agents using PET imaging that can image amyloid deposition in the brain and associated blood vessels in patients with lobar intracerebral hemorrhage.

A host of technologic advances to treat structural causes of ruptured intracranial vessels such as clips, coils, stents, balloons, embolization and focused radiation therapy have evolved over the past 40 years. Surgical techniques to remove hemorrhage in the brain and ventricles have unfortunately not demonstrated clear benefit for patients but are frequently used. Again, imaging, as shown in an atlas, provides the best way to highlight these therapeutic technologies.

The brain imaging, illustrated figures and pathologic images in this atlas are superb and the accompanying text is clear and straightforward. This book is a great way for students, resident physicians, stroke fellows and neurologic physicians to learn about hemorrhagic stroke. These powerful images will remain with the reader long after they close the book.

Joseph P. Broderick, MD
February, 2010

Preface

Hemorrhagic stroke has always been the poor sibling to its ischemic counterpart. Not only is hemorrhage much less common, but it also has significantly worse clinical outcomes, and relatively fewer emergent therapies. The reality that only about 20% of patients with a primary intracerebral hemorrhage (ICH, the most common type of major bleeding in the brain) survive to make an independent recovery should be a call to focus upon this important disease.

Hemorrhagic stroke is grabbing the attention of neurovascular clinicians for several reasons. First, an aging population facilitates the development of the most common forms of hemorrhagic stroke, primary ICH (due to hypertension and cerebral amyloid angiopathy), and subarachnoid hemorrhage (due to the development of intracranial aneurysms, with its chief risk factors of hypertension and tobacco use). Second, advancing neuroimaging is better at detecting not only acute hemorrhagic stroke but also at identifying subclinical hemorrhage, such as the gradient-echo magnetic resonance imaging (MRI) detection of microhemorrhage and cavernous malformations, and computed tomography (CT) and MR angiography's definition of unruptured intracranial aneurysms and vascular malformations. There is still a role for old-school conventional cerebral angiography in the management of many patients with hemorrhagic stroke.

An era of increased awareness of hemorrhagic stroke may soon translate into a wider proliferation of treatments. The success of recombinant factor VIIa in preventing the expansion of ICH was an important first step from a large international clinical trial evaluating an emergent drug therapy. Efforts to reduce the delayed impact of toxic by-products of free blood upon brain parenchyma may conceivably hold clinical benefit at much wider time windows than have proven helpful for therapies of acute ischemic stroke. In addition, although earlier efforts of neurosurgical evacuation of hemorrhage within the brain have been unsuccessful, ongoing studies are looking at less invasive means; e.g. endoscopic aspiration and thrombolytic agents delivered via external ventricular devices, in order to reduce clot burden; or are focusing upon subgroups of patients; e.g. those patients with lobar lesions. For complex neurovascular disorders, large comparative trials have either been completed (i.e. in intracranial aneurysms, comparing neurosurgical clipping versus endovascular coiling) or are under way (i.e. in unruptured vascular malformations, comparing conservative medical therapy versus aggressive interventions).

Finally, hemorrhagic stroke is bringing together neurovascular clinicians with distinct training backgrounds. Its in-hospital management gathers together vascular neurology, interventional neuroradiology, vascular neurosurgery, and neurocritical care medicine. For example, during the past 15–20 years, endovascular approaches have been developed to complement open neurosurgery in the management of intracranial aneurysms. In addition, radiation treatment is a viable option for some arteriovenous malformations.

Continuing from where our previous volume left off (*Ischemic Stroke: An Atlas of Investigation and Treatment*), we again intend to introduce clinicians, residents in training, and medical and nursing students to the breadth of the 'dark side' – hemorrhagic stroke – of neurovascular disorders. In addition to this survey of neuroimaging and neuropathology, case studies demonstrate the clinical management considerations surrounding various types of hemorrhagic stroke. The result is a broader range of clinical pathology than found in our earlier volume. We conclude this volume with a survey of *'Extreme'* Neurovascular Disorders, as a means to convey the wide array of interesting and challenging disorders we encounter as clinicians.

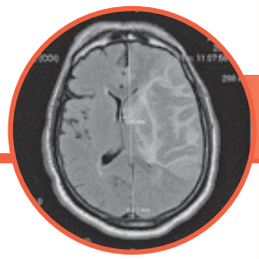
We hope that you find this volume on hemorrhagic stroke a useful companion to *Ischemic Stroke: An Atlas of Investigation and Treatment*.

