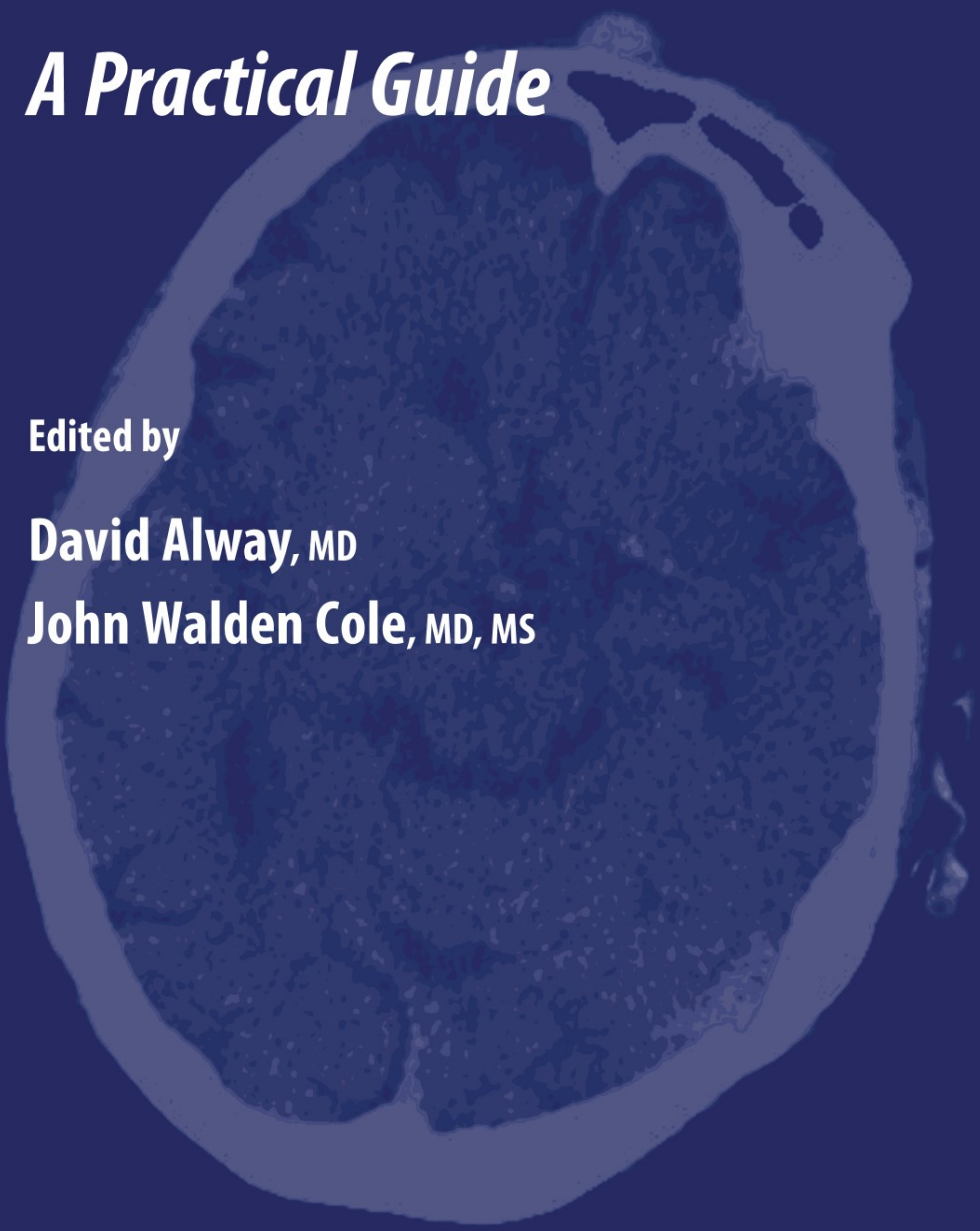
Stroke Essentials for Primary Care

A Practical Guide



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Stroke Essentials for Primary Care

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A Practical Guide

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Series Editor Introduction

A little inclination sometimes only nudges a physician to learn more when seeing a patient with a particular problem, and the right resource makes that inclination to learn easy to carry out. *Stroke Essentials for Primary Care: A Practical Guide*, by Drs. David Alway and John Cole is an excellent, easy-to-read practical resource for the practicing physician who takes care of patients with stroke. This resource is important because stroke is *the* most common serious acute neurologic condition seen in primary care. Stroke is the third most common cause of death in the United States, and among those who survive many are left with significant disability. Approximately 5.8 million individuals in the United States have a history of stroke, with 8% of persons over 65 years of age reporting a history of a stroke.[1] Talk to any older adult, and they will readily tell you that having a stroke is one of the things they are most afraid of, as it is common enough that most people have a family member or a close friend who has had a stroke and they are afraid of the loss of function, and potential loss of independence that too often occurs after a stroke. Almost half a million patients present each year with transient ischemic attacks, and 25% of those patients go on to have an additional event within the first 90 days after initial presentation.[2] Initial diagnosis and management are essential in achieving optimal outcomes, and risk factor management is essential in decreasing the incidence and recurrence of stroke.

Stroke Essentials for Primary Care: A Practical Guide starts with a discussion of differential diagnosis, and then covers each of the common types of stroke in depth. These types of strokes – ischemic, intracerebral hemorrhage, and subarachnoid hemorrhage –make up over 95% of strokes that present to primary care and are discussed in detail. The first chapter on each of these topics discusses the details of initial presentation and management. The next chapter discusses aspects of prevention of initial stroke, reoccurrence of stroke, and long-term management. The last five chapters of the book cover specific topics

[1] Prevalence of Stroke – United States, 2005. MMWR 2007; 56(19):469–474

[2] Solenski NJ. Transient Ischemic Attacks: Part I Diagnosis and Evaluation. Am Fam Physician 2004;69:1665–74

to be aware of in the presentation of stroke. In summary, *Stroke Essentials for Primary Care: A Practical Guide* offers a concise, practical overview of initial diagnosis and management as well as long-term follow-up of patients who present with acute stroke and should be a useful resource for all primary care physicians.

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Preface

This book focuses the reader on the *essential knowledge* required to evaluate and treat stroke patients. The first chapter assumes an emergency room setting and helps to orient the reader to the distinguishing features of presentation and initial evaluation of stroke types. We then devote two chapters each to the major stroke types (ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage). The first chapter focuses on acute presentation and evaluation (in-hospital evaluation and management) for a particular stroke type. The second such chapter focuses on prevention and long-term complications (out-patient/follow-up issues). The five remaining chapters review special topics that may apply to specific populations: stroke in the young adult, headaches as they relate to stroke, hypercoagulable states, carotid artery disease, and cerebral venous thrombosis. Where appropriate, most chapters include a quick summary of their content and conclusions, allowing for rapid review when necessary.

We hope you find this text useful for rapid access to essential stroke information.

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Chapter 1
Identifying Stroke and Stroke Type

David Alway

This chapter is a quick review of the typical presenting symptoms, signs, and CT imaging characteristics of the major stroke types (ischemic stroke, transient ischemic attack (TIA), intracerebral hemorrhage (ICH), subarachnoid hemorrhage (SAH), and cerebral venous thrombosis). It should be used to familiarize yourself with the common emergency room presentations of the major stroke types. Detailed discussions of these stroke types, and their management, will be presented in later chapters (2–7 & 12).

Identifying Stroke

The hallmark of all stroke types is a relatively sudden onset of neurological dysfunction which may involve any or all of the following: weakness, numbness, vision loss, diplopia, dysarthria, gait disorder, aphasia, lightheadedness, vertigo, or disturbed level of consciousness. Knowing a stroke is a stroke is difficult in perhaps 5–10% of cases, and no one, based on history and physical examination alone, is able to identify stroke and stroke type at all times. The many mimics of stroke to keep in mind include partial complex seizures, hypotensive episodes, the re-experience of old stroke symptoms in the setting of infection or metabolic derangement, multiple sclerosis, isolated cranial nerve dysfunction, nerve root disease, migraine with aura, CNS infections, etc. Assessment is especially difficult in cases where symptoms were transient and the patient now has a normal neurological exam. Here the timing of symptoms, what the patient and witnesses report, and the past medical history of the patient can help distinguish a TIA, for example, from alternatives. We must also consider the possibility of dual diagnoses. A patient who has experienced a cortical ICH may well present with signs and symptoms of both hemorrhage and, because of blood-induced cortical irritation, seizures.

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Typical Symptoms/Signs of Ischemic Stroke and Transient Ischemic Attack

Ischemic stroke is the most common stroke type, representing about 85% of all strokes. Ischemic stroke patients will typically present with the sudden onset of weakness, numbness, vision loss, diplopia, dysarthria, gait disorder, vertigo, aphasia, or disturbed level of consciousness. The location of the stroke will determine which particular pattern of symptoms occurs and will be covered in chapter 2. Ischemic stroke typically involves an absence of function. For example, an ischemic stroke patient will often report loss of vision in a single eye or in an entire hemifield. Rarely would an ischemic stroke patient experience positive visual phenomena, such as bright lines or objects in vision, or scintillations. These are the hallmarks of alternative diagnoses such as the visual aura of migraine, occipital lobe seizures, or retinal detachment. Ischemic stroke patients may experience numbness in part of the body. Rarely will they acutely experience extra sensations (paresthesias or pain) such as may occur with nerve root disease. Ischemic stroke patients may experience weakness or paralysis on one side of the body. Rarely will they experience extra, involuntary movements. All these examples of 'extra' sensations or movements are referred to as 'positive' phenomena, and they suggest a diagnosis other than ischemic stroke.

So long as the examination is performed within hours of symptom onset, and assuming the brainstem has not been markedly damaged, patients with ischemic stroke are more likely to have a preserved level of consciousness (compared with other stroke types) – meaning they will likely appear awake and be able to cooperate, to some degree, with a neurological exam. From the practical standpoint, if a patient has experienced the sudden onset of focal neurological dysfunction, without positive phenomena, has a head CT that is negative for evidence of blood, and alternative explanations for symptoms, based on the history, are not forthcoming, the patient is assumed to be suffering from an ischemic stroke until proven otherwise. In the event that the patient's symptoms resolve quickly within an hour and the head CT is negative, this may represent a TIA. Symptoms which last longer than an hour, even if they appear to resolve completely, may be due to small ischemic strokes, perhaps only evident on MR imaging.

Head CT results: The early head CT (within 1 h) in ischemic stroke is often normal, but is very useful to exclude the presence of blood or other intracranial lesions. Within 1–3 h there can be regions of discernible hypodensity or loss of gray–white matter differentiation, which may be the earliest imaging evidence of ischemia (see Figs. 1.1 and 1.2). Other findings may be a very bright artery in a non-contrast head CT (typically the middle cerebral artery) relative to another portion of the same artery or the opposite hemisphere artery (see Fig. 1.3) or regions of sulcal effacement or ventricular compression due to swelling. In the case of a TIA, the head CT is expected to be normal.

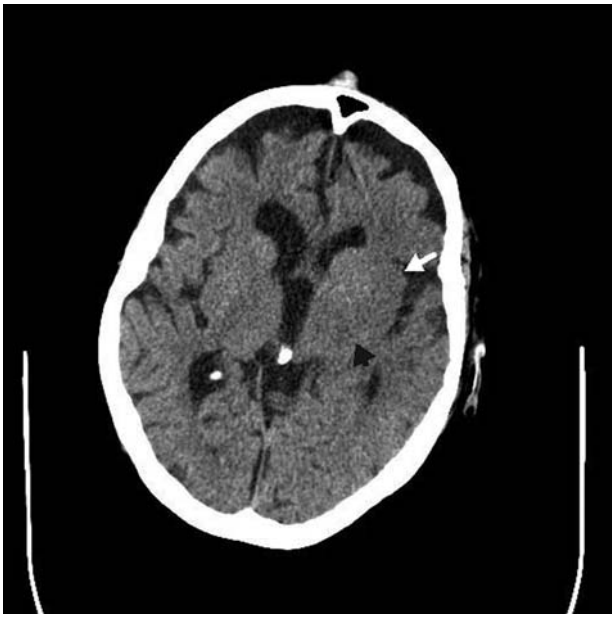

Fig. 1.1 Early head CT (within a few hours) demonstrating loss of gray–white differentiation in the insula

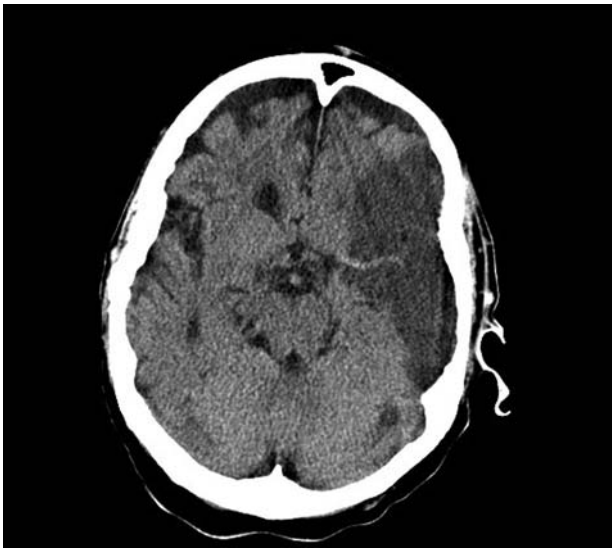

Fig. 1.2 Later head CT (day 2) revealing hypodensity within the left MCA distribution

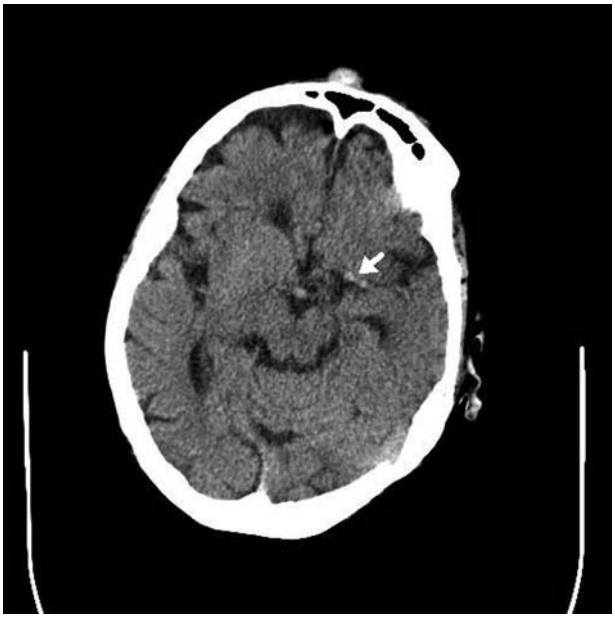

Fig. 1.3 Hyperdense left MCA in an acute ischemic stroke case

Typical Signs/Symptoms of Intracerebral Hemorrhage

Intracerebral hemorrhages (ICH) represent about 10% of all strokes, and in this text, the term refers to bleeding within the substance of the brain, including bleeding into the ventricles. (We are excluding, in this definition, bleeding over the surface of the brain [epidural, subdural] or into the subarachnoid space [SAH]). A patient suffering from an ICH may present with the sudden onset of neurological dysfunction, just as with other stroke types, including weakness, numbness, vision loss, diplopia, dysarthria, gait disorder, vertigo, aphasia, or disturbed level of consciousness. In addition, headache is more common with ICH, occurring in 40% of patient presentations. Nausea and vomiting due to increased intracranial pressure may also occur. The rapidity of neurological worsening is typically more marked than with ischemic strokes. For example, if the hemorrhage is large enough, pressure effects on the whole brain and brainstem may lead to a markedly diminished level of consciousness. In addition, a bleed that begins small (2 cm in diameter) may enlarge over the first few hours to become massive. This will lead to a rapid worsening of symptoms, including a rapid reduction in the patient's level of consciousness.

Head CT results: Head CT will reveal blood in the parenchyma (bright signal, see Fig. 1.4), possibly extending into the ventricular system as well.

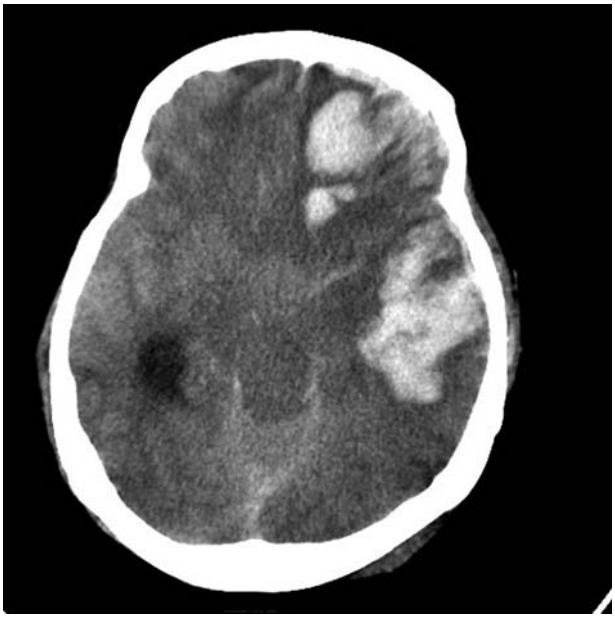

Fig. 1.4 Large intracerebral hemorrhage

Typical Signs/Symptoms of Subarachnoid Hemorrhage

Subarachnoid hemorrhage (SAH) represents about 5% of all strokes. SAH typically presents with a sudden severe headache which may be followed by a diminished level of consciousness or complete unconsciousness. The headache is often the most painful the patient has ever experienced, but lesser headaches may still occur with SAH. Due to blood irritation of meninges, patients may also experience neck stiffness, back pain, and photophobia. At times the blood of the SAH has an effect (mass or otherwise) on part of the brain to produce focal neurological symptoms or seizures. If the SAH is massive, the presentation may simply be the sudden loss of consciousness and collapse of the patient. In many cases, a detailed review of the patients' history will reveal a lesser headache or other focal neurological symptom in the days or weeks prior to the presenting event. This is felt to be due to a smaller bleed (sentinel bleed), most typically from an intracranial aneurysm.