Isaac E. Silverman, MD
Marilyn M. Rymer, MD
December 2009

Abbreviations

ACA	anterior cerebral artery
ACE	angiotensin-converting enzyme
A-Comm	anterior communicating artery
ADC	apparent diffusion coefficient
AICA	anterior inferior cerebellar artery
AIS	acute ischemic stroke
AP	anteroposterior
AV	arteriovenous
AVF	arteriovenous fistula
AVM	arteriovenous malformation
BA	basilar artery
CA	conventional angiography
CAA	cerebral amyloid angiopathy
CADASIL	cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
CCA	common carotid artery
CM	cavernous malformation
CNS	central nervous system
CS	cavernous sinus
CSF	cerebrospinal fluid
CT	computed tomography
CTA	CT angiography
CVP	central venous pressure
DM	diabetes mellitus
DVA	developmental venous anomaly
DWI	diffusion-weighted imaging
DW-MRI	diffusion-weighted magnetic resonance imaging
ECA	external carotid artery
ECASS	European Cooperative Acute Stroke Study
FLAIR	fluid attenuated inversion recovery
GCS	Glasgow Coma Scale
GE	gradient-echo
H&E	hematoxylin and eosin (stain)
HELPP	hemolysis, elevated liver enzymes, low platelets
HI	hemorrhagic infarction
HTN	hypertension
IA	intracranial aneurysms
ICA	internal carotid artery
ICH	intracerebral hemorrhage
ICP	intracranial pressure
ISAT	International Subarachnoid Aneurysm Trial
IV	intravenous
JNC-7	The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure
MCA	middle cerebral artery
MRA	magnetic resonance angiography
MRI	magnetic resonance imaging
MRV	magnetic resonance venography
NBCA	N-butyl cyanoacrylate
NIHSS	National Institutes of Health Stroke Scale
NINDS	National Institute of Neurological Disorders and Stroke
PCA	posterior cerebral artery
P-Comm	posterior communicating artery
PCWP	pulmonary capillary wedge pressure
PICA	posterior inferior cerebellar artery
PROGRESS	Perindopril Protection Against Recurrent Stroke Study
PT(INR)	prothrombin time (International Normalized Ratio)
rFVIIa	recombinant activated factor VII
RR	relative risk
SAH	subarachnoid hemorrhage
SCA	superior cerebellar artery
SDH	subdural hematoma
SHEP	Systolic Hypertension in the Elderly Program
SIADH	syndrome of inappropriate antidiuretic hormone secretion
SIVMS	Scottish Intracranial Vascular Malformation Study
STICH	Surgical Trial in Intracerebral Hemorrhage
T1WI	T1-weighted image
T2WI	T2-weighted image
TCD	transcranial Doppler
TIA	transient ischemic attack
t-PA	tissue plasminogen activator
VA	vertebral artery
VGM	vein of Galen malformation
VHL	Von Hippel–Lindau
WI	weighted image

Chapter 1



Intracerebral Hemorrhage

Epidemiology

Intracerebral hemorrhage (ICH) accounts for 10–15% of all strokes. Primary ICH occurs when small intracranial vessels are damaged by chronic hypertension (HTN) or cerebral amyloid angiopathy (CAA), and accounts for 78–88% of all ICH. Secondary causes for ICH are listed in *Table 1.1*.[1]

The incidence of ICH worldwide ranges from 10 to 20 cases per 100 000 population and increases with age. Certain populations, in particular, the Japanese and those of Afro-Caribbean descent, have a heightened incidence of 50–55 per 100 000 that may reflect a higher prevalence of HTN and/or decreased access to healthcare.[1] The incidence of hemorrhage increases exponentially with age and is higher in men than in women.[2]

Clinical presentation

Neurologic deficits from ICH reflect the location of the initial bleeding and associated edema. In addition, seizures, vomiting, headache, and diminished level of consciousness are common presenting symptoms. A depressed level of alertness on initial evaluation occurs infrequently in acute ischemic stroke (AIS) but is seen in approximately 50% of patients with ICH.[3]