Head CT findings: Blood in the subarachnoid space. Figure 1.5 shows a massive SAH, but imaging can be much more subtle. The head CT is 95–99% sensitive for subarachnoid blood, if performed within 12 h of the event. Sensitivity declines with each passing day after the event. Lumbar puncture may be needed if head CT is normal but suspicion remains high for SAH. (Testing of CSF fluid should include cell count in the first and

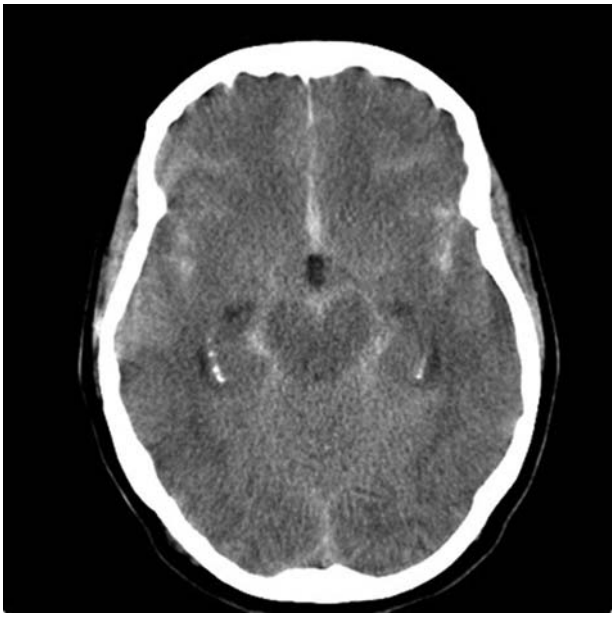

Fig. 1.5 A massive subarachnoid hemorrhage

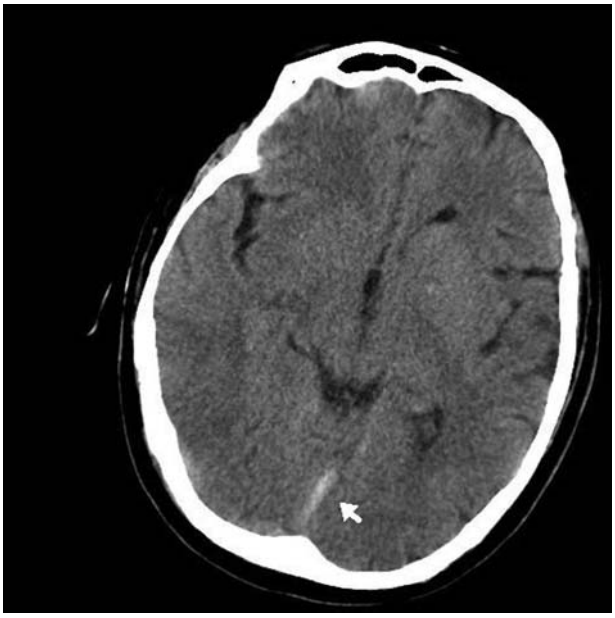

Fig. 1.6 Increased signal within the straight sinus due to a thrombus

Table 1.1 Chart comparing features of transient ischemic attack (TIA), ischemic stroke, intracerebral hemorrhage (ICH), subarachnoid hemorrhage (SAH), and cerebral venous thrombosis. LOC = level of consciousness

	TIA	Ischemic stroke	ICH	SAH	Cerebral venous thrombosis
Decreased LOC	Uncommon in history, absent after minutes	Possible, but uncommon	Common (50%)	Common if large	Variable, more likely if large vessel with increased ICP
Headache	Usually absent	10%, especially with arterial dissection	Common (40%)	Universal, unless patient unconscious	Variable, common if large vessel with increased ICP
Focal symptoms and signs	Absent after minutes	Almost always	Very common	Common if large	Variable
Seizures	Absent	Uncommon	6–7%	10–25%	Common
Nausea/vomiting	Absent	Uncommon	40–50%	Common	Common, if large vein involved
Head CT	Normal	Normal in first few hours, then hypodense regions	Blood in parenchyma	Blood in subarachnoid space	Normal or hypodense, but common to have hemorrhagic infraction. May see thrombus in cerebral vein

last collected tubes and testing for xanthochromia. Xanthochromia testing, performed on a centrifuged sample, may be positive if the lumbar puncture was performed 6 h or later after the SAH.)

Typical Signs/Symptoms of Cerebral Venous Sinus Thrombosis

Cerebral venous thrombosis is a much rarer diagnosis, and its frequency has been difficult to estimate. It may present with focal neurological symptoms if a small cortical vein is occluded. This can lead to both ischemia (though not in an arterial distribution) and hemorrhage into the region of ischemia. This may also result in seizures. If larger cortical veins or sinuses are obstructed, there may or may not be focal neurological symptoms. In these cases, patients may present with global symptoms such as headache, nausea, and vomiting. In addition, symptoms may be of longer duration and do not necessarily have to occur suddenly. Clinical suspicion must be high (known hypercoagulable state, history of prior venous thromboses, SLE or other connective tissue disease known or suspected) to keep this rarer stroke type in mind.

Head CT results: Head CT may be normal. Often, though, especially if the radiologist is asked specifically to look for such, there will be evidence of thrombosis within one of the cerebral veins (see Fig. 1.6). The larger the vein involved (such as the saggital sinus) the more likely it is to be seen on imaging (Table 1.1).

Chapter 2
Ischemic Stroke and Transient Ischemic Attack – Acute Evaluation and Management

W. Alvin McElveen and David Alway

Stroke is the third leading cause of death in the United States behind heart disease and all forms of cancer. Each year 750,000 Americans will have a new or recurrent stroke. Stroke is also the most common medical cause of disability. It is the most highly incident and prevalent neurological condition managed in the hospital setting.

Pathophysiology of Ischemic Stroke

Ischemic stroke is most often due to a lack of blood flow to all or part of the brain, resulting in the deprivation of neurons of vital glucose and oxygen. This deprivation, if severe and prolonged, results in the interruption of normal cellular processes and eventual cell death with breakdown of the neuronal cell membrane. Ischemia can also result from oxygen deprivation alone (hypoxic–ischemic damage, as may occur in patients who experience a cardiac arrest, respiratory collapse, or both) or glucose deprivation alone (as may occur with insulin overdoses in diabetic patients). A very low (or no) blood pressure can produce a distinct pattern of 'watershed' infarcts, which are typically regions of infarcted tissue between the major cerebral arterial territories. More commonly, ischemic stroke involves only a portion of the brain due to an occlusion of a large or small artery. It also may develop rapidly in multiple arterial territories in the event of multiple emboli or a single embolus which breaks up as it travels.

When an artery is occluded and the brain is deprived of blood flow, there is an almost immediate inhibition of the natural function of the neurons feed by that artery. The neurons cease to perform their normal function, and patients will experience symptoms relevant to the area of the brain involved (weakness, numbness, vision loss, etc.). There is a gradient of blood flow around the location of a large arterial occlusion. So, for example, at the center of the region of ischemia, blood flow may be less than 10 mL/100 g/min. This represents the

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ischemic 'core' of the infarcted region – and these neurons may undergo irreversible cell death in as little as 2 h, if blood flow is not reinstated [1]. As one moves away from this ischemic core, blood flow tends to improve, but is still not considered adequate to maintain survival. This region represents the ischemic penumbra. It is a region surrounding the ischemic core and is considered 'at risk' brain territory. While the existence of an ischemic penumbra in every stroke patient may be in debate, the concept holds that very early intervention (recanalization of the relevant artery within 1 h) is likely to result in no stroke at all while later recanalization (after 2 h) may result in a smaller infarct than otherwise would have occurred.

Transient ischemic attacks (TIAs) involve the same pathophysiology as ischemic strokes, but with an early (usually within 10 min) restoration of blood flow to the brain, and thus, no actual infarction. TIAs were previously defined as stroke symptoms that subsided within 24 h, however, MRI studies with diffusion-weighted imaging revealed that over half of patients whose symptoms lasted greater than 60 min actually had areas of infarction despite resolution of symptoms.

Even if the amount of infarcted tissue does not increase over time, infarcted tissue changes during the coarse of hospitalization, leading to edema or possibly to hemorrhage. Edema of the region of infarction can peak as early as 24 h or as late as 4 days after ischemic onset [2]. Over time, an initially large area of infarction can increase in size leading to increased intracranial pressure, or local pressure effects that can cause obstructive hydrocephalus, further infarction due to pressure on adjacent arteries, or herniation of brain into other compartments. Young patients with large infarctions are the most likely to develop problems related to edema formation.

Areas of infarction may also undergo hemorrhagic transformation, meaning that hemorrhage occurs in the infarcted region. This typically is less problematic than edema formation and may simply be 'petechial' hemorrhages, which are of no clinical significance. Frank hemorrhage with associated clinical deterioration and mass effect occurs in as many as 10% of ischemic stroke patients – typically within the first 2 weeks of the ischemic event. Bleeding disorders (including anticoagulation use), poor blood pressure control, and large infarctions are more prone to such hemorrhages.

Early Stroke Recognition and Identification of Stroke Type

For many years the management of ischemic stroke largely involved supportive care and physical therapy. Management of risk factors for prevention of secondary stroke was and remains an important aspect of stroke management. With the advent of tissue plasminogen activator (rt-PA) for the acute treatment of ischemic stroke in 1996, the management of stroke changed dramatically. The move toward treatment algorithms founded on evidence-based medicine has also altered the care of the stroke patient. Several states have adopted

legislative Stroke Acts which require emergency medical personnel to transport stroke victims to the nearest certified stroke center. The Joint Commission has developed certification criteria for Primary Stroke Centers based on the published medical literature.

Stroke Recognition by the Community

In order to improve stroke treatment, the community must be educated regarding the symptoms of stroke and the importance of early evaluation and treatment. Too often, patients develop symptoms and signs of stroke and wait several hours before seeking care, believing that the deficits will go away if they wait long enough. This is perhaps contributed to by the fact that ischemic strokes are typically painless and the symptoms are more difficult to recognize. One study performed in 1993 [3] found that the mean time between symptom onset and physician contact was 13.4 h, with a median of 4 h. Community awareness forums have been successful in educating certain populations about the need to recognize stroke symptoms and activate emergency medical services. Following a public awareness project in Durham, NC, USA 86% of patients with cerebral infarction presented to the hospital within 24 h of symptom onset, compared with 37% before their educational efforts [4]. Communities should be informed that the five most common symptoms of stroke include: (1) sudden numbness or weakness of face, arm, or leg, especially on one side of the body; (2) sudden confusion, trouble speaking, or understanding; (3) sudden trouble seeing in one or both eyes; (4) sudden trouble walking, dizziness, loss of balance, or coordination; and (5) sudden severe headache with no known cause.

The use of the Emergency Medicine System is also crucial in the early treatment of stroke. Proper training of the paramedics allows these frontline personnel to obtain crucial information from the family or other bystanders. This includes time of onset (or time patient was last seen to be normal) and medications the patient might be taking. This historical information, as well as physical findings such as aphasia, motor deficit, and vital signs, can be called to the hospital emergency department so that a stroke alert protocol can be activated, saving significant time in treatment.

Stroke Recognition in the Emergency Room

Chapter 1 reviews major considerations used to identify whether a patient is suffering from a stroke (versus a stroke mimic, such as a multiple sclerosis attack, migraine aura, or a partial seizure) and differentiating ischemic stroke from hemorrhagic stroke or cerebral venous thrombosis. Generally, ischemic stroke will present with the sudden onset of neurological dysfunction which may involve any or all of the following: weakness, numbness, vision

loss, diplopia, dysarthria, gait disorder, aphasia, lightheadedness, vertigo, or disturbed level of consciousness. While a headache can occur with ischemic stroke (up to 10% of cases, especially if arterial dissection is present), it is more suggestive of hemorrhagic stroke, migraine, or cerebral venous thrombosis. Positive neurological phenomena (extra movements, flashing lights in vision, paresthesias) are much more suggestive of migraine aura or seizure than of ischemic stroke. Since ischemia can co-occur with migraine or seizure, identifying migraine or seizure does not exclude ischemia.

Ischemic Stroke Types

Patients suffering from ischemic strokes often have symptoms and signs that suggest which arterial distribution is involved. One should always attempt to match a patient's presentation with these common stroke presentations. Ischemia within major arterial territories (anterior cerebral artery, middle cerebral artery, posterior cerebral artery, basilar artery, and vertebral arteries) have typical associated patterns of signs and symptoms. Patterns associated with small, deep strokes (lacunar strokes) should also be considered.

Anterior Cerebral Artery (ACA)

Patients experience ACA occlusion uncommonly (only 3%) compared to other ischemic stroke types. Weakness of the contralateral leg, with possibly some mild arm weakness, is the hallmark of the presentation. Patients may also have deviation of gaze towards the side of the lesion. Other frontal lobe symptoms include amotivational states (abulia, akinetic mutism), memory disturbance, emotional disturbances, paratonia (a tendency to resist movement of limbs in any direction), and a particular type of aphasia (transcortical motor) that presents as intact repetition and comprehension, but poor naming and fluency. In some cases, if the ACA is occluded very proximally, the recurrent artery of Heubner is affected; this can cause infarction of the anterior limb of the internal capsule, adding face and arm weakness (without sensory loss) to the clinical presentation. If the patient presents only with weakness of face, arm, and leg – it may be difficult to distinguish such a patient, on clinical grounds, from a pure motor lacunar infarction (see Lacunar Syndromes below).

Middle Cerebral Artery (MCA)

MCA infarcts can be devastating, and the degree of impairment will depend on how much and what portions of the MCA are occluded. General features

of these infarctions include contralateral hemiplegia (most often, the face and arm are much weaker than the leg), conjugate eye deviation to the side of the infarction, and contralateral sensory loss. If the infarct is in the dominant hemisphere (the left hemisphere in 99% of right-handed patients) then global (receptive and expressive) aphasia may result. If the upper division only of the MCA is occluded, an expressive (Broca's) aphasia may result while the lower division may result in a receptive (Wernicke's) aphasia. Patients may also experience a curious contralateral attentional deficit, most commonly with non-dominant hemisphere lesions. This neglect phenomenon involves poor awareness of the contralateral side, which may include the patient's own body (lack of recognition that it is their own), side of space (inability to pay attention to objects on that side of the body), or lack of awareness that they have suffered a stroke (anosognosia). To confuse matters somewhat, if the MCA is occluded very proximally, then smaller penetrating arteries (lenticulostriate arteries) supplying the ipsilateral basal ganglia are occluded. This leads to superimposed lacunar-type infarctions that add to the patient's presenting deficits, and may complicate the process of localization. Occlusion of these penetrating arteries causes a larger region of infarction, thereby increasing the likelihood of mass effect related to edema.

Posterior Cerebral Artery (PCA)

PCA occlusions have highly variable effects, depending on the portion of artery involved. Distal segment occlusions may lead to homonymous (both eyes) contralateral superior or inferior quadrant vision loss (a quadrantanopsia). Infarctions inferior to the calcarine fissure of the striate cortex will lead to a superior quadrantanopsia; infarctions superior to this location will cause an inferior quadrantanopsia. Infarctions of both areas will lead to a complete homonymous hemianopsia. More proximal occlusions can also affect the deep penetrating arteries that supply the midbrain and thalamus as well as the branch that supplies the medial temporal lobe. A complete discussion of the variety of presentations is beyond the scope of this text, but here some common presentations are described. Infarctions of the thalamus often cause contralateral sensory loss, sometimes with the subsequent development of chronic pain (thalamic pain syndrome). If both thalamii are affected, confusion and severe disruptions in the level of consciousness may occur. Midbrain lesions may lead to dysconjugate gaze, hemiplegia, or even stupor and coma. If the subthalamic nucleus is involved, movement disorders such as hemiballismus or hemichoreoathetosis may occur. Complete occlusion of the PCA may lead to memory impairment or to unique cortical dysfunctions such as an inability to read (alexia), to name (anomia), or to identify viewed objects (visual agnosia).

Basilar Artery (BA) and Vertebral Arteries (VA)

The most dramatic presentation of BA disease, due to proximal occlusion, is rapid onset coma. It is important to consider this possibility in the early differential diagnosis of coma. BA occlusion at any level, depending on collateral pathways (especially the presence of posterior communicating arteries), can lead to unilateral or bilateral PCA infarctions. Below the PCA arteries, in descending order, are the superior cerebellar arteries (SCA), anterior inferior cerebellar arteries (AICA), and finally the posterior inferior cerebellar arteries (PICA). A detailed description of the common presentations associated with occlusion of these large arteries is beyond the scope of this text. In general, ischemia due to compromise of the BA or VA can present with brainstem signs such as global depression of consciousness, vertigo, ataxia, nystagmus, nausea, vomiting, gaze palsies, and loss of facial sensation. Loss of facial sensation on one side, with contralateral loss of body sensation (crossed sensory findings) is highly suggestive of a brainstem lesion. A Horner's syndrome (ptosis, miosis, and anhydrosis on one side) may also occur with brainstem infarcts.

Lacunar Syndromes

Often infarctions are due to occlusion of small penetrating arteries within the brain. These infarcts are generally small (1.5 cm diameter or less) and are located deep within the brain. Common locations for lacunar infarctions are the basal ganglia, thalamus, internal capsule, cerebellum, and brainstem. The recognition of common lacunar syndromes can guide the early treatment of ischemic stroke patients, may aid in localization, and will help with prognostication. In general, recovery from lacunar infarctions occurs more rapidly and more completely than from large artery ischemic strokes and are associated with less mortality. The five most common lacunar syndromes are described as follows:

(a) Pure motor: This involves contralateral (to the stroke) weakness affecting, roughly equally, face, arm, and leg. Facial weakness is sometimes absent. Infarct locations commonly associated with this syndrome include: corona radiata, internal capsule, pons, or medullary pyramid.
(b) Ataxia hemiparesis: This involves any combination of weakness and poor coordination on the same side of the body. The poor coordination should be 'out of proportion' to the degree of weakness. Common sites associated with this presentation include the anterior limb of the internal capsule and the corona radiata.
(c) Clumsy-hand dysarthria: This involves severe slurring of speech, with mild hand weakness as well as hand dyscoordination. Sometimes weakness of the arm or leg is present. The pons is the most likely localization for this infarct, although an internal capsule lacune may also cause these symptoms.

(d) Pure sensory: This presents as sensory loss affecting, roughly equally, the contralateral face, arm, and leg. The infarct is typically in the thalamus, although other locations have been reported.
(e) Mixed sensory motor: This is the combination of pure sensory and pure motor lacunar syndromes. These can result from infarcts involving the thalamus, internal capsule, basal ganglia, or pons. These infarcts tend to be larger than those associated with other lacunar syndromes.

A Word About Tissue Plasminogen Activator (tPA)

Recombinant tissue plasminogen activator (rt-PA) is chemically similar to endogenous tissue plasminogen activator (tPA). tPA is a serine protease which converts plasminogen to plasmin, a fibrinolytic enzyme (Fig. 2.1). Upon administration, recombinant tPA increases plasmin enzymatic activity, resulting in fibrinolysis. It is often referred to as a "clot buster" and is used to dissolve a clot with restoration of blood supply to an area of cerebral ischemia.

Tissue plasminogen activator (rt-PA) was approved by the FDA in 1996 for the treatment of acute ischemic stroke based on the findings of the 1995 NINDS stroke trial [5]. This double blind placebo controlled trial demonstrated that patients treated with rt-PA within 3 h of symptom onset had a 30% greater likelihood of having minimal to no disability 90 days following treatment compared to a placebo treated group. There was a 6.4% risk of symptomatic intracerebral hemorrhage in the rt-PA treated group compared to 0.6% in the placebo group. However, even considering the risk of bleeding, the mortality at 90 days was 21% in the placebo group and only 17% in the rt-PA group.

Although the NINDS trial demonstrated improvement within a 3-h time frame (compared to placebo) patients have even better outcomes if treated earlier. This is demonstrated in Fig. 2.2.

Therefore, if appropriate, the administration of IV tPA (and, indeed, the management of acute stroke overall) should be carried out expeditiously.

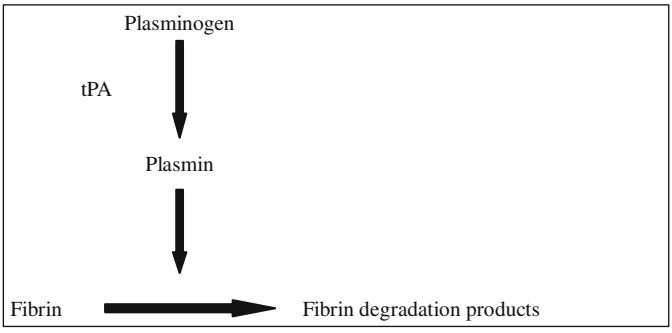

Fig. 2.1 Mechanism of tPA action

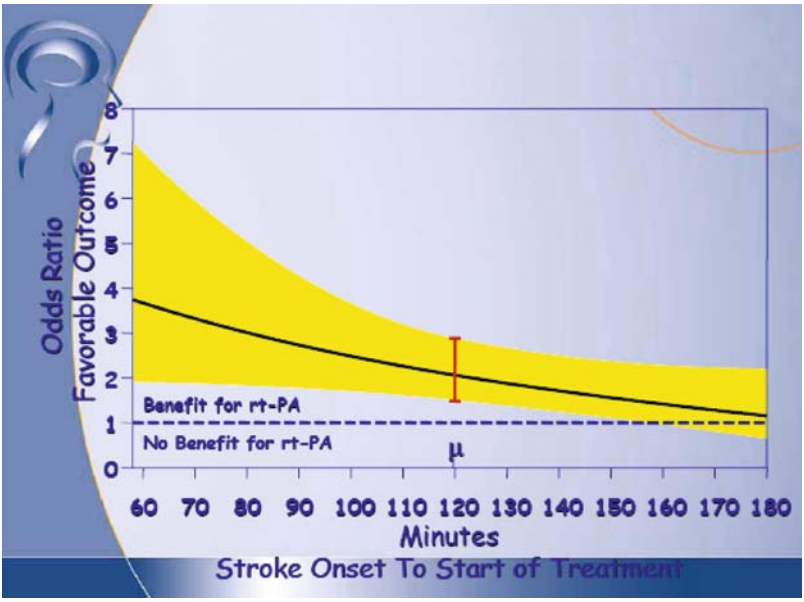

Fig. 2.2 NINDS TPA stroke study parts 1 and 2. Relation of time to treatment to odds ratio of favorable outcome. (Marler, JT et al. Neurology 2000: 55, 1649–1655)

Emergency Department Management of Ischemic Stroke

As with any acutely ill patient, a stroke patient should first undergo assessment of airway, breathing adequacy/oxygenation, and circulation with subsequent correction of any discovered problems. Because of the importance of timely intervention in treating patients with stroke, it is beneficial if not imperative that hospitals develop a set of orders outlining the protocol to be followed when a stroke patient arrives. If the patient is transported by emergency medicine services, the hospital can institute the protocol immediately. Several capabilities should be available in the emergency department including the timely interpretation of studies and the availability of neurosurgical intervention should the patient develop symptomatic intracranial hemorrhage.

Rapid Testing

The laboratory should be available to perform the following blood tests immediately: PTT, INR, blood glucose, and CBC with platelet count. As it may take time to process these studies, obtaining them early reduces the time to treatment. Blood should be drawn and sent to the lab prior to head CT. The head CT scan should be performed as soon as possible to exclude a hemorrhagic stroke.

Level of Consciousness	0 Alert 1 Drowsy 2 Stuperous 3 Coma								
LOC	0 Answers Both Correctly 1 Answers One (1) Correctly 2 Incorrect								
LOC	0 Obeys Both Correctly 1 Obeys One (1) Correctly 2 Incorrect								
Best Gaze	0 Normal 1 Partial Gaze Palsy 2 Forced Deviation								
Visual	0 No Visual Loss 1 Partial Hemianopia 2 Complete Hemianopia 3 Bilateral Hemianopia Blind								
Facial Palsy	0 Normal 1 Minor 2 Partial 3 Complete								
Motor Arm	0 No Drift 1 Drift 2 Some Effort Against Gravity 3 Limb Falls 4 No Movement	R	L	R	L	R	L	R	L
Motor Leg	0 No Drift 1 Drift 2 Some Effort Against Gravity 3 Limb Falls 4 No Movement	R	L	R	L	R	L	R	L
Limb Ataxia	0 Absent + = Present 1 One (1) Limb - = Absent 2 Two (2) Limbs Score →	R U L **Total:**	L	R U L **Total:**	L	R U L **Total:**	L	R U L **Total:**	L
Sensory	0 Normal 1 Mild to Moderate Loss 2 Severe to Total Loss								
Best Language	0 Normal 1 Mild to Moderate Aphasia 2 Severe Aphasia 3 Mute								
Dysarthria	0 Normal 1 Mild to Moderate 2 Severe								
Extinction/ Inattention	0 Normal 1 Partial Neglect 2 Complete Neglect								
Total / Initial:									

Fig. 2.3 The NIH Stroke Scale

The CT scan may also demonstrate subtle early signs of infarction. Although the presence of these signs is associated with a poor outcome, this does not preclude the use of rt-PA unless there is evidence of hemorrhage. The scans are generally performed without contrast unless there is reason to suspect a tumor.

The NIH Stroke Scale

Evaluation of the patient should also include performance of the NIH stroke scale (Fig. 2.3). Training for this as well as certification for performing the evaluation can be obtained through several routes including accessing the American Stroke Association website. Initially utilized in research trials, this 15-item scale has proven valuable in quantifying the deficits of the stroke patient and can be useful when discussing the patient's condition with the treating neurologist. It is also beneficial in following the patient in the hospital

to assess improvement or deterioration in neurological condition. (It does have some limitations in that it does not capture brainstem deficits well. For example, palatal weakness is not scored on this scale, but a lesion associated with dysphagia secondary to a stroke can be quite disabling).

Deciding Whether to Administer IV tPA

First, accurately establish the time of symptom onset. If a patient's symptoms have been present for less than 3 h, many criteria must be reviewed prior to tPA administration. These are listed in Fig. 2.4.

Glucose must be measured since hypoglycemia can be associated with a focal neurological deficit that is reversible with glucose administration. PTT, INR, and platelet count must be obtained to prevent the use of thrombolytic therapy in patients with coagulation defects. By obtaining these lab values soon after the patient arrives in the emergency department, treatment delays can be avoided.

Caveats and Special Considerations

While the judgment of the treating physician, based on other studies or special circumstances, may allow for the bending of some rules (such as treating

If any of the following are answered YES, Patient may NOT receive tPA:

Yes	No	Stroke Symptom onset more than 3 hours (Last time patient was known to be without stroke symptoms)
Yes	No	Age 18 or younger
Yes	No	Comatose or unresponsive
Yes	No	Stroke Symptoms clearing spontaneously. Stroke symptoms minor and isolated.
Yes	No	Intracranial/Subarachnoid hemorrhage (SAH). Clinical history suggestive of SAH even if CT negative
Yes	No	Active internal bleeding or acute trauma (fracture) on examination
Yes	No	INR greater than 1.7
Yes	No	Platelet count less than 100,000
Yes	No	Glucose less than 50
Yes	No	HTN uncontrolled despite medication with Systolic BP greater than 185 or. Diastolic BP greater than 110

History of:

Yes	No	Active malignancy
Yes	No	Recent MI or pericarditis within the past 3 months
Yes	No	Recent arterial puncture at noncompressible site within previous 7 days (such as subclavian)
Yes	No	Lumbar puncture within 3 days
Yes	No	History of GI or urinary hemorrhage within 21 days
Yes	No	Pregnancy, lactation, or childbirth within 30 days
Yes	No	History of Intracranial hemorrhage
Yes	No	Major surgery or serious trauma within in last 14 days
Yes	No	Seizure with postictal residual neurological impairment .
Yes	No	Major ischemic stroke or head trauma within the last 3 months
Yes	No	Heparin within 48 hrs with PTT greater than upper limits of normal
Yes	No	Known AV Malformation or aneurysm
Yes	No	Known bleeding disorder

Fig. 2.4 Criteria for tPA Administration

someone under the age of 18) it should be noted that non-adherence to these guidelines (especially as regards a well-defined time of stroke onset and control of elevated blood pressure) has led to poorer outcomes. In a multi-hospital survey in Cleveland, a higher rate of symptomatic hemorrhages and a high-mortality rate were found in those treated with tPA [6]. An analysis of those treated in the Cleveland area found multiple protocol violations, especially as regards carefully establishing a time of onset of symptoms and treatment with tPA despite blood pressures being higher than the protocol allows. A follow-up study, also surveying Cleveland area hospitals, showed that after improved adherence to the guidelines, good outcomes similar to those of the original NINDS trail were obtained [7].

The determination that a neurological deficit is rapidly improving has been somewhat problematic. Improvement over the baseline NIH score is not considered rapid improvement if the patient continues to have a significant deficit. A good rule of thumb has been to assume the patient is not going to show further improvement in his condition. Is the deficit mild enough that he can continue to function at a high level? Even mild weakness might be devastating to an individual whose occupation depended on fine motor movements, so rt-PA would be a consideration in that patient even with a low NIHSS value. On the other hand, in the NINDS trial, patients with too high of an NIHSS value (greater than 23) tended to do poorly with IV tPA administration and physicians can reasonably withhold tPA under these circumstances.

If a patient's blood pressure is prohibitively elevated for tPA administration (greater than or equal to 185/110 mmHg) it is permissible to lower the blood pressure with various agents so that tPA can be administered. Acceptable agents for this purpose include IV labetolol, IV hydralazine, or IV nicardipine. Lowering a patient's blood pressure more than 15%, for this purpose, is generally not recommended [8].

Beyond the 3-h Time Frame

It should be noted that patients who are suffering from an ischemic stroke, who are considered ineligible for tPA or who are beyond the 3-h time frame, should be considered for other interventions (to be described below). Hospitals which do not themselves have the capability of performing these procedures should emergently contact hospitals which do, in order to arrange for immediate transfer of the patient if deemed appropriate.

Some studies have indicated that intra-arterial thrombolytic therapy may be beneficial in the patient who is treated within 6 h of symptom onset (PROACT I and II) [9, 10]. tPA is typically the agent of choice used in practice. Intra-arterial therapy involves the use of an intra-arterial catheter to instill a small-tPA dose that is concentrated at the level of the arterial occlusion. With basilar artery occlusions, because of its very poor natural history, patients may be treated up to 24 h or longer after symptom onset.

Additional acute therapies are also available. Mechanical catheter retrieval devices, which physically remove thrombus, have been approved for use in restoring cerebral flow in patients with occlusion of a major intracerebral artery. Some such devices are FDA approved for use within 6 h of an ischemic stroke. Although some patients have had remarkable recovery utilizing these procedures, one must be aware of the risks involved. The Safety and Efficacy of Mechanical Embolectomy in Acute Ischemic Stroke Trial [11] demonstrated 48% recanalization rate with the MERCI (Mechanical Embolus Removal in Cerebral Ischemia) catheter. Because the MERCI trial did not have a placebo group for direct comparison, this can be compared to only 18% recanalization for the placebo group in the PROACT II trial. However, the mortality rate for use of the catheter was 43.5% in the treated group at 90 days compared to 27% in the placebo group of the PROACT II trial. Many stroke neurologists would only consider mechanical clot retrieval in patients who are deemed inappropriate for tPA. Both mechanical retrieval and intra-arterial thrombolysis are limited to facilities that have immediate access to cerebral angiography and the availability of trained neurointerventionalists.

Inpatient Care

All patients should undergo an EKG on the first day of admission and should undergo telemetry monitoring for at least the first 24 h of admission. The continued management of patients who have been treated with tPA, or those who were not candidates for the medication, is important in achieving optimal outcomes. Among the parameters to consider are blood pressure, fluid balance, glucose, anticoagulation, and platelet inhibition.

Blood Pressure

If tPA is administered, the patient must be monitored for at least 24 h in an intensive care setting. Vital signs should initially be checked every 15 min after tPA administration, for the first 30 min. Thereafter, vitals are checked every 30 min for the next hour and then every hour for the following 16 h. . Blood pressure parameters and treatment protocols should be standardized. The present recommendations, for the first 24 h post-tPA, are to keep systolic BP below 185 mmHg and diastolic below 110 mmHg. Labetolol, hydralazine, or nicardipine are the best agents to lower blood pressure in this setting. A lower limit for diastolic blood pressure of 60 mmHg should be used.

Twenty-four hours after tPA administration, and immediately for patients who did not receive tPA, blood pressure is typically allowed to run higher. The reason for this approach is the frequent loss of cerebral autoregulation. Cerebral autoregulation in the normal state results in steady cerebral blood flow for

mean arterial pressures between 60 and 160 mmHg. However, autoregulation is often lost in the acute stroke setting, and as a result, decreasing blood pressure will often decrease cerebral blood flow. Unless there is a cardiac, renal or other medical reason that the pressure needs to be lowered, the current recommendation is to lower the blood pressure only if it is above 220/120 mmHg. Agents such as sublingual nifedipine, that lower the blood pressure quickly, should be avoided. A reasonable decrease in blood pressure would be 15% over 24 h. For patients who have preexisting hypertension, it is generally agreed that antihypertensive medications should be restarted after 24 h if patients are neurologically stable unless a specific contraindication to restarting treatment is known. In cases of larger strokes, where the peak effects of edema may cause elevations in intracranial pressure or herniation syndromes, delaying use of antihypertensives until past the time of peak edema, is considered prudent.

IV Fluids

Hypotonic and glucose containing intravenous fluids are not recommended in the acute setting of cerebral infarction. Cytotoxic edema resulting from cellular membrane disruption with resulting swelling of the cell body develops with infarct. The use of these solutions can increase the cellular damage with influx of water into the cell. Normal saline is therefore generally utilized in these patients.

Glucose

Euglycemia should be the clinical goal in the setting of stroke. In addition to the negative effects of hypoglycemia for stroke outcome, it has also been noted that patients with sustained glucose greater than 140 mg/dL have less favorable stroke outcomes [12, 13]. Glucose levels should be monitored and, if found to be greater than 140–180 mg/dL, treatment with insulin is indicated.

Anticoagulation

The use of anticoagulation in acute ischemic stroke is controversial. The present clinical recommendations are to avoid anticoagulation in the acute phase (the first few weeks) of stroke. Present data does not indicate that the use of heparin or heparinoids in the acute management of stroke results in a decrease in the risk of early recurrence of stroke. However, there is an increased risk of conversion to a symptomatic hemorrhagic stroke with the use of anticoagulation, especially in patients with moderate- to large-sized strokes. An example of this is seen in Fig. 2.5. This recommendation also holds for strokes felt to be of cardioembolic origin, such as in the setting of atrial fibrillation. No subgroup or arterial distribution has been identified in which anticoagulation has

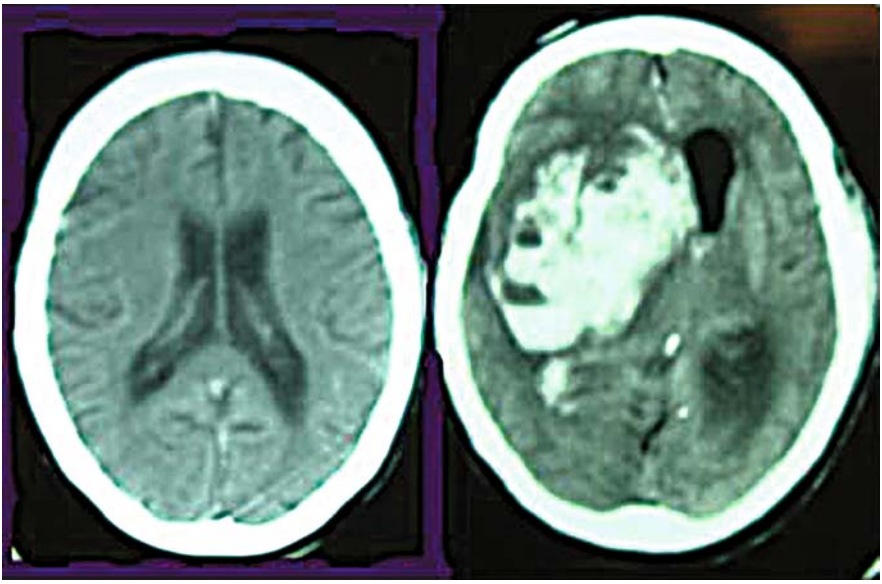

Fig. 2.5 Patient presents at 10 A.M. with left hemiparesis and scan on left is obtained. Heparin was started. At 4 P.M. patient becomes obtunded and scan on right is obtained, showing large hemorrhage (*See* Color Insert)

demonstrated a significant benefit in the setting of acute stroke, due to the concomitant increased risk of bleeding. (Exceptions might include the use of anticoagulation in the setting of cerebral venous thrombosis. It is also common, though unproven, to use anticoagulation in the setting of large artery dissections with presumed embolic ischemic strokes.) Anticoagulation of any form (and antiplatelet therapy) should not be utilized within 24 h of tPA administration.

Platelet Inhibition

Aspirin is the only antiplatelet agent studied showing benefit in the acute management of stroke. Two large trials have been performed. When the results of the Chinese Acute Stroke Trial and the International Stroke Trial were combined, a modest benefit was obtained [14]. This has led to the recommendation of instituting aspirin at a dose of 325 mg per day within the first 48 h after stroke. The use of aspirin is not recommended within 24 h of rt-PA administration. A 2007 published study by Kennedy et al. [15] compared clopidogrel plus aspirin to aspirin alone given within 24 h of stroke onset. There was a 7% recurrent stroke incidence in the combined group compared to 11% in the aspirin group. However, this did not reach statistical significance. Other trials, such as the MATCH trial, have found double the risk of significant bleeding

when using aspirin plus clopidogrel compared to clopidogrel alone [16]. Hence combined use of these two antiplatelet agents is not recommended for acute stroke treatment.

Preventing and Treating Stroke Complications

Deep Venous Thrombosis (DVT)

Stroke patients frequently have deficits that impair their ability to ambulate safely or that may cause them to be confined to bed. This limitation in mobility can lead to a deep vein thrombosis (DVT) and subsequently to a pulmonary embolism; therefore, measures should be taken to prevent this complication. The heparinoid enoxaparin appears to be quite effective in this setting. A study by Sherman et al. indicated a 43% improvement in venous thromboembolism with patients treated with enoxaparin given 40 mg subcutaneously once a day compared to subcutaneous unfractionated heparin [17]. The risk of intracerebral hemorrhage with the use of low dose anticoagulants appears to be low [18]. Sequential compression devices may also be used to prevent deep vein thrombosis especially in patients who have a contraindication to anticoagulation. Additionally, early mobilization of patients and the early involvement of physical therapists helps to prevent DVTs and improves stroke outcomes.

Infection Prevention and Treatment

One of the major dangers following stroke is aspiration, which may be silent, resulting in aspiration pneumonia. Therefore patients should be kept NPO until a swallow screening evaluation can be performed. The presence of a gag reflex does not guarantee that swallowing is safe. A video swallowing study may be necessary in some patients. If the patient is at aspiration risk, gastric feeding tubes are often utilized. Multiple day use of in-dwelling foley catheters should also be avoided, since this carries a high risk of urinary tract infections (UTIs).

If an infection does occur, aggressive treatment is the rule. Antibiotics should be administered early to control infection and use of acetaminophen and other measures to control fever. A clear correlation between fever and worse stroke outcomes has been established [19, 20].

Cerebral Edema

As mentioned earlier, cerebral edema can cause significant morbidity and mortality due to increased intracranial pressure, local pressure effects causing obstructive hydrocephalus, further infarction due to pressure on adjacent

arteries, or herniation of brain into other compartments. Edema may become maximal anywhere between 24 and 96 h after ischemic stroke onset. An emergent CT scan should be performed if a patient worsens neurologically. Emergent neurosurgical consultation may be indicated to consider placement of an intraventricular drain (in the case of hydrocephalus). Decompressive surgery must be considered in the case of cerebral edema with impending herniation syndrome [21] (most typically due to MCA or ICA occlusion in a young patient) or in cases of large cerebellar infarctions with significant edema. The use of corticosteroids for treatment of cerebral edema in stroke is not recommended. Complications such as increased glucose levels and infections may be aggravated by steroids. Reasonable measures to reduce intracerebral pressure are reviewed in Chapter 4 and include intubation with hyperventilation and use of osmotherapy (such as IV mannitol). These measures, while logical, are generally considered 'last ditch' efforts to save the life of the patient. Data regarding their effects on mortality and neurological outcome are mixed.