Table 1.1 Common secondary causes of intracerebral hemorrhages

Causes	Chapter number	Primary means of diagnosis
Arteriovenous malformation	3	MRI, CA
Intracranial aneurysm	2	MRA, CTA and CA
Cavernous angioma	4	Gradient-echo MRI
Venous angioma	4	MRI with gadolinium, CA
Venous sinus thrombosis	1	MRV, CA
Intracranial neoplasm		MRI with gadolinium
Coagulopathy	1	Clinical history, serologic studies
Vasculitis		Serologic markers, MRI with gadolinium, CA, brain biopsy
Drug use (e.g., cocaine, alcohol)		Clinical history, toxicology screens
Hemorrhagic transformation	1	Non-contrast CT and gradient-echo MRI scans

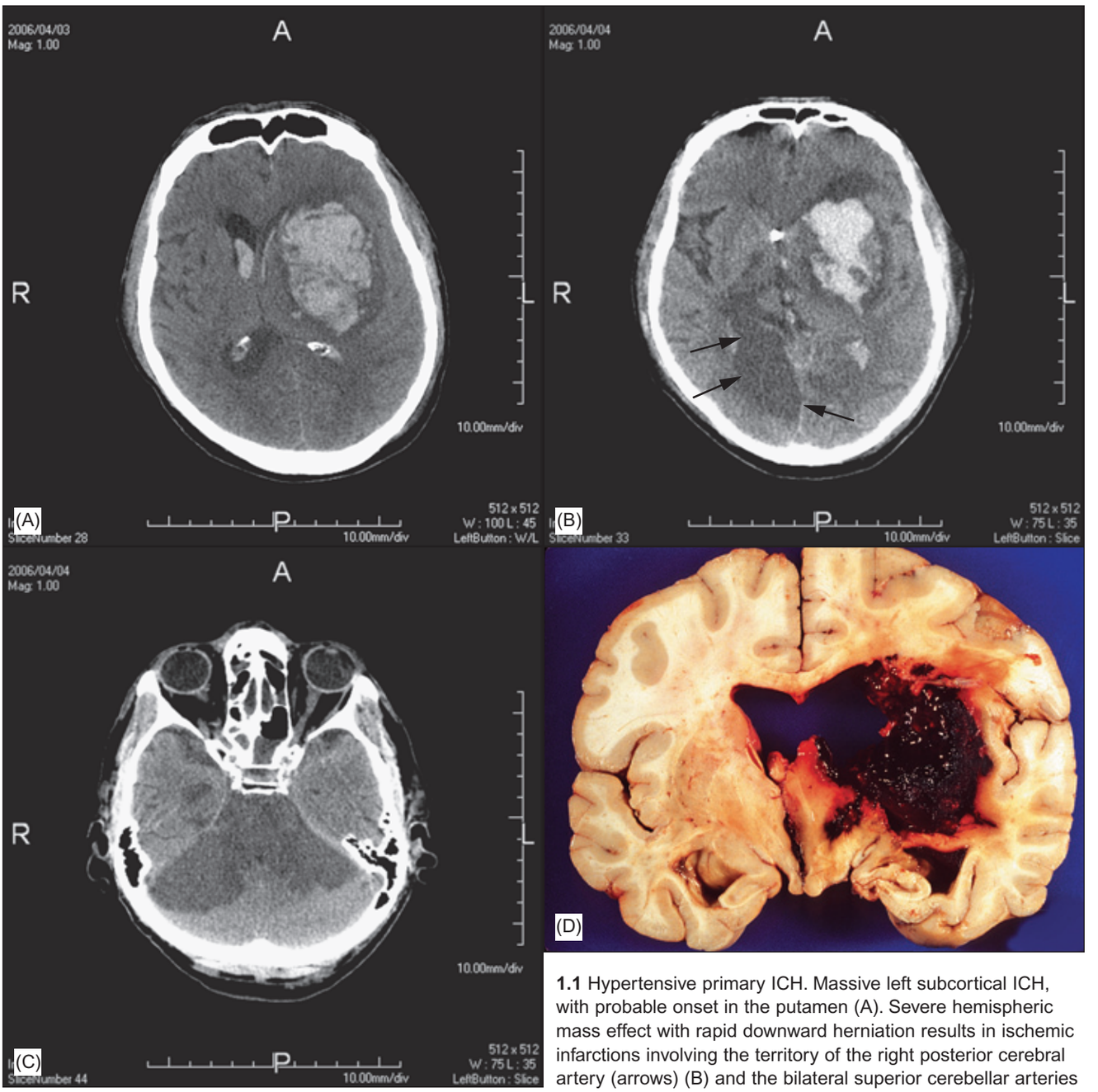
CA, cerebral angiography.
Adapted with permission from Qureshi *et al*.[1]