Hemorrhagic Transformation

A region of cerebral ischemia may 'transform' into a region of superimposed hemorrhage. This may be only petechial hemorrhaging and therefore be of no clinical significance. More significant confluent regions of ischemia may not require further changes in therapy. Frank hemorrhage, beyond the area of infarction, with associated mass effect and clinical deterioration, occurs in as many as 10% of ischemic strokes, and would significantly complicate management, possibly even requiring surgical evacuation. For further information regarding management of these hemorrhages, see Chapter 4.

In-Patient Testing for Stroke/TIA Etiology

The treating physicians should search for stroke etiologies, especially those that will affect immediate management, expeditiously during the patient's hospitalization. In the majority of cases, it is most useful to order a standard in-patient work up (hopefully as part of an available order set) immediately upon admission.

TIA patients should also undergo admission and a rapid work up, if the event occurred within 3 days. Following a TIA, 10.5% of patients will have a stroke within 90 days with 50% of these occurring within 2 days of the TIA. Twenty-one percent of these strokes are fatal with another 64% resulting in disability [22]. TIAs, therefore offer an opportunity to intervene and prevent a significant number of strokes. Indeed, two European studies [23, 24], have found that early evaluation and management can decrease the risk of stroke in the 90-day period by 80%.

Risk factors for TIA and ischemic stroke include hypertension, atrial fibrillation, carotid stenosis, cardiomyopathy, hyperlipidemia, vasculitis, cigarette smoking, hypercoaguable states, diabetes, syphilis, elevated C-reactive protein, and elevated homocystine levels, among others. Much of the work-up for TIA and ischemic stroke is a 'plumbing' evaluation, meaning that the etiology of a stroke can be anywhere from the heart through the 'pipes' that lead to the site of the stroke. It is therefore mandatory to image all of these regions. Standard evaluations and reasons for testing include the following:

- Brain MRI – This may provide significant additional information including the existence of a stroke not detected on head CT, the detection of patterns of ischemia that could suggest an etiology (for example, infarctions in multiple arterial territories, suggestive of embolic disease), and an indication of the acuity of the infarcts.
- Imaging of intracranial and extracranial vasculature – Modalities include Magnetic resonance angiography (MRA), CT angiography (CTA), carotid duplex, transcranial doppler (TCD), or cerebral catheter arteriography. If a patient will already be getting an MRI of the brain, MRA of the head and neck is typically ordered at the same time. CT angiogram of the head and neck vessels is also reasonable, and is performed by some emergency departments as part of their ischemic stroke protocol. The intracranial portion of this testing can identify important information such as extensive atherosclerotic disease, vascular occlusions, or evidence of cerebral vasculitis. Extracranial imaging is important to identify carotid atherosclerotic disease with stenosis or arterial dissections. Carotid ultrasound has a sensitivity for significant stenosis of approximately 85% compared to digital arteriography. In combination with MR angiography, the sensitivity of detecting carotid stenoses is close to 100%. CT angiography is also helpful in assessing for carotid stenosis with a sensitivity of 88–98%, depending on the study. If a question remains regarding the degree of stenosis, catheter arteriography may be necessary. Dissections are most effectively imaged by catheter angiography, but they can also be evaluated by CT or magnetic resonance angiography.
- Transthoracic echocardiogram (TTE) – This can identify embolic stroke sources including cardiac thrombus, enlarged left atrium (a risk factor for the development of atrial fibrillation), patent foramen ovale (PFO), atrial septal aneurysm, endocarditis, or very low ejection fraction. If a 2D-echocardiogram does not suggest an ischemic stroke cause or is of poor quality, and clinical suspicion remains high that an event was cardioembolic in origin, a transesophageal echocardiogram (TEE) should be performed. TEE is more effective in identifying left atrial appendage thrombus, aortic artery disease, and has better overall resolution. Transcranial Doppler studies implementing a bubble test are also useful for PFO detection.
- Blood work – Blood testing should be driven by clinical suspicion. Commonly performed blood tests for all ischemic stroke patients include

complete blood count (CBC) with differential, erythrocyte sedimentation rate (ESR), blood urea nitrogen (BUN), serum creatinine, prothrombin time (PT), activated partial thromboplastin time (aPTT), blood glucose, hemoglobin A1c, fasting lipid profile, RPR, and FTA. Evidence of or suspicion for atherosclerotic disease may also prompt testing for C-reactive protein and homocysteine levels. Suspicion for a hypercoagulable state might prompt much more extensive testing (see Chapter 10 regarding appropriate blood work). Fever with concern for endocarditis should prompt multiple blood cultures. Suspicion for rare disorders such as CNS vasculitis is beyond the scope of this chapter but will include testing for measures of inflammation, infection, and autoimmune disease.

Beginning Preventative Treatment in the Hospital

Many preventative measures should be instituted while the patient is still hospitalized (for a fuller discussion of all long-term preventative measures, see Chapter 3). Basic preventative measures to consider include: control of chronic hypertension, anticoagulation for atrial fibrillation, surgical or endovascular treatment of carotid artery stenosis, cholesterol control, smoking cessation, and use of an antiplatelet medication (if the patient is not on anticoagulation).

Hypertension

Blood pressure may be transiently elevated following a TIA or stroke and often decreases spontaneously. However, in sustained hypertension the long-term risk of stroke increases significantly. Lowering a patient's blood pressure has been proven to be effective in lower stroke risk by 30–40% in meta-analyses of randomized controlled trials [25,26]. Therefore tight control of blood pressure, in the long term, is recommended. Starting an antihypertensive while the patient is still in the hospital is reasonable and often leads to improved long-term compliance. While a normal blood pressure of $<120/80$ mmHg would be ideal, the appropriate goal for each patient must be individualized.

Atrial Fibrillation

Atrial fibrillation may produce a cardioembolic source of cerebral ischemia. This risk increases with age and comorbid conditions such as congestive heart failure, hypertension, and diabetes. The use of warfarin decreases ischemic stroke risk by 68% in older age groups [27]. Aspirin decreases the risk slightly, but is significantly less effective than warfarin. There is no data to support the use of combination therapy using warfarin together with aspirin or other antiplatelet agents. In cases of atrial fibrillation and TIA, anticoagulation can

be started while the patient is hospitalized, and this would generally be recommended. In cases of moderate to large strokes, anticoagulation can reasonably be delayed for 2–4 weeks to prevent symptomatic hemorrhagic conversion.

Carotid Artery Stenosis

In patients with symptomatic carotid stenosis of greater than 70%, the North American Symptomatic Carotid Endarterectomy Trial [28] found that carotid endarterectomy reduced the risk of ipsilateral stroke to 9% after 2 years, compared to 26% in the medical management arm. The greatest benefit occurred when surgery was performed within 2 weeks of symptom onset. There was no significant difference between the two groups for less severe stenosis. In general, for patients with ipsilateral ischemic stroke or TIA, and at least 70% carotid stenosis, CEA should be strongly considered. The surgical/arteriographic risk for these procedures, in the study, was less than 3%. For patients who are at higher risk of complications due to concurrent medical conditions compared to those in the study, the benefits of endarterectomy compared to medical therapy would be less robust and medical management might be preferable. For patients with contraindications to surgery, such as prior radiation treatment to the neck or lesions that cannot be approached surgically, carotid stents have been approved to manage the stenosis. For a more detailed analysis of carotid stenosis and indicated therapy, please see Chapter 11.

Hyperlipidemia

Hyperlipidemia is a risk for cardiovascular disease and to a lesser degree cerebrovascular disease. The current recommendations call for an LDL value of less than 100 mg/dL in patients who have had cerebral ischemic events. If there are multiple ischemic stroke risk factors, an LDL of less than 70 mg/dL is recommended. Statin agents have been shown to decrease the risk of stroke. This may not be solely on the basis of cholesterol control as they also have anti-inflammatory properties and have been discovered to lower C-reactive protein levels (a known stroke risk factor). Statins should be initiated during stroke or TIA admissions to improve long-term compliance.

Smoking Cessation

Cigarette smoking is a major modifiable risk factor. All smokers should receive counseling and education regarding the importance of smoking cessation. Several agents and techniques are available to help patients with this endeavor.

Antiplatelet Medication

The use of antiplatelet agents decreases the risk of recurrent stroke. Aspirin has been shown to decrease the risk of stroke by 18% compared to placebo [29, 30]. Clopidogrel (Plavix) has a relative risk reduction that is 8% better than aspirin, using a combined endpoint of stroke, myocardial infarction, and peripheral vascular arterial events [31]. Controlled release dipyridamole plus aspirin (Aggrenox) has been shown to lead to a decreased stroke rate that is 23% better than aspirin and 37% better than placebo [32]. The use of these agents, in patients who are not anticoagulated, therefore is of paramount importance in preventing recurrent stroke.

Conclusion

The acute management of stroke requires emergent and structured protocols for efficient patient management. When the patient has had an ischemic stroke, early treatment can result in improved clinical outcomes. Proper medical management, even in patients who are not candidates for thrombolytic or neurointerventional procedures, results in better outcomes. Studies have demonstrated a significant decrease in the number of patients with severe disability when they are treated on a dedicated stroke floor, compared to those treated on a general medical ward. Many hospitals are now becoming certified as Primary Stroke Centers, and accreditation for these programs has been established.

The timely evaluation of transient cerebral ischemia must be stressed. Patients should not be discharged from an emergency department to be evaluated in a few days by their primary care physician. Admission of the patient for observation to obtain the necessary testing within 24 h is recommended. With the high incidence of early stroke after TIA, the use of rt-PA might be facilitated by the admission as well. The development of dedicated clinics that allow for the immediate evaluation of a patient has been possible in some communities. This approach also allows for the timely evaluation and institution of appropriate treatment, but so far is not widely available. With proper care and patient management, the risk of stroke and its devastating effects can be overcome.

Brief Summary

- Ischemic stroke is commonly the result of arterial occlusion with loss of blood flow to part of the brain, depriving neurons of oxygen and glucose. An event is referred to as a TIA when blood flow is spontaneously restored quickly enough that no neuronal death ensues.
- Treatment of stroke is greatly improved by public recognition of stroke symptoms, a well-coordinated emergency medical service, hospitals with stroke protocols, and a hospital with the capabilities to treat all types of stroke patients and stroke-related complications.

- The symptoms of ischemic stroke or TIA may include the sudden onset of weakness, numbness, vision loss, diplopia, dysarthria, gait disorder, aphasia, lightheadedness, vertigo, or disturbed level of consciousness.
- In order to localize the stroke, it is helpful to be familiar with the usual presentations of large artery occlusions (MCA, ACA, PCA, BA, VA) as well as common lacunar syndromes.
- An acute stroke protocol (see Table 2.1) is helpful in expediting and organizing patient evaluation.
- Deviation from IV/IA tPA protocols can result in poorer outcomes.
- Decisions regarding tPA administration are often complex. In general, patients with severe deficits (NIHSS>23) are unlikely to benefit from tPA. Patients with mild deficits may be offered tPA, even if the NIHSS is low, based on the likely effect of the deficit on that person's life and livelihood. Unless impairment makes this impossible, the patient should be involved in the decision and the patient or family should be aware of the risks and benefits.
- Mechanic retrieval systems (MERCI device) are FDA approved to remove thrombus in the setting of acute stroke (within 6 h), but are not yet well-proven therapies.
- In-patient care should focus on the following:
  - EKG and telemetry monitoring × 24 h
  - Post-tPA patients should have ICU admission with high-frequency assessments

Table 2.1 Emergency room protocol for suspected ischemic stroke

- Assess airway, breathing adequacy, circulation, vitals
- Rapid Assessment:
  - Determine *time of onset* or time last seen normal
  - Perform *rapid physical* combined with NIHSS
  - Order *stat Head CT* (in some protocols, CTA head/neck also performed)
  - *Draw blood for rapid testing*: CBC, PTT, INR, blood glucose
  - While other testing is underway, obtain *past medical history* and more *detailed history* of current presentation from patient or witnesses.
  - Perform EKG
- When vitals, head CT, neurology exam, and blood results obtained:
  - Review IV-tPA criteria and determine if appropriate for patient.
  - If blood pressure is too high (>185/110 mmHg), consider lowering by 15% or less using IV hydralazine, IV nicardipine, or IV labetolol in order to make patient eligible for IV-tPA.
  - Consent patient (if possible) or family member after explaining regarding risks and benefits of IV-tPA
  - Order IV-tPA if/when appropriate
  - If tPA administered, transfer patient to ICU and use post-tPA order set.
- If patient outside of 3 h IV-tPA window
  - Consider neuroradiology consultation for *IA-TPA or MERCI retriever* if within 6 h window. (Or within 24 h if suspected basilar artery occlusion)

- Blood pressure should be reduced as follows:
  - Within 24 h of tPA
    - SBP <185 and DBP < 110 mmHg
  - No tPA or 24 h after tPA
    - SBP <220 and DBP <120 mmHg
  - Use IV labetolol, nicardipine, or hydralazine to control elevated BP
  - Lower BP at a rate of only 15% per 24 h
- Use only IV normal saline – avoid hypotonic or glucose-containing solutions
- Aim for euglycemia in the hospitalized stroke patient
- There are few acute ischemic stroke cases that will benefit from anticoagulation
- Aspirin is beneficial in acute ischemic stroke

- Preventing and treating stroke complications
  - DVT prophylaxis in the non-mobile patient
    - Use enoxaparin SQ (if not available – use heparin SQ)
    - If neither can be used, apply sequential compression stockings
    - Institute early mobilization and early physical therapy
  - Infection prevention and treatment
    - Patients should be NPO until swallow screening is done
    - Avoid multi-day use of in-dwelling urinary catheters
    - Treat infections early with antibiotics
    - Treat fever with acetaminophen and/or a cooling blanket
  - Cerebral edema and hemorrhagic transformation
    - Obtain emergent head CT in the event of neurological worsening
    - Neurosurgical consultation may be needed for impending herniation syndrome, obstructive hydrocephalus, or hemorrhage with mass effect and neurological worsening
    - Measures to reduce intracranial pressure also include intubation with hyperventilation and osmotherapy (such as IV mannitol)

- See Table 2.2 for in-patient testing for stroke/TIA etiology
- Stroke preventative treatment in the hospital
  - Many preventative measures should be started in the hospital
  - Medicine for chronic hypertension can be started while the patient is still hospitalized
  - Anticoagulation can be started while the patient is still hospitalized in the setting of a TIA.
  - When to start AC in the setting of an ischemic stroke is controversial.

Table 2.2 In-hospital testing for ischemic stroke/TIA etiology

It is best to order all appropriate tests on the day of admission to avoid delay in treatment or hospitalization. TIA patients, within 3 days of their event, should be admitted to undergo an expedited evaluation.

- Brain MRI (no contrast agent is required unless a tumor is suspected)
- Vascular imaging
  - MRA (with contrast) or CTA of head and neck vessels
  - Carotid duplex is reasonable to:
    - Evaluate carotids in the setting of an anterior circulation ischemic stroke or TIA
    - Confirm a result obtained by CTA or MRA
- Transthoracic echocardiogram (TTE)
  - May add 'bubble study' of PFO detection sought
  - May order transesophageal echocardiogram (TEE) if cardio/aorto-embolic source suspected despite normal TTE.
- Blood testing:
  - Standard testing includes: CBC with differential, ESR, BUN, creatinine, PT, aPTT, blood glucose, hemoglobin A1c, fasting lipid profile, RPR, and FTA.
  - Suspected atherosclerosis: add homocysteine level, C-reactive protein
  - Suspected hypercoagulable state: see Chapter 10
  - Fever with concern for endocarditis: perform multiple blood cultures

- Significant carotid stenosis, if referable to a patient's symptoms, should be treated within 2 weeks of a TIA. CEA is probably a better choice than angioplasty with stenting.
- If significant carotid stenosis is related to an ischemic stroke, many surgeons/interventional radiologists will wait a few weeks before treating to avoid exacerbation of cerebral edema and/or risk of reperfusion hemorrhage.
- If LDL >100 mg/dL (>70 mg/dL if more than one stroke risk factor) then beginning treatment with a statin is indicated.
- Smoking cessation counseling, programs, and medications should be offered to patients who smoke.
- If a patient is not on anticoagulation, they should be discharged on an antiplatelet medication (aspirin, Aggrenox, Plavix).

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Chapter 3
Ischemic Stroke and Transient Ischemic Attack: Long-Term Management and Secondary Prevention

Holly E. Hinson and John W. Cole

Introduction

Stroke is the third leading cause of death and the primary cause of long-term disability in the United States [1]. Each year about 700,000 people experience a new or recurrent stroke. About 500,000 of these are first strokes, and 200,000 are recurrent strokes. Stroke accounted for about one of every 16 deaths in the United States in 2004 [2]. Given these dramatic numbers, prevention should be aggressively pursued in every patient after stroke. Clinicians must identify the patient's modifiable risk factors and work both continually and aggressively with the patient to optimize the risk factor profile. This often includes eliminating behavioral risk factors (poor diet, smoking, sedentary lifestyle, etc.) and implementing pharmacologic therapies to combat known vascular risk conditions [3] (hypertension, diabetes, hyperlipidemia, etc.). The physician and patient alike must understand that this is not a one time intervention, but rather a *lifelong* effort to continually optimize the patient's vascular risk factor profile. Figure 3.1 lists numerous vascular risk factors including established risk estimates (odds ratios for ischemic stroke) and the prevalence of each risk factor within the US population. As risk factors act synergistically with one another, the effects of individual risk factor estimates tend to multiply rather than add. Therefore, a patient's cumulative risk estimate is higher than the sum of the individual risk estimates. Table 3.1 provides a succinct listing of the current American Heart Association Guidelines for the prevention of secondary stroke [4]. These guidelines should be applied to all survivors of ischemic stroke or transient ischemic attack.