Outcomes

Spontaneous, or non-traumatic, ICH has a much poorer outcome than AIS.[1] There is a 62% mortality rate by 1 year, and only about 20% of survivors are living independently by 6 months.[3] About half of the deaths due to ICH over the first 30 days will occur within the first 2 days, largely from cerebral herniation.[3] Later, mortality is more commonly due to medical complications, such as aspiration pneumonia or venous thromboembolism.

The primary predictors for outcomes from ICH are:

- *Lesion size*. Larger hemispheric lesions >30 ml volume have a high mortality rate (**1.1**).



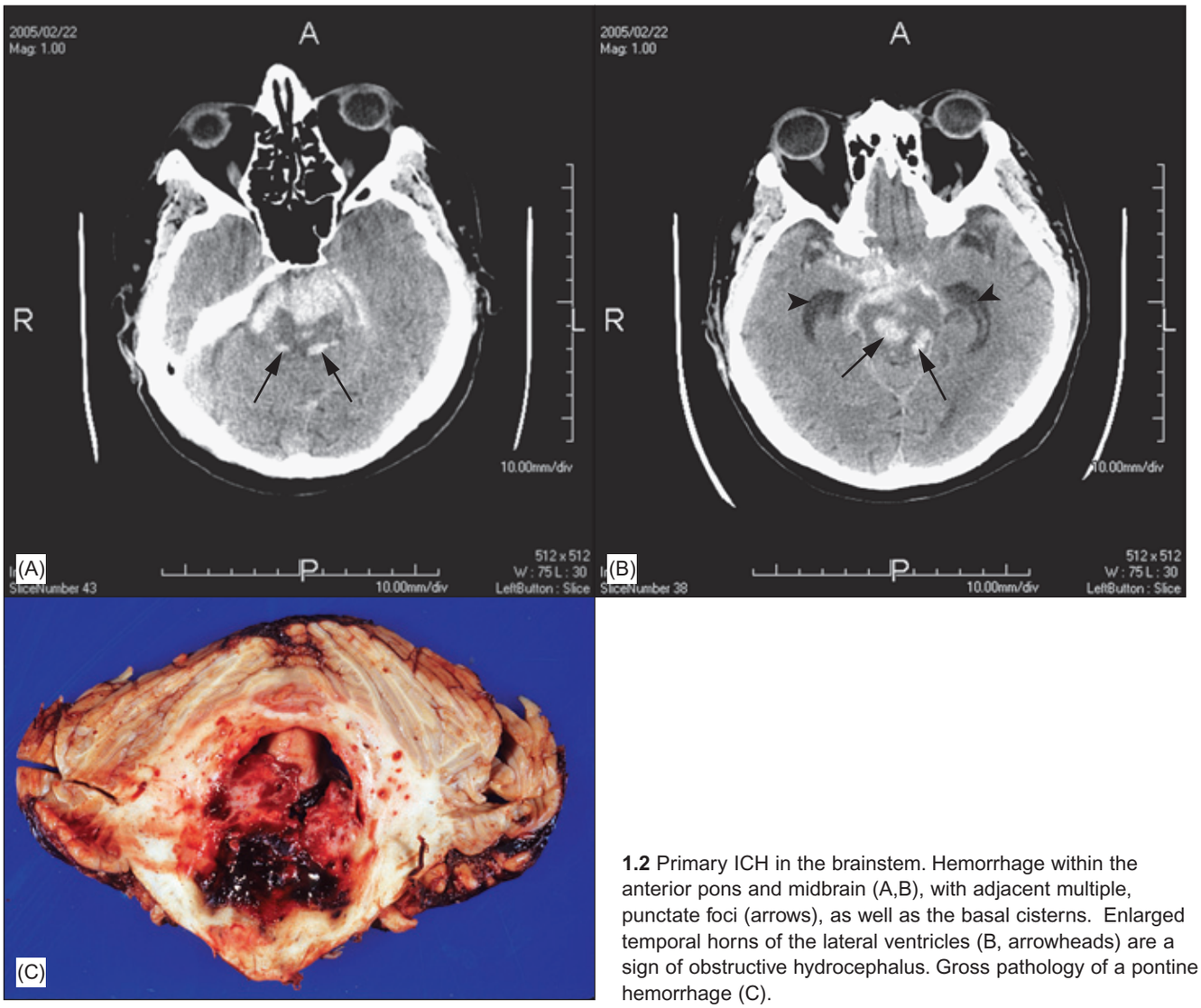
1.1 Hypertensive primary ICH. Massive left subcortical ICH, with probable onset in the putamen (A). Severe hemispheric mass effect with rapid downward herniation results in ischemic infarctions involving the territory of the right posterior cerebral artery (arrows) (B) and the bilateral superior cerebellar arteries (SCAs) and pons (C), with effacement of the basal cisterns. Gross pathology of a comparable lesion (D).

- *Level of consciousness.* Patients with Glasgow Coma Scale (GCS) <9 points and hematoma >60 ml have a 90% mortality rate.[3]
- *Intraventricular component.*[1,4] In one study, intraventricular involvement predicted a mortality rate of 43% at 30 days, versus 9% without ventricular involvement.[5]
- *Lesion location.* Deep hemispheric lesions (e.g., brainstem, thalamus) have a poorer prognosis than subcortical or cerebellar hematomas.[2] Even 5–10 ml of hemorrhage into the brainstem can be devastating (**1.2**).
- *Age.* Advanced age, >80 years, carries a higher risk of mortality.

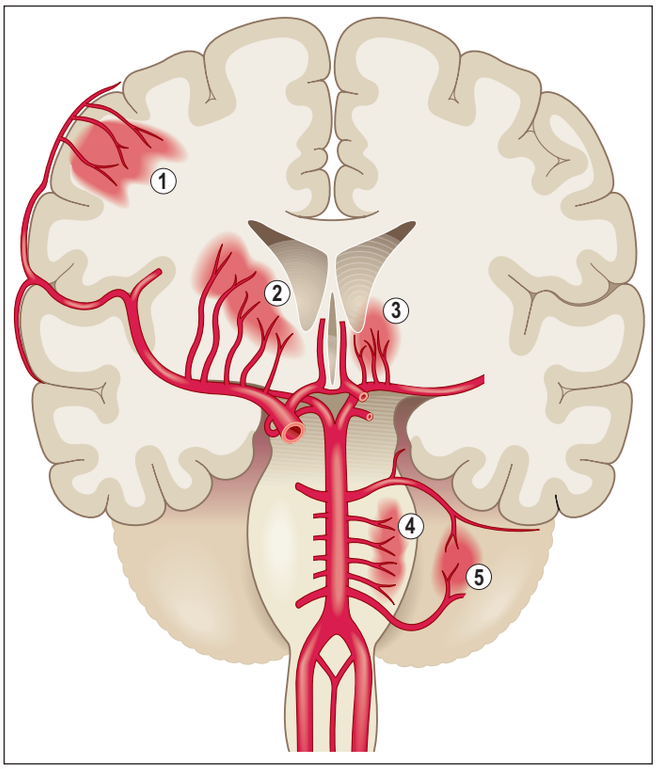
Risk factors

Hypertension

By far the most important modifiable risk factor for spontaneous ICH is HTN.[3] Primary hypertensive hemorrhage results from the rupture of small penetrating arteries originating in the anterior, middle (i.e., lenticulostriate), and posterior cerebral (i.e., thalamostriate) arteries and the pons (i.e., paramedian perforators) (**1.3**). HTN causes vessel rupture at or near the bifurcation of affected vessels, where degeneration of components of the arterial wall (media and smooth muscle) are identified.[1] The annual risk of recurrent hemorrhage is 2% without antihypertensive treatment.[6]



1.2 Primary ICH in the brainstem. Hemorrhage within the anterior pons and midbrain (A,B), with adjacent multiple, punctate foci (arrows), as well as the basal cisterns. Enlarged temporal horns of the lateral ventricles (B, arrowheads) are a sign of obstructive hydrocephalus. Gross pathology of a pontine hemorrhage (C).