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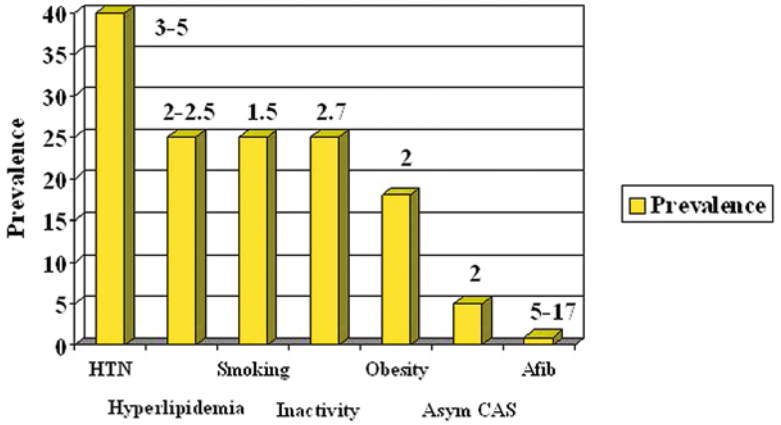

Fig. 3.1 Ischemic stroke risk factors illustrating prevalence and increased risk (odds ratio)

Table 3.1 Secondary prevention guidelines: current AHA/ASA guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack

Risk factor	Recommendation
Treatable vascular risk factors	
Hypertension	1. Antihypertensive treatment is recommended for prevention of recurrent stroke and other vascular events in persons who have had an ischemic stroke and are beyond the hyperacute period. 2. Because this benefit extends to persons with and without a history of hypertension, this recommendation should be considered for all ischemic stroke and TIA patients. 3. An absolute target BP level and reduction are uncertain and should be individualized, but benefit has been associated with an average reduction of $\approx$ 10/5 mmHg and normal BP levels have been defined as <120/80 mmHg by JNC-7. 4. Several lifestyle modifications have been associated with BP reductions and should be included as part of a comprehensive approach to antihypertensive therapy. 5. Optimal drug regimen remains uncertain; however, available data support the use of diuretics and the combination of diuretics and an ACEI. Choice of specific drugs and targets should be individualized on the basis of reviewed data and consideration, as well, of specific patient characteristics (e.g., extracranial cerebrovascular occlusive disease, renal impairment, cardiac disease, and DM).
Diabetes	1. More rigorous control of blood pressure and lipids should be considered in patients with diabetes.

Table 3.1 (continued)

Risk factor	Recommendation
	2. Although all major classes of antihypertensives are suitable for the control of BP, most patients will require >1 agent. ACEIs and ARBs are more effective in reducing the progression of renal disease and are recommended as first-choice medications for patients with DM. 3. Glucose control is recommended to near-normoglycemic levels among diabetics with ischemic stroke or TIA to reduce microvascular complications. 4. The goal for Hb A_{1c} should be $\leq$7%
Cholesterol	1. Ischemic stroke or TIA patients with elevated cholesterol, comorbid CAD, or evidence of an atherosclerotic origin should be managed according to NCEP III guidelines, which include lifestyle modification, dietary guidelines, and medication recommendations. 2. Statin agents are recommended, and the target goal for cholesterol lowering for those with CHD or symptomatic atherosclerotic disease is an LDL-C of <100 mg/dL and LDL-C <70 mg/dL for very-high-risk persons with multiple risk factors. 3. Patients with ischemic stroke or TIA presumed to be due to an atherosclerotic origin but with no preexisting indications for statins (normal cholesterol levels, no comorbid CAD, or no evidence of atherosclerosis) are reasonable to consider for treatment with a statin agent to reduce the risk of vascular events. 4. Ischemic stroke or TIA patients with low HDL-C may be considered for treatment with niacin or gemfibrozil.
Modifiable behavioral risk factors	
Smoking	1. All ischemic stroke or TIA patients who have smoked in the past year should be strongly encouraged not to smoke. 2. Avoid environmental smoke. 3. Counseling, nicotine products, and oral smoking cessation medications have been found to be effective for smokers.
Alcohol	1. Patients with prior ischemic stroke or TIA who are heavy drinkers should eliminate or reduce their consumption of alcohol. 2. Light to moderate levels of $\leq$2 drinks per day for men and 1 drink per day for non-pregnant women may be considered.
Obesity	1. Weight reduction may be considered for all overweight ischemic stroke or TIA patients to maintain the goal of a BMI of 18.5–24.9 kg/m^2 and a waist circumference of <35 in. for women and <40 in. for men. Clinicians should encourage weight management through an appropriate balance of caloric intake, physical activity, and behavioral counseling.

Table 3.1 (continued)

Risk factor	Recommendation
Physical Activity	1. For those with ischemic stroke or TIA who are capable of engaging in physical activity, at least 30 min of moderate intensity physical exercise most days may be considered to reduce risk factors and comorbid conditions that increase the likelihood of recurrence of stroke. For those with disability after ischemic stroke, a supervised therapeutic exercise regimen is recommended.
Interventional approaches to patients with stroke caused by large-artery atherosclerotic disease	
Extracranial carotid disease	1. For patients with recent TIA or ischemic stroke within the last 6 months and ipsilateral severe (70–99%) carotid artery stenosis, CEA is recommended by a surgeon with a perioperative morbidity and mortality of <6%. 2. For patients with recent TIA or ischemic stroke and ipsilateral moderate (50–69%) carotid stenosis, CEA is recommended, depending on patient-specific factors such as age, gender, comorbidities, and severity of initial symptoms. 3. When degree of stenosis is <50%, there is no indication for CEA. 4. When CEA is indicated, surgery within 2 weeks rather than delayed surgery is suggested. 5. Among patients with symptomatic severe stenosis (>70%) in whom the stenosis is difficult to access surgically, medical conditions are present that greatly increase the risk for surgery, or when other specific circumstances exist such as radiation-induced stenosis or restenosis after CEA, CAS is not inferior to endarterectomy and may be considered. 6. CAS is reasonable when performed by operators with established periprocedural morbidity and mortality rates of 4–6%, similar to that observed in trials of CEA and CAS. 7. Among patients with symptomatic carotid occlusion, EC/IC bypass surgery is not routinely recommended.
Extracranial vertebrobasilar disease	1. Endovascular treatment of patients with symptomatic extracranial vertebral stenosis may be considered when patients are having symptoms despite medical therapies (antithrombotics, statins, and other treatments for risk factors).
Intracranial arterial disease	1. The usefulness of endovascular therapy (angioplasty and/or stent placement) is uncertain for patients with hemodynamically significant intracranial stenoses who have symptoms despite medical therapies (antithrombotics, statins, and other treatments for risk factors) and is considered investigational.

Table 3.1 (continued)

Risk factor	Recommendation
Cardioembolic stroke and valvular heart disease	
Atrial fibrillation	1. For patients with ischemic stroke or TIA with persistent or paroxysmal (intermittent) AF, anticoagulation with adjusted-dose warfarin (target INR, 2.5; range, 2.0–3.0) is recommended. 2. In patients unable to take oral anticoagulants, aspirin 325 mg/d is recommended.
Acute MI and LV thrombus	1. For patients with an ischemic stroke caused by an acute MI in whom LV mural thrombus is identified by echocardiography or another form of cardiac imaging, oral anticoagulation is reasonable, aiming for an INR of 2.0–3.0 for at least 3 months and up to 1 year. 2. Aspirin should be used concurrently for the ischemic CAD patient during oral anticoagulant therapy in doses up to 162 mg/d, preferably in the enteric-coated form.
Cardiomyopathy	1. For patients with ischemic stroke or TIA who have dilated cardiomyopathy, either warfarin (INR, 2.0–3.0) or antiplatelet therapy may be considered for prevention of recurrent events.
Rheumatic mitral valve disease	1. For patients with ischemic stroke or TIA who have rheumatic mitral valve disease, whether or not AF is present, long-term warfarin therapy is reasonable, with a target INR of 2.5 (range, 2.0–3.0). 2. Antiplatelet agents should not be routinely added to warfarin in the interest of avoiding additional bleeding risk. 3. For ischemic stroke or TIA patients with rheumatic mitral valve disease, whether or not AF is present, who have a recurrent embolism while receiving warfarin, adding aspirin (81 mg/d) is suggested.
Mitral valve prolapse (MVP)	1. For patients with MVP who have ischemic stroke or TIAs, long-term antiplatelet therapy is reasonable.
Mitral annular calcification (MAC)	1. For patients with ischemic stroke or TIA and MAC not documented to be calcific antiplatelet therapy may be considered. 2. Among patients with mitral regurgitation resulting from MAC without AF, antiplatelet or warfarin therapy may be considered.
Aortic valve disease	1. For patients with ischemic stroke or TIA and aortic valve disease who do not have AF, antiplatelet therapy may be considered.
Prosthetic heart valves	1. For patients with ischemic stroke or TIA who have *modern mechanical prosthetic heart valves*, oral anticoagulants are recommended, with an INR target of 3.0 (range, 2.5–3.5). 2. For patients with *mechanical prosthetic heart valves* who have an ischemic stroke or systemic embolism despite

Table 3.1 (continued)

Risk factor	Recommendation
	adequate therapy with oral anticoagulants, aspirin 75–100 mg/d, in addition to oral anticoagulants, and maintenance of the INR at a target of 3.0 (range, 2.5–3.5) is reasonable. 3. For patients with ischemic stroke or TIA who have *bioprosthetic heart valves* with no other source of thromboembolism, anticoagulation with warfarin (INR, 2.0–3.0) may be considered.
Recommendations for antithrombotic therapy for noncardioembolic stroke or TIA	
	1. For patients with noncardioembolic ischemic stroke or TIA, antiplatelet agents rather than oral anticoagulation are recommended to reduce the risk of recurrent stroke and other cardiovascular events. 2. Aspirin (50–325 mg/d), the combination of aspirin and extended-release dipyridamole, and clopidogrel are all acceptable options for initial therapy. 3. Compared with aspirin alone, both the combination of aspirin and extended-release dipyridamole and clopidogrel are safe. The combination of aspirin and extended-release dipyridamole is suggested over aspirin alone. 4. Clopidogrel may be considered over aspirin alone on the basis of direct-comparison trials. Insufficient data are available to make evidence-based recommendations with regard to choices between antiplatelet options other than aspirin. Selection of an antiplatelet agent should be individualized based on patient risk factor profiles, tolerance, and other clinical characteristics. 5. Addition of aspirin to clopidogrel increases the risk of hemorrhage and is not routinely recommended for ischemic stroke or TIA patients. 6. For patients allergic to aspirin, clopidogrel is reasonable. 7. For patients who have an ischemic cerebrovascular event while taking aspirin, there is no evidence that increasing the dose of aspirin provides additional benefit. Although alternative antiplatelet agents are often considered for noncardioembolic patients, no single agent or combination has been well studied in patients who have had an event while receiving aspirin.
Stroke patients with other specific conditions	
Arterial dissection	1. For patients with ischemic stroke or TIA and arterial dissection, warfarin for 3–6 months or antiplatelet agents are reasonable. 2. Beyond 3–6 months, long-term antiplatelet therapy is reasonable for most ischemic stroke or TIA patients. Anticoagulant therapy beyond 3–6 months may be considered among patients with recurrent ischemic events.

Table 3.1 (continued)

Risk factor	Recommendation
	3. For patients who have definite recurrent ischemic events despite antithrombotic therapy, endovascular therapy (stenting) may be considered. 4. Patients who fail or are not candidates for endovascular therapy may be considered for surgical treatment.
Patent foramen ovale (without atrial septal defect)	1. For patients with an ischemic stroke or TIA and a PFO, antiplatelet therapy is reasonable to prevent a recurrent event. 2. Warfarin is reasonable for high-risk patients who have other indications for oral anticoagulation such as those with an underlying hypercoagulable state or evidence of venous thrombosis. 3. Insufficient data exist to make a recommendation about PFO closure in patients with a first stroke and a PFO. PFO closure may be considered for patients with recurrent cryptogenic stroke despite medical therapy.
Hyperhomocysteinemia	1. For patients with an ischemic stroke or TIA and hyperhomocysteinemia (levels >10 μmol/L), daily standard multivitamin preparations are reasonable to reduce the level of homocysteine, given their safety and low cost. However, there is no evidence that reducing homocysteine levels will lead to a reduction of stroke occurrence.
Hypercoagulable states	
Inherited Thrombophilias	1. Patients with an ischemic stroke or TIA with an established inherited thrombophilia should be evaluated for deep venous thrombosis, which is an indication for short- or long-term anticoagulant therapy, depending on the clinical and hematologic circumstances. 2. Patients should be fully evaluated for alternative mechanisms of stroke. 3. In the absence of venous thrombosis, long-term anticoagulation or antiplatelet therapy is reasonable. 4. Patients with a history of recurrent thrombotic events may be considered for long-term anticoagulation.
Antiphospholipid antibody syndrome	1. For cases of cryptogenic ischemic stroke or TIA and positive APL antibodies, antiplatelet therapy is reasonable. 2. For patients with ischemic stroke or TIA who meet the criteria for the APL antibody syndrome with venous and arterial occlusive disease in multiple organs, miscarriages, and livedo reticularis, oral anticoagulation with a target INR of 2–3 is reasonable.
Sickle-cell disease	1. For adults with SCD and ischemic stroke or TIA, general treatment recommendations cited above are applicable with regard to the control of risk factors and use of antiplatelet agents.

Table 3.1 (continued)

Risk factor	Recommendation
	2. Additional therapies that may be added include regular blood transfusion to reduce Hb S to <30–50% of total Hb, hydroxyurea, or bypass surgery in cases of advanced occlusive disease.
Cerebral venous sinus thrombosis	1. For patients with cerebral venous sinus thrombosis, UFH or LMWH is reasonable even in the presence of hemorrhagic infarction. 2. Continuation of anticoagulation with an oral anticoagulant agent is reasonable for 3–6 months, followed by antiplatelet therapy.
Pregnancy	1. For pregnant women with an ischemic stroke or TIA and high-risk thromboembolic conditions such as known coagulopathy or mechanical heart valves, the following options may be considered: A. Adjusted-dose UFH throughout pregnancy such as a subcutaneous dose every 12 h with APTT monitoring; Adjusted-dose LMWH with factor Xa monitoring throughout pregnancy; or UFH or LMWH until week 13, followed by warfarin until the middle of the third trimester, when UFH or LMWH is then reinstituted until delivery. B. Pregnant women with lower-risk conditions may be considered for treatment with UFH or LMWH in the first trimester, followed by low-dose aspirin for the remainder of the pregnancy.
Postmenopausal HRT	For women with stroke or TIA, postmenopausal HRT is not recommended.
Cerebral hemorrhage	1. For patients who develop an ICH, SAH, or SDH, all anticoagulants and antiplatelets should be discontinued during the acute period for at least 1–2 weeks after the hemorrhage and the anticoagulant effect reversed immediately with appropriate agents (i.e., vitamin K, FFP). 2. For patients who require anticoagulation soon after a cerebral hemorrhage, intravenous heparin may be safer than oral anticoagulation. Oral anticoagulants may be resumed after 3–4 weeks, with rigorous monitoring and maintenance of INRs in the lower end of the therapeutic range. 3. Special circumstances: a. Anticoagulation should not be resumed after an SAH until the ruptured aneurysm is definitively secured. b. Patients with lobar ICHs or microbleeds and suspected CAA on MRI may be at a higher risk for recurrent ICH if anticoagulation needs to be resumed. c. For patients with hemorrhagic infarction, anticoagulation may be continued, depending on the specific clinical scenario and underlying indication for anticoagulant therapy.

Traditional Risk Factors

Hypertension – Blood pressure (BP) is a powerful determinant of stroke risk. Subjects with BP less than 120/80 mmHg have about half the lifetime risk of stroke compared to subjects with hypertension [5]. Several trials have looked at various classes of anti-hypertensives and their relationship to BP reduction and its affect on stroke risk. One notable trial, the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) examined BP regimens including an angiotensin converting enzyme inhibitor (ACEI). The combination of an ACEI plus the diuretic indapamide lowered BP by an average of 12/5 mmHg and resulted in a 43% reduction in the risk of recurrent stroke with beneficial effects present in both hypertensive and normotensive subjects [6]. This study underscores the point that even modest reductions in BP can profoundly positively affect a person's stroke risk. The American Stroke Association (ASA) guidelines recommend anti-hypertensive treatment for both the prevention of recurrent stroke and the prevention of other vascular events in persons who have had an ischemic stroke or TIA, and who are beyond the hyper-acute period, even if these patients were not known to be previously hypertensive. BP goals should be tailored to each individual patient. The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) [3] defines BP goals as $<$140/90 mmHg for most patients, and $<$130/80 mmHg for patients with diabetes or chronic kidney disease. Although it remains unclear if agent specific benefits exist, it is well established that continuous and aggressive BP control decreases both primary and secondary stroke risk.

Hyperlipidemia – The direct link between elevated cholesterol and stroke is less definite than the link between elevated cholesterol and heart disease. A recent meta-analysis examining the connection between statins and stroke prevention concluded that statins reduce the relative risk of stroke in patients with underlying coronary artery disease by 26% [7]. Additional support in favor of statin use in patients after stroke with or without hyperlipidemia came from the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial. In the study, patients treated with atorvastatin 80 mg reduced their LDL cholesterol levels 37%, from 133 mg/dL at baseline to 73 mg/dL, which translated into a 16% reduction in the primary end point of non-fatal or fatal stroke over a 5-year period [8]. American Heart Association (AHA) guidelines recommend that patients with stroke and either co-morbid coronary artery disease with elevated lipids or evidence of an atherosclerotic origin of their stroke be treated with statins. Lipid goals include a total cholesterol of 200 mg/dL or less and low-density lipoprotein (LDL) of 100 mg/dL or less. Diabetics are generally treated more aggressively, with recent guidelines suggesting LDL levels of 70 mg/dL or less as optimal [9].

Diabetes mellitus – Diabetics have a 1.5–2.5 greater risk for ischemic stroke. Up to one third of patients with ischemic stroke are diabetic [10]. Likewise, the

metabolic syndrome as defined by insulin resistance, abdominal obesity based on waist circumference, hypertriglyceridemia, low HDL cholesterol, and hypertension is significantly associated with stroke (OR, 2.16; 95% CI, 1.48–3.16), including adjustment for age, sex, race, and cigarette smoking [11]. Secondary prevention in diabetic patients should be particularly aggressive. Optimization of glycemic control, BP and lipids are critical. While there is data to support that tight glycemic control reduces small vessel (microvascular) complications, there is less of a direct link between glycemic control and large vessel (macrovascular) complications. However, patients should be encouraged to check their serum glucose frequently and adhere to an appropriate medical therapy regimen. Recommended hemoglobin A1C values should be 7% or less. AHA guidelines also recommend rigorous control of BP within diabetics via the use of ACEIs and angiotensin receptor blockers (ARBs) as these agents have been shown to slow the progress of renal disease, and should be considered as first line agents [12]. As already mentioned, diabetics are encouraged to aggressively lower their cholesterol values. The Heart Protection Study suggested an additional benefit to diabetics taking statins, specifically that Simvastatin was associated with a 28% reduction in ischemic strokes in diabetics over placebo independent of the patient's baseline LDL measurement [13].

Smoking status – Any amount of smoking is detrimental to the vascular system and increases stroke risk. Therefore, smoking cessation should be aggressively pursued among all patients. Smoking is thought to increase risk by a combination of injury to the vascular wall inducing inflammation and atherosclerosis, and by inducing a hypercoagulable state. Cigarette smoke contains over 4000 different chemical compounds that are absorbed into the blood stream and distributed throughout the body via the vascular system. Many of these compounds can act as free radicals initiating undesirable chemical reactions, with several of these chemicals known to be directly toxic to the endothelium. Patients should be told that smoking increases the risk of ischemic stroke by 50%; and that of subarachnoid hemorrhage (SAH) by 100%. Furthermore, a dose–response relationship exists between smoking and stroke risk. In other words, "*the more you smoke, the more you stroke*". The relative risk of stroke in heavy smokers (more than 40 cigarettes a day) is twice that of light smokers (less than ten cigarettes per day). On a positive note, stroke risk decreases significantly 2 years after cessation of cigarette smoking and is at the level of non-smokers by 5 years [14]. Smoking cessation is critical and should be encouraged in all patients. Furthermore, second hand tobacco smoke exposure should also be minimized. Pharmacologic and behavioral interventions can be implemented (Varenicline, Bupropion), as well as nicotine replacement therapies (gum, patch).

Obesity – While the link between obesity and other stroke risk factors such as hypertension and dyslipidemia has been demonstrated, a direct link between obesity and ischemic stroke has not been definitively shown in all groups. In men, obesity seems to be an independent risk factor for ischemic stroke [15], whereas in women the data have been less consistent. Additionally, weight loss

has never been demonstrated to decrease stroke risk. More attention is now being placed on the metabolic syndrome, which includes abdominal obesity. Waist circumference of >102 cm (40 in.) in men and 88 cm (35 in.) was an independent risk factor for stroke across racial groups in the Northern Manhattan Stroke Study [16]. A desirable body mass index (BMI) of 18.5–24.9 kg/m^2 and desirable waist circumference of <35 in. for women and <40 in. for men should be encouraged for patients after ischemic stroke.

Racial factors – Blacks have almost twice the risk of first-ever stroke compared with whites. Moreover, blacks have more than twice the age-adjusted death rate and estimated years of potential life lost from stroke when compared with whites [17, 18]. Some studies suggest these striking numbers might be related to a higher prevalence of risk factors among blacks. An analysis of stroke risk factor profiles in black subjects with previous ischemic stroke enrolled in the African American Antiplatelet Stroke Prevention Study found that 76% were overweight or obese (70% of men and 81% of women), and that hypertension, dyslipidemia, and type 2 diabetes mellitus were present in 43% of the men and 29% of the women in the obese category [19]. Although ethnicity itself cannot be modified, clinicians should be mindful of these statistics when planning risk factor modifying strategies with their patients.

Atrial fibrillation – Atrial fibrillation (AF) is an independent risk factor for stroke, increasing risk about fivefold in patients with non-valvular AF [20]. Patients with AF and valvular heart disease such as mitral valve stenosis are at even greater risk [2]. The standard of care established through multiple investigations consists of anticoagulation with warfarin, with a goal INR of between 2.0 and 3.0. Warfarin reduces the relative risk of ischemic stroke or systemic embolization by almost two thirds as compared with placebo [21]. The patients most at risk for thromboembolic complications are those with (a) a previous stroke, TIA or thromboembolic event; (b) age greater than 75 and an additional co-morbidity such as hypertension, diabetes, or vascular disease; and (c) clinical evidence of valvular disease or heart failure. These patients should be anticoagulated unless it is contraindicated. Contraindications include a prior intracranial hemorrhage or poor compliance. In patients for whom warfarin cannot be given, aspirin or other antiplatelet therapy should be administered. Patients with atrial flutter should be given antithrombotic treatment in a similar manner [2]. Anticoagulation is generally life-long or until contraindicated by a change in the patient's medical status. Clinicians should be mindful of developing dementia, propensity to falls, or other potential trauma among all patients on warfarin therapy. Concern for any of these may necessitate limiting treatment to antiplatelet therapy. As stroke preventatives, antiplatelets and warfarin should not be given simultaneously. Among patients with AF, the risk of ICH for aspirin monotherapy is approximately 0.3% per year compared with 0.5% per year for warfarin monotherapy [22]. One final caveat regarding anticoagulation in the setting of atrial fibrillation relates to the need for a short-term discontinuance of therapy in the setting of a pending medical or dental procedure. All patients will at some time need to transiently stop their anticoagulation therapy for one

reason or another. When these situations arise, it becomes important to contact the treating neurologist for recommendations. In general, we recommend limiting time off anticoagulation therapy to as short a time as possible. In concerning cases, such as atrial fibrillation in the setting of a low ejection fraction as an example, patients should be treated with short half life anticoagulation (low molecular weight heparin) up until the procedure and then after the procedure until goal INR has been re-attained.

Emerging Risk Factors and Special Considerations

Intracranial stenosis – The Warfarin–Aspirin Symptomatic Intracranial Disease Study (WASID) randomized patient's with intracranial stenosis of 50–99% of a major intracranial artery to receive warfarin (target international normalized ratio, 2.0–3.0) or aspirin (1,300 mg per day) in a double-blind, multicenter clinical trial. The study found that patients treated with warfarin were more likely to suffer an adverse complication such as death, major hemorrhage, myocardial infarction or sudden death than those randomized to aspirin. Additionally, warfarin showed no added benefit in preventing ischemic stroke over aspirin in the trial [23]. While the study dose of aspirin (1,300 mg per day) does not reflect common clinical practice, in cases of severe stenosis this may be appropriate; however, aspirin (325 mg per day) or aspirin-extended-release dipyridamole combination therapy remain the recommended treatments of choice for intracranial stenosis. Interestingly, the practice of permissive hypertension to prevent worsening ischemia in the territory of the stenotic artery has been shown to be more harmful than helpful. A recent study demonstrated in patients with intracranial stenosis, higher BP is associated with increased (not decreased) risk of ischemic stroke and increased stroke in the territory of the stenotic vessel. These findings argue strongly against the common clinical practice of maintaining high BP in patients with intracranial stenosis [24].

Obstructive sleep apnea – In a recent observational cohort study, sleep apnea conferred an increased risk for stroke or death (hazard ratio, 1.97; 95% CI, 1.12–3.48; $P = 0.01$), even when adjusted for age, sex, and co-morbidities [25]. Sleep apnea is associated with several processes that promote cardiovascular disease such as endothelial dysfunction, increased inflammatory mediators, and increased pro-thrombotic factors, specifically enhanced platelet aggregation and activity [26, 27]. Additionally, obstructive apnea has been shown to increase intracranial pressure and decrease cerebral blood flow [28]. These mechanisms could potentially explain the link between sleep apnea and ischemic stroke, but no direct causal link has been rigorously shown at present [29]. It is not known if CPAP therapy directly decreases a patient's stroke risk; however, CPAP has been shown to decrease BP [30]. Patients with a history of snoring, and/or excessive daytime fatigue in the setting of snoring, should be screened for sleep apnea and treated if the condition is present.

Patent foramen ovale – Patent foramen ovale (PFO), the persistence of an embryonic defect in the interatrial septum, is present in up to 27% of the general population [31]. Atrial septal aneurysms (ASA), defined as >10-mm excursions of the interatrial septum, are less common, affecting ~2% of the population. Therapeutically, patients with PFO should be classified into one of two categories: (1) PFO *without* atrial septal aneurysm (ASA) who should be treated with antiplatelet therapy, or; (2) PFO *with* ASA who should be treated with anticoagulation. Furthermore, anticoagulation is reasonable for high-risk patients who have other indications for oral anticoagulation such as those with an underlying hypercoagulable state or evidence of venous thrombosis. These PFO patients are susceptible to paradoxical embolism. Historically, several studies suggested PFO was an important cause of cryptogenic stroke [32]. In contrast, other studies, including a recent large population-based study, demonstrated that PFO was not a risk factor for cryptogenic ischemic stroke or transient ischemic attack [33]. Although the literature is conflicting, treatment as described earlier is common within the stroke community. In all cases of stroke with PFO (+/– ASA), vascular neurology, and cardiology input should be sought.

Anti-phospholipid antibodies – Anti-phospholipid antibodies (aPL) have been associated with hypercoagulability and subsequent thrombotic events. The association between aPL antibodies and stroke is strongest for adults <50 years of age [34].

Anti-phospholipid antibody prevalence ranges from 1 to 6.5%, higher in the elderly and in patients with lupus [35]. The aPL antibody syndrome consists of venous and arterial occlusive disease in multiple organs, miscarriages, and livedo reticularis [36].

The Anti-phospholipid antibodies and stroke investigators (APASS) concluded that the mere presence of anti-phospholipid antibodies in patients with ischemic strokes did not predict increased risk for subsequent vascular occlusive events over 2 years. Additionally, patients with aPL did not have a differential response to aspirin or warfarin than the aPL negative group. The authors concluded that routine screening for aPL in patients with ischemic stroke was not indicated [37]. However, a screening test is recommended for young stroke patients with a paucity of standard risk factors, or in a stroke patient who has a prior history of venous occlusion, particularly in the setting of a PFO. Recommendations regarding stroke prevention indicate that for cases of cryptogenic ischemic stroke or TIA and positive APL antibodies, antiplatelet therapy is reasonable. For patients with ischemic stroke or TIA who meet the criteria for the APL antibody syndrome, oral anticoagulation with a target INR of 2–3 is reasonable.

Homocysteine – Elevated homocysteine has been observed in patients with cardiovascular disease, particularly ischemic stroke, leading to the hypothesis that lowering serum homocysteine levels might confer some protective effect against stroke. In the Vitamin Intervention for Stroke Prevention (VISP) study, low and high doses of folic acid, pyridoxine (vitamin B_6), and cobalamin

(vitamin B_{12}), were given to lower total homocysteine levels in patients with prior ischemic stroke. The mean reduction of total homocysteine was 2 μmol/L greater in the high-dose group than in the low-dose group, but there was no treatment effect on any end point, including recurrent ischemic stroke [38].

At present, it is unclear what role homocysteine plays in ischemic stroke, whether it serves as a biomarker for cardiovascular disease or can be implicated in the pathophysiology of the disease. Current recommendations are that for patients with ischemic stroke or TIA and hyperhomocysteinemia (levels >10 μmol/L), daily standard multivitamin preparations with adequate B_6 (1.7 mg/d), vitamin B_{12} (2.4 μg/d), and folate (400 μg/d) are reasonable to reduce the level of homocysteine, given their safety and low cost. However, there is no evidence that reducing homocysteine levels will lead to a reduction in stroke recurrence.

Sickle cell anemia – For children and adults, stroke can be a complication of sickle cell anemia. Ischemic strokes may occur both due to progressive blockage of large arteries or due to the hypercoagulable state of sickle cell disease. Progressive blockage of the large arteries around the circle of Willis (moyamoya changes) can be accompanied by the development of fine neovascularization in the brain. These finer blood vessels can rupture and produce hemorrhages. In the Stroke Prevention in Sickle Cell Anemia (STOP I) trial, children were screened with transcranial doppler to monitor intracranial blood flow velocities. Those with elevated flow velocities on TCD were randomized to either standard of care or serial blood transfusions. Subjects who received the serial transfusions were more than 90% less likely to experience stroke than those who received standard of care. Subjects who were not transfused had a 10% per year chance of stroke. As a result of this trial, it is recommended that children with sickle cell disease be systematically screened with transcranial doppler and those with elevated flow velocities be transfused [39].

Although sickle cell disease (SCD) is considered a hypercoagulable state, with stroke risk dependent on genotype, there has been no systematic experience with antiplatelet agents, anticoagulation, or anti-inflammatory agents for stroke prevention. For adults with SCD and ischemic stroke or TIA, general treatment recommendations emphasize the control of standard risk factors and the use of antiplatelet agents. Additional therapies that may be considered include regular blood transfusion (as mentioned earlier) to reduce hemoglobin S to <30–50% of total hemoglobin, hydroxyurea, or bypass surgery in cases of advanced occlusive disease.

Pregnancy – The risk of ischemic stroke or intracerebral hemorrhage during pregnancy and the first 6 weeks postpartum was 2.4 times greater than for nonpregnant women of similar age and race, according to the Baltimore–Washington Cooperative Young Stroke Study [40]. Although no formal guidelines exist, pregnant patients should modify and, if at all possible, eliminate risk factors for stroke. We particularly emphasize smoking cessation, which is known to contribute to a hypercoagulable state and is also directly toxic to the unborn fetus.

Current AHA guidelines indicate several options for pregnant women with ischemic stroke or TIA and high-risk thromboembolic conditions including

known coagulopathy or mechanical heart valves. In these situations the following options may be considered: (1) adjusted-dose unfractionated heparin (UFH) throughout pregnancy, e.g., a subcutaneous dose every 12 h with activated partial thromboplastin time monitoring; (2) adjusted-dose low molecular weight heparin (LMWH) with factor Xa monitoring throughout pregnancy, or: (3) UFH or LMWH until week 13, followed by warfarin anticoagulation until the middle of the third trimester, when UFH or LMWH is then reinstituted until delivery. Pregnant women with lower-risk conditions may be considered for treatment with UFH or LMWH in the first trimester, followed by low-dose aspirin for the remainder of the pregnancy. In complicated situations or high-risk patients, neurology, hematology, as well as high-risk obstetrical consultations are recommended.

Medical Therapy

Antiplatelet therapy – Antiplatelet agents have become the standard of care in stroke prevention except in instances where they are directly contraindicated or the patient requires anticoagulation for a specific condition. No benefit has been shown for combination antiplatelet therapy, including the combination of aspirin and clopidogrel. The MATCH trial evaluated the efficacy and safety of combined clopidogrel–aspirin therapy compared to clopidogrel therapy alone in high-risk patients with completed stroke or transient ischemic attack who also had one or more of five additional risk factors. The combined endpoint of ischemic stroke, myocardial infarction, vascular death, or recurrent hospitalization for an ischemic event was used. The study demonstrated an insignificant trend for greater efficacy with the combination therapy on the primary endpoint, but a highly statistically significant increased risk for life-threatening bleeding [41]. To emphasize, the addition of aspirin to clopidogrel increases the risk of hemorrhage and is not routinely recommended for ischemic stroke or TIA patients. However, in patients with an intra-arterial stent, the need for dual therapy to maintain stent patency may outweigh the risk of bleeding. Current AHA guidelines indicate that for patients with non-cardioembolic ischemic stroke or TIA, antiplatelet agents rather than oral anticoagulation are recommended to reduce the risk of recurrent stroke and other cardiovascular events. Aspirin (50–325 mg/d), the combination of aspirin and extended release dipyridamole, and clopidogrel are all acceptable options for initial therapy. Consider clopidogrel in aspirin intolerant patients, including those with aspirin allergies and gastrointestinal disorders.

Anticoagulation – Generally speaking, anticoagulation with agents such as warfarin for the long-term prevention of stroke is reserved for special cases. Several randomized trials have addressed the use of oral anticoagulants in stroke prevention among patients with non-cardioembolic stroke. The Warfarin–Aspirin Recurrent Stroke Study (WARSS) trial compared the effectiveness

of warfarin versus aspirin (325 mg) and demonstrated that warfarin was, in fact, no better than aspirin in preventing recurrent ischemic stroke. Regrettably, the treatment goals of the study included sub-optimal INR values between 1.4 and 2.8. The rates of major bleeding were not significantly different between the warfarin and aspirin groups (2.2 and 1.5% per year, respectively). A variety of subgroups were evaluated, with no evidence of efficacy observed across stroke subtypes, including large-artery atherosclerotic and cryptogenic categories [4]. Of note, the Warfarin–Aspirin Symptomatic Intracranial Disease (WASID) Study, mentioned earlier in this chapter, was stopped prematurely secondary to safety concerns among the warfarin treatment group. As mentioned previously, anticoagulation for the long-term prevention of stroke is reserved for special cases. Such cases include patients with atrial fibrillation or prosthetic heart valves. In cases of atrial fibrillation, the recommended INR goal is between 2.0 and 3.0 [4]. Regarding prosthetic heart valves, current guidelines recommend an INR of 2.5–3.5 for patients with mechanical prosthetic valves and 2.0–3.0 for those either with bioprosthetic valves or lower-risk patients with bileaflet mechanical valves (such as the St. Jude Medical device) in the aortic position [42].

In patients where anticoagulation is absolutely contraindicated, an antiplatelet agent should be substituted. A risk-benefit analysis should be conducted for each patient when a relative contraindication exists, such as increased fall risk. Risk factors for intracranial hemorrhage include advanced age, elevated BP, intensity of anticoagulation, and previous cerebral ischemia [43]. Anticoagulation is generally held for 2 weeks after ischemic stroke to reduce the risk for hemorrhagic transformation [44]. This waiting period may be extended if the ischemic stroke territory was very large or reduced slightly if recurrent ischemic stroke is of major concern. Patients with intracranial hemorrhage should not receive anticoagulation.

Statins – Statins reduce the incidence of strokes among patients who are at increased risk for cardiovascular disease through a variety of mechanisms including lowering total cholesterol and LDL. Recently, the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study investigated whether the administration of high-dose atorvostatin (80 mg) might reduce recurrent strokes. This was the first study to specifically investigate the effect of statins in patients with a prior stroke or transient ischemic attack (TIA) but with normal cholesterol levels and no evidence of coronary heart disease. Results showed that treatment with atorvastatin at a dose of 80 mg per day was associated with a 16% relative risk reduction for recurrent stroke in this population [8].

Estrogen – Estrogen does not protect against stroke, and in fact, may confer additional risk for ischemic stroke. The Women's Health Initiative primary prevention clinical trial found that among 16,608 women (95% of whom had no pre-existing cardiovascular disease) estrogen plus progestin (PremPro) increased ischemic stroke risk by 44%, with no effect on hemorrhagic stroke

[45]. Additionally, the Women's Estrogen for Stroke Trial (WEST) found that estrogen alone (1 mg of 17B-estradiol) in a group of women with a mean age of 71 years also had no significant overall effect on recurrent stroke or fatality, but there was an increased rate of fatal stroke and an early rise in overall stroke rate in the first 6 months [46]. Therefore, estrogen supplementation (hormone replacement therapy) should be avoided if at all possible, or used for the shortest period of time permissible, for menopausal symptoms.

Oral contraceptive pills – The amount of estrogen in oral contraceptive pills (OCP) has been shown to increase stroke risk in a dose-dependent fashion [47]. However, these studies included OCPs with much higher doses of estrogen than the low-dose estrogen OCPs now commonly used. The issue remains as to the safety of the low-dose estrogen formulations with respect to stroke risk. A recent meta-analysis of oral contraceptives and cardiovascular risk showed summary risk estimates associated with current use of low-dose oral contraceptives to be 2.12 (95% CI, 1.56, 2.86) for ischemic strokes [48]. On the other hand, another large meta-analysis, which aggregated data from 20 distinct populations (four cohort and 16 case-control studies) with the pooled OR from the cohort studies, demonstrated no increased stroke risk with OCP use (0.95; 95% CI, 0.51–1.78; $P = 0.01$), while the pooled OR from the case-control studies showed a significant association (2.13; 95% CI, 1.59–2.86; $P<0.001$). These mixed results cast doubt on the absolute risk of stroke associated with the use of low-dose OCPs [49]. At this time, the general consensus is that when considering current use of all forms of oral contraceptives, there is, overall, a small but significant increase in the risk of ischemic stroke. Importantly, past use of oral contraceptives is not associated with increased stroke risk. We refer readers to an excellent review of this topic at Medlink Neurology, entitled: "Oral contraceptives and stroke", Helms A, et. al., (http://www.medlink.com)

While the precise risk association between OCP use and stroke remains unclear, an important caveat should be addressed: women with migraines on OCPs must not smoke. Considerable evidence indicates a markedly elevated stroke risk in the setting of these three factors. A relatively recent review article eloquently summarizes the relationships between estrogens, migraine, and stroke according to age [50]:

Findings in women aged <50: (1) Thirty percent of women in this age category are affected by migraine. Migraines are strongly influenced by estrogens, as evidenced by their onset at puberty, the existence of menstrual migraine, and their tendency to improve during pregnancy. (2) Migraine is a risk factor for ischemic stroke, with a relative risk of 3. The risk is higher in migraine with aura and is further increased by tobacco smoking and OCP use. (3) The absolute risk of ischemic stroke is very low, and therefore there is no overall contraindication to OCP use in migraineurs but rather a firm recommendation that users not smoke and use either low-estrogen content pills or progestogen-only pills.