1.3 Common sites for primary ICH. Small, penetrating arterial branches are the source of the vast majority of primary ICH: (1) penetrating cortical branches of the major intracranial arteries; (2) lenticulostriate branches; (3) thalamoperforator branches; (4) paramedian pontine branches; and (5) penetrating branches from the major cerebellar arteries (from Qureshi *et al*.[1] with permission).

Cerebral amyloid angiopathy

Cerebral amyloid angiopathy (CAA) is a leading cause, along with HTN, for spontaneous ICH in patients >60 years old. It is a degenerative condition in which β-amyloid protein deposits within the walls of blood vessels of the cerebral cortex and leptomeninges predispose to leakage of blood into brain parenchyma (**1.4**).[7] The diagnostic criteria are a combination of clinical, neuroimaging, and pathologic findings (*Table 1.2*).[8] The annual risk of recurrent hemorrhage is 10.5%.[9]

Antithrombotic agents

- Oral anticoagulation with warfarin increases the risk of ICH two to five times and is directly related to the intensity of anticoagulation.[10] In contrast to primary ICH, the bleeding associated with warfarin may persist for 12–24 hours.[10] A fatal outcome occurs in two-thirds of patients with an International Normalized Ratio (INR) >3.0 at presentation.[11]

Table 1.2 Boston criteria for diagnosis of CAA-related hemorrhage

1. **Definite CAA – Full post-mortem examination demonstrating:**
- Lobar, cortical, or corticosubcortical hemorrhage
- Severe CAA with vasculopathy
- Absence of other diagnostic lesion

2. **Probable CAA with supporting pathology – Clinical data and pathologic tissue (evacuated hematoma or cortical biopsy) demonstrating:**
- Lobar, cortical, or corticosubcortical hemorrhage
- Severe CAA with vasculopathy
- Absence of other diagnostic lesion

3. **Probable CAA – Clinical data and MRI or CT demonstrating:**
- Multiple hemorrhages restricted to lobar, cortical, or corticosubcortical regions (cerebellar hemorrhage allowed)
- Age ≥55 years
- Absence of other cause of hemorrhage*

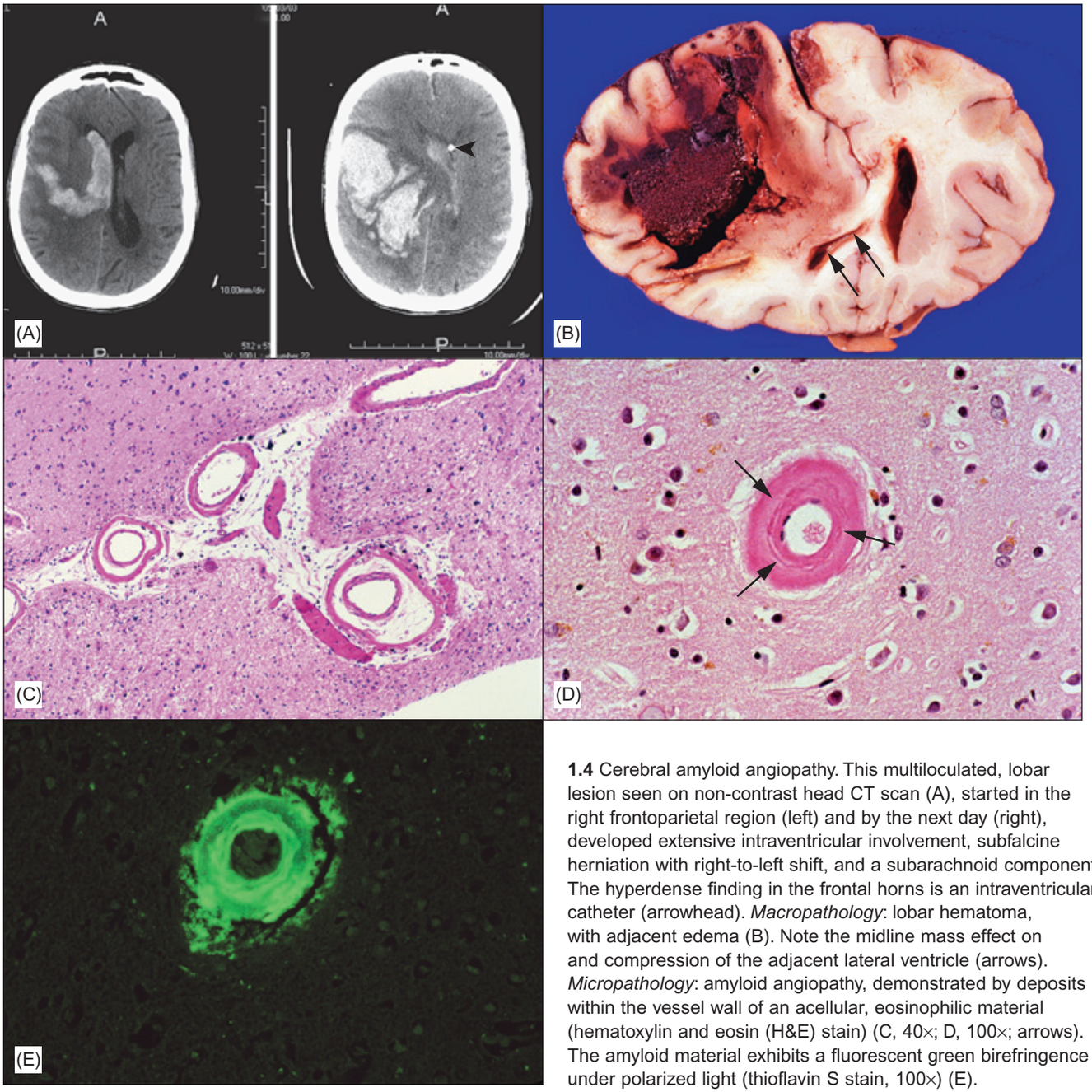
4. **Possible CAA – Clinical data and MRI or CT demonstrating:**
- Single lobar, cortical, or corticosubcortical hemorrhage
- Age ≥55 years
- Absence of other cause of hemorrhage*