Findings in women after menopause: (1) Migraine improves in 50–60% of cases but tends to worsen with hormone replacement therapy. (2) Migraine is not proven as a risk factor for ischemic stroke in this population. (3) Stroke is very frequent in this population, affecting one of five women, and the risk is significantly increased by use of hormone replacement therapy (HRT). (4) There are no specific data thus far on the association between migraine and HRT in regard to the risk of stroke. Thus, migraine in itself is not a contraindication to the use of HRT and decisions should be made on a case-by-case basis.

Surgical Therapy

Carotid endarterectomy – Internal carotid artery stenosis (ICAS) is responsible for approximately 30% of ischemic strokes [51]. Multiple studies have shown the benefit of carotid endarterectomy (CEA) in symptomatic patients with high-grade ipsilateral carotid stenosis. The Asymptomatic Carotid Atherosclerosis Study (ACAS) evaluated CEA versus medical therapy in patients with asymptomatic ICAS with a degree of stenosis in the range of 60–99%. ACAS demonstrated a calculated 5-year relative risk reduction favoring surgery of 53% compared with medical therapy [52]. While this projection is impressive, the results are somewhat controversial. Follow-up studies have shown that the perioperative complication rate varies widely with the experience of the surgeon and the volume of procedures done at the institution in question [53]. Carotid endarterectomy for asymptomatic ICAS is likely only appropriate for patients with 80% or greater stenosis, who are medically stable enough for surgery, who are expected to live at least 5 years. Additionally, the procedure should only be performed by surgeons who have demonstrated a low complication rate (<3%). Carotid stenting is another intervention that is currently being investigated, however, data on the efficacy of the procedure are lacking at present. While stenting may represent a therapeutic option in select patients who are unable to undergo surgery, randomized trials comparing the safety and efficacy of the two procedures are ongoing. In a 2005 systematic review of five randomized trials comparing the two treatment options, there were no significant differences in major risks of the two treatments. However, the reviewers concluded more research is needed before carotid stenting can be recommended as the treatment of choice for suitable patients with carotid artery stenosis [54].

Lifestyle Interventions

Exercise – Several studies examine physical activity as not only a method of stroke prevention, but also a method of regaining function. A meta-analysis of reports of 31 observational studies conducted mainly in the United States

and Europe found that moderate and high levels of leisure-time and occupational physical activity protected against total stroke, hemorrhagic stroke, and ischemic stroke [55]. In an evaluation of walking and sports participation in 73,265 men and women in Japan, risk of stroke death was reduced by 29 and 20%, respectively, for those in the highest intensity activity category [56]. In a study of 47,721 men and women in Finland, significant trends toward lower stroke risk were associated with moderate and high levels of leisure-time physical activity and active commuting [57]. Bottom-line: moderate regular physical activity is beneficial and reduces the likelihood of incident and/or recurrent stroke. . .so get your patients (and yourself) moving!

In summary, the goal of this chapter is to educate the reader on methods of stroke prevention, through a review of the current evidence on stroke risk factors and therapeutic interventions that modify these risks.

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Chapter 4
Intracerebral Hemorrhage: Acute Evaluation and Management

David Alway

Intracerebral hemorrhage (ICH) refers to bleeding within the substance (parenchyma) of the brain. In this chapter, the term excludes bleeding into the epidural, subdural, or subarachnoid spaces.

Presenting Signs and Symptoms

As with ischemic stroke, there is a variety of possible presentations for intracerebral hemorrhage. A patient may present with the sudden onset of neurological dysfunction such as weakness, numbness, vision loss, diplopia, dysarthria, gait disorder, vertigo, aphasia, or disturbed level of consciousness. Many symptoms, while possibly occuring also in ischemic stroke, occur more frequently with ICH. These include headache (40% of patient presentations), nausea, and vomiting. In addition, patients with ICH are much more likely to present with a low level of consciousness and hypertension. Finally, the rapidity of neurological worsening is typically more marked than with ischemic strokes. For example, if the hemorrhage is large enough, pressure effects on the whole brain and brainstem may lead to a markedly diminished level of consciousness. Or a hemorrhage that begins small (2 cm in diameter) may enlarge over the first few hours to become massive. This will lead to a rapid worsening of symptoms, including, again, a rapid reduction in the patient's level of consciousness. In light of the similarities with ischemic stroke, imaging is always required to diagnose ICH.

Diagnostic Testing

A non-contrast head CT is the most reliable method for diagnosing ICH, due to its wide availability, accuracy, and speed. Its sensitivity is likely greater than 95% for ICH. The head CT will reveal blood in the parenchyma (bright signal,

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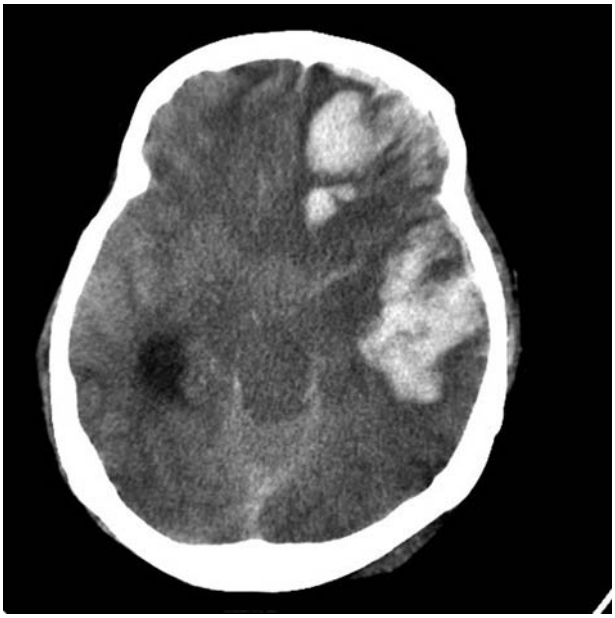

Fig. 4.1 Two regions of acute intracerebral hemorrhage

see Fig. 4.1). This blood sometimes also extends into the ventricular system. MRI is at least equivalent, and may even be superior, to head CT for the detection of ICH, but is typically not as rapid or as available.

Etiology/Pathophysiology

ICH is categorized into primary and secondary. Secondary causes of ICH include head trauma, cerebral amyloid angiopathy (CAA), vascular malformations, ruptured aneurysms, brain tumors, use of anticoagulant and thrombolytic agents, congenital and acquired bleeding disorders, use of sympathomimetic drugs, or prior/recent ischemic stroke in the same area. Hemorrhages associated with CAA are often in a superficial but still subcortical location (lobar) and there may be multiple lesions.

Primary ICH has no obvious cause although hypertension and age are its most important risk factors. Chronic hypertension is thought to cause lipohyalinosis, an arterial disorganization in the small (40–200 μm) diameter penetrating arteries in the brain, which may lead to weakness in the walls and their subsequent rupture. Primary ICH tends to be in the basal ganglia, thalamus, pons, internal capsule, or cerebellum. An ICH is probably primary if the following are found to be true:

(1) A thorough search for secondary causes was negative.
(2) The patient is known to have hypertension or has evidence on exam of end-organ damage from hypertension.
(3) The location of hemorrhage is typical for primary ICH.

Treatment

Despite advances in treatment, mortality from ICH remains high (about 50%) and many management issues are plagued with uncertainty, largely due to a paucity of relevant randomized controlled clinical trials. The remainder of this chapter addresses the treatment of primary ICH. Management of secondary ICH, such as the management of tumors or vascular malformations, is beyond the scope of this chapter.

Management of ICH is best viewed as a list of potential interventions, to be applied on a case-by-case basis. In addition, many serious complications can arise and suddenly take priority over other management concerns.

General Measures

All acute ICH patients should undergo brain imaging for initial diagnosis and blood work should be performed emergently to rule out a bleeding disorder (PT/PTT/CBC/fibrinogen level). If the hemorrhage is recent, patients should be admitted to an ICU and initially undergo frequent (per hour) neurological checks by nursing; physicians being alerted immediately in the event of neurological worsening. A repeat head CT (usually) or brain MRI (if immediately available) should be obtained whenever there is neurological worsening. A neurologist or neurointensivist consultation should always be obtained. Even if surgery for hematoma evacuation is not deemed appropriate, neurosurgical consultation is routinely obtained for medicolegal issues, in case hematoma evacuation is felt to be appropriate at a later time, and in anticipation of the need for surgical intervention to aid in the management of hydrocephalus or to establish intracranial pressure (ICP) monitoring. Steroids have no proven benefit in the management of ICH [1] and can damage patients due to a higher number of infections and elevated glucose [2]. Steroids may be indicated in cases of tumor with associated vasogenic edema. To prevent deep venous thromboses (DVTs), patients should be placed in compression stockings and intermittent pneumatic compression devices should be utilized.

Bleeding Disorders

A bleeding disorder should be reversed as rapidly as possible in the event of an acute ICH. If this is due to warfarin use or other causes of elevated PT/INR,

rapid infusion of fresh frozen plasma (FFP) and IV vitamin K administration is performed. Once normalized, periodic (at least every 6 h) retesting of PT/INR values is suggested in case the hypercoagulable state re-emerges. Platelets are administered if thrombocytopenia is discovered. A hematologist may be required to address unusual causes of bleeding disorders.

Blood Pressure

It is controversial how best to manage blood pressure acutely after ICH. An elevated blood pressure is a theoretical contributor to enlargement of the hematoma, and is associated with a worse prognosis. The American Stroke Association guidelines [3] recommend that, for patients with a history of hypertension, mean arterial pressure be kept below 130 mmHg within 24 h of the event. This is not appropriate, though, in cases of elevated ICP. If ICP is known or suspected to be elevated, it is more important to prevent widespread ischemia by keeping cerebral perfusion pressure (mean arterial pressure minus ICP) at least above 70 mmHg.

Fever

Fever has been shown to worsen outcomes in cases of ICH [4]. Temperatures above 101°F (38.5°C) should be treated with acetaminophen and, if necessary, cooling blankets should be used. A search for infections should be sought and antibiotics should be instituted to treat known or suspected infections.

Hyperglycemia

Elevated blood sugars are associated with worse outcomes in ICH [5]. It is still unknown whether elevated glucose causes worse prognosis or whether the ICH itself leads to a stress reaction, contributing to elevated blood glucose. Some institutions intervene aggressively, with use of intravenous insulin if necessary, in order to rapidly lower blood glucose levels, in cases of acute ICH. It would seem prudent to control blood glucose, but the overall effect on ICH outcome is still unknown.

Seizure Prophylaxis

Seizures occur in 6–7% of ICH patients. They are more likely to occur the closer the hemorrhage is to the cerebral cortex. While seizures should be treated when documented or suspected (see Section Seizures and Status Epilepticus later in this chapter) the role of seizure prophylaxis, in the absence of observed seizure

activity, is not established. In light of the potentially adverse effects of seizures (initial hypertension possibly followed by hypotension, increased ICP, hypoxia, aspiration pneumonia) it would seem prudent to prophylax against them. Many antiepileptic drugs can be used, but medications available in intravenous form have the advantage of being usable in patients with a poor level of consciousness, allow bypass of a potentially poorly functioning gastrointestinal system, and allow for a rapid attainment of adequate blood levels. The most commonly used antiepileptic drug in this context is phenytoin (Dilantin) or fosphenytoin (Cerebyx), but levetiracetam (Keppra) or valproate sodium (Depacon) are also reasonable alternatives. Once an intravenous load has been performed, maintenance dosing should be instituted. If no seizures occur after 1 month, it is reasonable to discontinue the antiepileptic drug.

Surgical Intervention for Hematoma Evacuation

The indications for surgical hematoma evacuation depend on its location.

Cerebellar Hemorrhages

Surgery for cerebellar hemorrhages is indicated in many circumstances. Most expert neurologists and neurosurgeons agree that if operated on before coma develops, surgical evacuation of cerebellar hematomas is often life-saving and patients tend to have good outcomes with minimal long-term disability. Indeed, lesions of this type are generally excluded from randomized studies of surgical intervention for ICH. The American Stroke Association guidelines [6] recommend that cerebellar hematomas that are greater than 3 cm in diameter, in patients who are neurologically worsening, or which are leading to hydrocephalus or early brainstem compression, should undergo emergent surgical evacuation.

Supratentorial Hemorrhages

There are few firm recommendations regarding surgical intervention for supratentorial hemorrhages. Many surgeons have tended to avoid surgical hematoma evacuation for small deep hematomas in patients without signs of increased ICP or clinical worsening, but felt more comfortable evacuating hematomas in patients who are clinically worsening or who have more superficial/accessible hematomas and significant neurological disability. A recently completed randomized study [7] compared best medical management to early (within 24 h of randomization) surgical evacuation for supratentorial hemorrhages. Surgeons were allowed to use whatever techniques they felt were indicated, including craniotomy or minimally invasive techniques for clot aspiration and lysis. Surgery was allowed in any patient who worsened, even if he/she was originally in the medical arm. Using an intention to treat analysis, there

was no significant difference found in neurological outcomes after 6 months. In light of these results, surgery for supratentorial intracerebral hemorrhages must be considered an unproven intervention. Surgical interventions will require continual reappraisal in light of the fact that newer surgical techniques are constantly being developed and may prove beneficial in future studies.

Controversial Interventions

Many interventions have been explored but await more definitive evidence to consider them outside of a research setting. These include:

(1) Induction of hypothermia
(2) Acute factor VIIa administration. (This is a pro-coagulant which shows considerable promise, but awaits further study)
(3) Intraventricular thrombolysis for ICH. This refers to the use of thrombolytics to help clear blood from the ventricular system in order to prevent hydrocephalus.

ICH Complications and Their Treatments

A number of serious complications frequently affect patients suffering from ICH. These include: hematoma enlargement or marked edema formation, hydrocephalus, increased ICP, seizures, herniation syndromes, and secondary infarcts.

Hematoma Enlargement

Hematoma enlargement is very common early after an ICH. One study [8] found that 52% of patients experienced hematoma enlargement within the first 6 h of the initial event. Hematoma enlargement contributes significantly to mortality, resulting in a much higher chance of poor neurological outcome or death [9]. Any worsening in neurological symptoms of a patient might be due to hematoma enlargement, and necessitates an emergent head CT. The risk of hematoma enlargement markedly reduces after the first 24 h.

Edema Formation

Tissue that is directly adjacent to the hematoma appears to suffer damage due to neurotoxic effects of the hematoma and a breakdown of the blood brain barrier, leading to edema [10]. Edema surrounding a hematoma peaks between 3 and 4 days of the initial event. It can be severe enough to equal roughly double the volume of the hematoma itself, exerting considerable pressure effects on the

surrounding brain. Any gradual worsening in clinical symptoms may be due to edema formation.

Hydrocephalus

Pressure from the original hematoma, rebleeding, or edema formation can affect the brain's ventricular system, causing an outflow obstruction. This may then cause ballooning of one or more ventricles (hydrocephalus) and increase in total brain pressure. A head CT will easily identify this development. Neurosurgical intervention is often appropriate in such cases, with placement of a ventricular drain into one of the lateral ventricles. This has the effect both of relieving the backpressure in the ventricular drainage system and of reducing the volume of the ventricles. In addition, the drain itself can then be used as an ICP monitor to guide future treatment.

Increased Intracranial Pressure

A rise in ICP can be suspected if a patient develops a new headache, nausea, vomiting, or decline in level of awareness. More ominous findings are irregular respirations, widening pulse pressures, or bradycardia. The rise in brain pressure can cause many complications, including a global inability to perfuse the brain. If elevated ICP is suspected, a neurosurgeon can place an ICP monitor, which will allow direct measurement of brain pressures. The surgeon has the option to place a subdural or epidural "bolt", a small fiberoptic pressure monitor in the parenchyma, or an intraventricular catheter. Once placed, this form of direct pressure monitoring allows for the calculation of cerebral perfusion pressure (mean arterial pressure minus ICP). The American Stroke Association guidelines recommend that CPP not be allowed to fall below 70 mmHg, else global ischemia is risked. Therefore, blood pressures should be allowed to rise in order to maintain cerebral perfusion pressure.

ICPs above 20 mmHg are usually treated. Options for treatment listed in order of most common use are as follows:

(1) Elevate head of bed to 30 degrees
    This leads to better venous drainage and reduce ICP.

(2) Osmotic therapy

    a. Mannitol infusions increase serum osmolality, thereby causing fluid in tissues, including the brain, to be pulled into the blood vessels. There are different protocols for administration. One protocol is to give a large bolus of mannitol (1 g/kg over 30 min) then check osmolality every 4 h, giving a dose of mannitol (50 g) every 4 h for osmolality values under 300 mOsm/kg. The effect of mannitol infusion on ICP may be lost after prolonged therapy (greater than 5 days). Risks associated with mannitol

use include: dehydration, transient hypotension during infusion, congestive heart failure, pulmonary edema, and renal failure.

b. Hypertonic saline (from 3 up to 23.4%) infusion is also sometimes used to create an osmotic gradient, in order to lower ICP. To date, no large controlled randomized studies have been completed regarding this therapy, though it remains a treatment option and does show promise. Potential complications include pulmonary edema, congestive heart failure, and a theoretical concern for the development of central pontine myelinolysis (rapid demyelination within the pons).

(3) Hyperventilation

Patients are intubated and hyperventilated with a goal *p*CO2 of 25–30 mmHg. This leads to a rapid reduction in ICP, although the response may last only a few hours. There is a risk that vasoconstriction will contribute to brain ischemia. Hyperventilation, once begun, will need to be discontinued only with caution, since a rebound increase in ICP might occur. Weaning is usually performed slowly, over 24–48 h.

(4) Intraventricular shunt placement.

This option is used if there is evidence of hydrocephalus on imaging or if a ventricle is large enough to be easily surgically accessed. Risks include infection and the possibility of causing brain damage or bleeding during the procedure.

(5) Steroids

Steroids are generally not indicated in this context, since they may worsen outcome [11]. They could be reasonably used if edema from a tumor was felt to be contributing to elevated ICP.

(6) Drug-induced coma

This treatment remains controversial. The proported concept is to reduce the brain's metabolic demand by suppressing neuronal activity. The actual mechanism of benefit may also involve reduction in cerebral blood flow and volume. Induction of coma with thiopental, a short-acting barbituate, has been shown to reduce elevated ICPs. Other options include phenobarbital (a long-acting barbituate) or propofol (a short-acting anesthetic agent). Once such a coma is induced, the neurological exam becomes nearly useless. Patients in a drug-induced coma are at risk for hypotension and may be more prone to infection.

Seizures and Status Epilepticus

Seizures are most likely to occur in patients with hematomas at or near the cerebral cortex, or in patients with increased ICP or hydrocephalus. Seizures or status epilepticus have the potential to markedly worsen outcomes in cases of ICH due to the possibilities of (1) increasing the size of the hematoma due to elevated

blood pressures, (2) causing increased ICPs, (3) excessively utilizing oxygen and glucose, thus inducing ischemia in regions which otherwise might have been spared, and (4) causing global ischemia due to the development of hypotension.

Isolated Seizure

An isolated seizure should prompt the physician to administer an intravenous benzodiazepine (diazepam, lorazepam, midazolam), perform repeat head CT (to rule out further structural changes, hematoma expansion, hydrocephalus), and investigate for metabolic derangements or infections, since these may make seizures more likely. Patients should also be started on a longer-acting anti-epileptic drug; traditionally this has been intravenous phenytoin or intravenous fosphenytoin. Once a loading dose has been initiated, levels should be checked and maintenance dosing should be ordered.