**Other causes of ICH*: supratherapeutic anticoagulation (prothrombin time (International Normalized Ratio) PT(INR)) >3.0); antecedent head trauma or ischemic stroke; central nervous system (CNS) tumor, vascular malformation, or vasculitis; and blood dyscrasia, or coagulopathy.
Adapted with permission from Knudsen *et al*.[8]

- Antiplatelet agents: aspirin use alone may be a weaker risk factor for continued bleeding due to ICH and poor outcomes;[12] however, combination antiplatelet treatment with aspirin and clopidogrel increases the risk for ICH over either agent alone.[13]

Alcohol

Alcohol impairs coagulation and injures cerebral vessels. Recent heavy alcohol exposure (e.g., during the preceding week) is a risk factor for ICH.[14]



1.4 Cerebral amyloid angiopathy. This multiloculated, lobar lesion seen on non-contrast head CT scan (A), started in the right frontoparietal region (left) and by the next day (right), developed extensive intraventricular involvement, subfalcine herniation with right-to-left shift, and a subarachnoid component. The hyperdense finding in the frontal horns is an intraventricular catheter (arrowhead). *Macropathology*: lobar hematoma, with adjacent edema (B). Note the midline mass effect on and compression of the adjacent lateral ventricle (arrows). *Micropathology*: amyloid angiopathy, demonstrated by deposits within the vessel wall of an acellular, eosinophilic material (hematoxylin and eosin (H&E) stain) (C, 40×; D, 100×; arrows). The amyloid material exhibits a fluorescent green birefringence under polarized light (thioflavin S stain, 100×) (E).

Other risk factors

Illicit drug use and coagulopathic disorders (*Table 1.3*) are associated with an increased risk of ICH. Over-the-counter stimulants, particularly if taken in excessive quantities, may predispose to ICH (**case study 1**). A large case–control study associated phenylpropanolamine use with ICH in young patients.[15]

Pathogenesis

Up to 70% of patients with primary ICH develop some measurable amount of lesion expansion over the initial few hours (**1.5**).[16] Hematoma growth is an independent determinant of both mortality and functional outcome after ICH.[16,17] The mass effect of primary bleeding may cause

lesions to migrate and dissect through less dense white matter, with patches of intact brain tissue surrounding a hematoma (**1.6**). Although continued bleeding from the primary lesion source is one mechanism for expansion, another could be the mechanical disruption of local vessels by which multiple adjacent microbleeds develop, accumulate, and contribute to overall lesion volume (**1.2**A,B).

Table 1.3 Coagulation disorders associated with intracerebral hemorrhage

Excessive anticoagulation with warfarin, and other antithrombotic agents
- Aspirin use (RR = 1.35)
- Aspirin plus warfarin (RR = 2.4)
- Warfarin (RR = 2.5)
- Clopidogrel

Coagulation factor deficiencies (VIII, IX) and mutations (XIII)
Thrombocytopenia, especially <10 000/mm^3
Systemic disease
- Hepatic and renal failure
- Leukemia
- Bone marrow failure
- Cancer chemotherapy

Platelet dysfunction
- Idiopathic thrombocytopenic purpura
- HELPP syndrome (hemolysis, elevated liver enzymes, low platelets)
- Essential thrombocythemia

Prothrombotic states
- Disseminated intravascular coagulation
- Thrombotic thrombocytopenic purpura

Genetic polymorphisms
- Factor XIII
- α_1-antichymotrypsin
- Apolipoprotein E (α_2, α_4)

Hereditary disorders of hemostasis
- Von Willebrand's disease
- Afibrinogemia
- Glanzmann's thrombasthenia (GpIIb/IIIa receptor dysfunction)

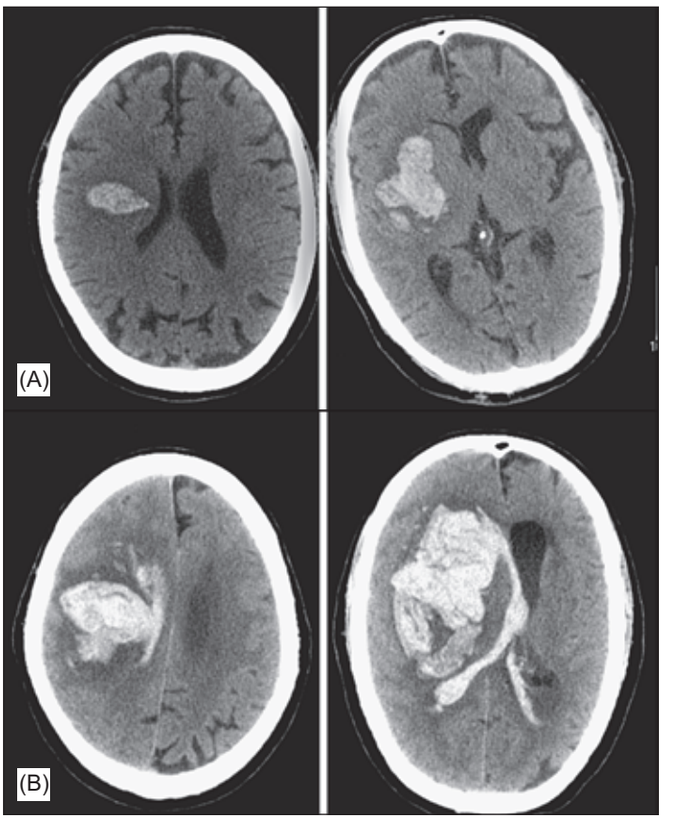
RR, relative risk.
Adapted with permission from Coull and Skaff.[46]

A hematoma incites local edema and neuronal damage in the adjacent brain parenchyma (**1.7**). This edema typically increases in size over an interval as long as 3 weeks following the initial bleeding, with the greatest growth rate over the first 2 days.[2] Thrombin within the hematoma plays a central role in promoting perihematomal edema.[2] Hemoglobin and its products, heme and iron, are potent mitochondrial toxins, thereby increasing cell death.[18]

Lesion locations

Subcortical intracerebral hemorrhage

The most common site for hypertensive hemorrhage is the putamen, but ICH frequently occurs in all other subcortical locations (**1.8**).



1.5 Early expansion of subcortical hemorrhage. The time elapsed between the two CT studies (A,B) was 80 minutes. First, a patient presenting with headache, dysarthria, and left hemiparesis, due to a right subcortical hemorrhage (A); the second scan was obtained due to rapidly deteriorating mental status and a dilated right pupil from uncal herniation (B). Note significant intraventricular extension, and diffuse edema effacing sulci throughout the right hemisphere.