Status Epilepticus

Status epilepticus is defined as unending seizure activity for more than 30 min or repeated seizures within 30 min without return of consciousness to baseline between seizures. It is ideally treated by a neurologist. Generalized convulsive status epilepticus is the most dangerous form, with evidence supporting aggressive treatment. Most epileptologists emphasize an early start in treating convulsive seizures, treating them as you would a case of status epilepticus if they last more than 5–10 min. Other seizure types, including non-convulsive status epilepticus or partial complex status epilepticus, should prompt consultation with a neurologist.

Simultaneous with status epilepticus treatment, patients should undergo evaluations for potential causes of seizure (as explained in the Isolated Seizure section above). There are many status epilepticus protocols, and even within these, options abound. Most protocols for status epilepticus emphasize the early use of benzodiazepines (diazepam, lorazepam, midazolam) – using the maximal doses within the first 5 min. Whether or not seizure activity stops, this is followed by intravenous loading doses of phenytoin, fos-phenytoin, or valproate. If these are not effective in ending seizures, depending on the protocol, other options include further doses of these medications, or continuous EEG monitoring with IV administration of drugs to induce a burst-suppression pattern of EEG activity. Medications used to induce this pattern include: propofol, thiopental, midazolam, valproate, phenobarbital, or pentobarbital.

Herniation Syndromes

Brain is said to be herniating when it is pushed outside of its normal compartment. Herniating syndromes include subfalcian, temporal, central, and

cerebellar. These may be due to the local pressure effects of a hematoma, global effects of increased ICP, or the combination of the two. Cerebellar herniation into the brainstem is one of the indications for emergent surgical evacuation of a cerebellar hematoma. If hematoma evacuation is not considered an option, most developing herniations, except subfalcian hernations and cerebellar herniations, are treated by the same methods as those used to treat elevated ICP.

Secondary Infarcts

Ischemic infarction can occur in many ways after ICH. Brain herniation can lead to compression of an artery, with eventual occlusion. Global or local reductions in blood pressure, especially if ICP is elevated and CPP is below 70 mmHg, can lead to focal or global ischemia. Ischemic brain tissue not only contributes to a patient's total disability but, after a few days, may contribute further to elevated ICP due to edema within the area of infarction. There is no specific treatment for ischemia in this context, other than to attempt to correct the underlying causes (low cerebral perfusion pressure, elevated ICP, removal of the compressing hematoma).

Brief Summary

- Intracerebral hemorrhage (ICH) refers to bleeding within the substance of the brain.
- Patients present with the sudden onset of neurological symptoms, such as weakness, numbness, vision loss, diplopia, dysarthria, gait disorder, vertigo, aphasia, or disturbed level of consciousness.
- Compared to ischemic stroke, patients suffering from ICH are more likely to experience headache, reduced level of consciousness, nausea, vomiting, hypertension, and early worsening in neurological status.
- Brain imaging, with CT or MRI, is required for diagnosis.
- Primary ICH is associated with chronic hypertension and advanced age.
- Locations typical for primary ICH include: basal ganglia, thalamus, pons, internal capsule, and cerebellum.
- General management measures:
    - Manage airway, breathing, and circulation
    - Check CBC, fibrinogen, and PT/PTT/INR
    - Obtain neurosurgery and neurology consultations
    - Place patient in ICU with frequent neurological checks
    - Identify secondary causes of ICH if possible.
    - Prevent DVTs with compression stockings, intermittent pneumatic compression devices.

- Correct bleeding disorders
  - IV FFP infusion and IV vitamin K for elevated PTT/INR.
  - Platelet transfusion for thrombocytopenia.
  - Consider hematology consultation.
- Control blood pressure
  - Keep mean arterial blood pressure below 130 mmHg within first 24 h.
  - Keep cerebral perfusion pressure above 70 mmHg.
- Treat fever, control blood glucose, and consider seizure prophylaxis.
- Surgery
  - Cerebellar hematoma: surgery indicated if patient develops brainstem compression, hydrocephalus, and/or worsening neurological condition.
  - Supratentorial hematoma: obtain neurosurgical opinion.
- ICH complications:
  - Hematoma enlargement
  - Edema formation
  - Hydrocephalus (pursue placement of ventriculostomy)
- Increased intracranial pressure (ICP)
  - Measurement of pressures with manometer is helpful
  - Treatments to reduce ICP include head elevation, hyperventilation, mannitol infusion, hypertonic saline infusion, ventriculostomy (sometimes), drug-induced coma (sometimes).
- Seizures
  - More common with hemorrhages near the cerebral cortex.
  - Treat as with other seizures; consider neurology consultation.
- Herniation syndromes
  - Treatment as with elevated ICP
- Secondary infarctions

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Chapter 5
Intracerebral Hemorrhage: Long-Term Complications and Prevention

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Introduction

Primary intracerebral hemorrhage (ICH), spontaneous bleeding into brain parenchyma, constitutes 10–15% of all strokes [1]. It is the most devastating stroke subtype, with high-mortality rates and severe disability in those who survive [2]. ICH has an estimated prevalence of 65,000 cases per year in the United States [3]. Chapter 4 discussed the epidemiology and treatment of ICH. This chapter will discuss the long-term effects and prevention of ICH.

Outcome After Intracerebral Hemorrhage

ICH has a higher mortality rate and causes more disability than ischemic stroke. The 30-day mortality rate after ICH is as high as 50% [4, 5, 6, 7] and the 1-year survival rate is only 38% [7, 8, 9, 10]. Of those who survive, only 21–38% are independent at 6 months [6].

Numerous predictors of outcome after ICH have been identified. Consistent predictors include Glasgow Coma Scale (GCS) score at presentation, hemorrhage volume, and presence and volume of intraventricular hemorrhage [7, 11]. Broderick et al. found that patients with an ICH volume of over 60 cm^3 and a GCS score of 8 or less had a predicted 30-day mortality of 91%, while those with a volume of less than 30 cm^3 and a GCS score of 9 or more had a predicted 30-day mortality of 19% [7]. Anticoagulation with warfarin increases the risk of ICH [12, 13] and is associated with an increased risk of hematoma expansion, thereby worsening the prognosis [13, 14, 15, 16]. Other ICH outcome predictors include age [17], nonlobar location, cerebral edema [18], hematoma growth [19], hydrocephalus [20], active bleeding [21], degree of midline shift [22], hyperglycemia [22], diabetes [23],

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hypertension [22, 24], widened pulse pressure [25], and number of asymptomatic microbleeds detected on MRI [26]. On the other hand, predictors of good outcome at 3 months include cortical location of hemorrhage, minimal deficits on clinical exam, and low-fibrinogen concentration [27]. At least 18 models have been developed to predict short-term outcome after ICH [28]. The most widely used model is the ICH score, a model that incorporates GCS score, ICH volume, presence of intraventricular hemorrhage, infratentorial origin of hemorrhage, and age, to generate a score ranging from 1 to 6 [17]. This score correlates well with outcome.

The most common cause of early mortality after ICH is limitation or withdrawal of life-sustaining measures [29]. This has led some to conclude that withdrawal of support in patients felt likely to have a poor outcome leads to self-fulfilling prophecies and biases predictive models [30]. One statewide study that supported this theory found that patients treated in a hospital that used "do not resuscitate" orders 10% more often than another hospital with a similar case mix increased a patient's odds of dying during the hospitalization by 13% [31]. On the other hand, another study found ethnic differences in decisions to withdraw care without finding differences in 30-day mortality rates, suggesting that the patients in whom care is withdrawn are the very patients who are likely to have high-mortality rates as a result of their hemorrhage [29].

Early Deterioration After Intracerebral Hemorrhage

In one fourth of patients with ICH who are initially alert, clinical deterioration occurs within the first 24 h after presentation [32, 33, 34]. Hematoma expansion is the prevailing cause of clinical worsening within the first 24 h [33, 34]. Patients with large hematoma volumes and intraventricular hemorrhage are at highest risk of early deterioration. Hematoma expansion was first noted in retrospective studies [35, 36] and later confirmed in the Cincinnati study [37]. In the Cincinnati study, patients who presented within 3 h of symptom onset underwent serial CT scans. ICH expansion occurred in 26% of patients within the first hour after hospital admission and in another 12% within 20 h after admission [37]. Hematoma expansion correlates with outcome; therefore, research efforts are focused on developing therapies designed to halt hematoma expansion. When neurological deterioration occurs 24 h after symptom onset, worsening cerebral edema is usually the cause [33, 34]. A multitude of therapies are currently available for reducing cerebral edema and are beyond the scope of this chapter.

Neurologic and Medical Complications After Intracerebral Hemorrhage

Patients with ICH are prone to numerous neurologic and medical complications. Seizures are the most common neurologic complication, with approximately 10% of all patients with ICH and half of all patients with lobar ICH

developing seizures [38]. Seizures typically occur at onset of hemorrhage or within the first 72 h [39, 40]. One study using continuous EEG monitoring after ischemic stroke and ICH found that (1) nonconvulsive and convulsive seizures occur to a greater extent in patients with ICH (27.8%) compared with ischemic stroke (6%); (2) seizures occur in both lobar and subcortical hemorrhage; (3) posthemorrhagic seizures are associated with worsening neurologic function; (4) seizures are associated with progressive midline shift after ICH; (5) there is a trend toward worsened outcome after ICH complicated by seizures; and (6) continuous EEG monitoring detected four times as many electrographic seizures as occurred clinically [40]. Given the high frequency of seizures in the setting of ICH, empiric therapy with anticonvulsants is reasonable in critically ill patients [41]. Generally, anticonvulsants can be discontinued 1 month after ICH [42], but those who have seizures more than 2 weeks after ICH are at higher risk for further seizures and may require long-term administration of anticonvulsants [43].

Common medical complications after ICH include deep venous thrombosis, pulmonary embolism, pneumonia, and myocardial infarction. One study determined the frequency of deep venous thrombosis in patients with ICH by performing lower extremity duplex ultrasonography within 120 days after ICH in patients undergoing rehabilitation and found that 16% of ICH patients had evidence of deep venous thrombosis [44]. Often physicians withhold prophylactic anticoagulation for prevention of deep venous thrombosis in patients with ICH; however, data suggests that it is safe to start prophylactic anticoagulation 24–48 h after ICH, provided there is no evidence of ongoing hematoma expansion [45].

Recurrent Intracerebral Hemorrhage

The risk of ICH recurrence depends on the underlying pathophysiology of the index hemorrhage. The principal etiologies of primary ICH are hypertensive vasculopathy and cerebral amyloid angiopathy (CAA). Hypertensive vasculopathy typically causes deep hemorrhages, while CAA typically causes lobar hemorrhages. The recurrence rate for all survivors of ICH is 2.4% per year [46, 47]. Patients with lobar ICH, however, have a 3.8-fold increased risk of recurrent ICH compared to those with nonlobar ICH [46].

Hypertension is the most important predictor of recurrence in nonlobar ICH [48]. Predictors of recurrence in lobar ICH include number of microbleeds, leukoaraiosis, and apolipoprotein E genotype [26, 49, 50]. There is a correlation between the total number of cerebral microbleeds at time of index lobar hemorrhage and the risk of future symptomatic hemorrhage (3-year cumulative risks of 14, 17, 38, and 51% for subjects with 1,2, 3–5, or >/– 6 baseline hemorrhages, $p = 0.003$) and time until hemorrhage recurrence [26]. Severity of white matter disease correlates with risk of hemorrhage recurrence [49]. The

apolipoprotein E genotype can identify patients with lobar ICH who are at highest risk for early recurrence (carriers of the *e2* or *e4* allele had a 2-year recurrence rate of 28% compared with only 10% for patients with the common apolipoprotein E *e3*/*e3* genotype) [50]. No study to date has examined predictors of recurrence after warfarin-related hemorrhage, but independent predictors of initial ICH in patients on warfarin include intensity of anticoagulation, age and presence of a prosthetic valve [51]. These factors will likely also predict ICH recurrence in patients on warfarin.

Risk of Ischemic Stroke

Often patients with ICH are also at risk for ischemic stroke and transient ischemic attack (TIA). One study found that the annual risk of ischemic stroke and TIA ranges from 1.1 to 3.0% per year [46, 47]. These patients pose a therapeutic dilemma. They often have an indication for antiplatelet or anticoagulant therapy to prevent ischemic stroke, but initiation of such medications after ICH increases their risk of recurrent hemorrhage. For example, patients with nonlobar hemorrhages may have underlying small vessel disease making them prone to lacunar infarctions. They therefore could benefit from antiplatelet therapy for preventing infarction from small vessel disease, but they run the risk of developing recurrent hemorrhage. In addition, patients with atrial fibrillation or mechanical valves who develop ICH in the setting of anticoagulation run the risk of ischemic stroke if their warfarin is discontinued and recurrent ICH if their warfarin is resumed. The therapeutic challenges involved in antiplatelet and anticoagulant therapy in the setting of ICH are discussed in the next sections of this chapter.

Antiplatelet Use After Intracerebral Hemorrhage

Is it safe to start a patient with a history of ICH on antiplatelet therapy? Pooled data from large randomized trials of patients without a history of ICH reveals that aspirin use is associated with a small but significant risk of ICH, with an absolute excess incidence of approximately 1 per 1,000 persons [52]. Aspirin use is more often associated with lobar than deep ICH and with asymptomatic lobar cerebral microbleeds, suggesting that CAA may be relevant to the pathophysiology of antiplatelet-related hemorrhage [53, 54]. There is limited data on risk of recurrent hemorrhage in patients with a history of ICH treated with aspirin. The only study to date to look at this issue was an observational study that found that in 207 patients, antiplatelet exposure was associated with no increased risk of recurrent hemorrhage in lobar ICH survivors (HR 0.8; 95% CI, 0.3–2.3; $p = 0.73$) or deep ICH survivors (HR 1.2; 95% CI 0.1–14.3; $p = 0.88$) [55]. The recurrence risk was greater in lobar ICH survivors than

deep ICH survivors (2-year recurrence rate of 22 vs 4% $p = 0.007$) [55]. Given these results, antiplatelet therapy should not be withheld in ICH patients with cardiovascular disease or risk for ischemic stroke.

Anticoagulant Use After Intracerebral Hemorrhage

Is it safe to start a patient with a history of ICH on warfarin? In patients with a history of warfarin-associated hemorrhage, the risk of hemorrhage recurrence is high, particularly if the index hemorrhage was lobar. Warfarin is therefore often avoided in patients with a history of hemorrhage. There are subgroups, however, in which withholding anticoagulation can lead to a significant risk of ischemic stroke. In the absence of clinical trials to address this question, Eckman et al. used a decision-analysis model to compare anticoagulation vs withholding anticoagulation in patients with a history of ICH and clear indication for anticoagulation. They found that the risk of recurrent hemorrhage outweighs the benefit of anticoagulation in patients with both nonvalvular atrial fibrillation and a history of lobar hemorrhage, but patients with a history of deep hemorrhage may benefit from anticoagulation if their ischemic stroke risk is high [56]. Aspirin, which has a lower risk than warfarin [52, 57], may be a reasonable option for patients with deep ICH with a high thromboembolic risk [56].

There are some situations, such as mechanical heart valves and a left ventricular thrombus, in which the risk of ischemic stroke without anticoagulation outweighs the risk of recurrent hemorrhage in the setting of anticoagulation. In such patients, there is limited data on optimal timing of initiating anticoagulation. A Mayo retrospective study found that the 30-day probability of ischemic stroke after warfarin cessation in patients with atrial fibrillation, prosthetic heart valves, history of cardioembolic ischemic stroke, and history of recurrent TIA despite antiplatelet therapy was 2.6–4.8%, and thus concluded that temporary discontinuation of warfarin for 7–14 days was probably safe [58]. Similarly, for patients with atrial fibrillation, the HAEST trial and International Stroke Trial suggest that it is safe to withhold warfarin for 2 weeks [59, 60].

Primary Prevention of Intracerebral Hemorrhage

Tight control of risk factors for ICH can play a role in mitigating the burden of ICH. Hypertension has an important role in causing deep intracranial hemorrhage [61, 62, 63]. Treatment of hypertension can significantly reduce the incidence of ICH [62, 63, 64, 65]. With the advent of new imaging techniques, we have the ability to diagnose underlying hypertensive vasculopathy in patients who do not have frankly elevated cuff pressures. Physicians should

consider initiating antihypertensive medications, even if cuff pressures are not elevated, in patients who are found to have deep microbleeds on MRI indicative of hypertensive vasculopathy. Since heavy alcohol consumption impairs coagulation and affects the integrity of cerebral vessels, limiting alcohol consumption reduces the risk of ICH [66, 67, 68, 69, 70].

There are currently no medications to prevent CAA-related hemorrhage, but there are several potential therapies aimed at altering the metabolism or activity of Aβ. One approach to reach early clinical trial is the use of a low molecular-weight anionic molecule that interferes with the interaction of Aβ with sulfated glycosaminoglycans in the basement membrane of vessel walls [71].

Warfarin-related hemorrhage is associated with advancing age, cerebrovascular disease, CAA, and intensity of anticoagulation [13, 51, 72, 73, 74]. Warfarin-related hemorrhages can be prevented by withholding therapy in patients at high risk for hemorrhage on warfarin and through better control of the INR. Imaging can be used to identify patients with high risk of warfarin-related hemorrhage by identifying those with lobar microbleeds suggestive of CAA, history of prior strokes and evidence of leukoaraiosis. Although APOE genotype can identify patients with ICH who are at risk for hemorrhage recurrence, it is neither sensitive nor specific for the primary diagnosis of CAA, and therefore is not likely to be helpful in identifying patients at high risk for hemorrhage on warfarin. Home INR machines that facilitate tight control of INR and antithrombotic medications that do not need monitoring, such as direct thrombin inhibitors, are other strategies aimed at lowering the risk of anticoagulant-related hemorrhage.

Secondary Prevention of Intracerebral Hemorrhage

Secondary prevention strategies of ICH depend on the underlying cause of the index hemorrhage. Although control of hypertension reduces the risk of recurrent deep hemorrhage [48, 75, 76, 77, 78], it probably has little effect on recurrent lobar hemorrhage. [50] Control of other common accompanying risk factors (such as smoking, alcohol use, and diabetes) may reduce recurrence of ICH [48]. Secondary prevention of warfarin-associated hemorrhage involves strict control of the INR.

Conclusion

ICH has a high-mortality rate and those who survive have significant disability. Consistent predictors of outcome after ICH include GCS score at presentation, hemorrhage volume, and presence and volume of intraventricular hemorrhage. Hematoma expansion and cerebral edema are the most common causes of neurologic worsening after ICH. Medical and neurological complications of

ICH include aspiration pneumonia, myocardial infarction, deep venous thrombosis, seizures, and ischemic stroke while anticoagulant or antiplatelet agents are withheld. Hypertension is the most important predictor of recurrence in nonlobar ICH, while number of microbleeds, leukoaraiosis, and apolipoprotein E genotype are predictors of lobar ICH recurrence. Patients with ICH are at risk of ischemic stroke and the risks of withholding antiplatelet or anticoagulant therapy must be weighed against the risk of hemorrhage recurrence if antiplatelets or anticoagulants are resumed. Primary and secondary prevention of ICH involves strict blood pressure control, reduction or cessation of tobacco and alcohol use, diabetes treatment, and tight control of INR in patients on warfarin. While risk factor control will help reduce the burden of disease, therapies aimed at preventing neurologic worsening and avoiding medical and neurologic complications will improve outcomes after ICH.

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Chapter 6
Subarachnoid Hemorrhage: Diagnosis and Acute Management

Mahmut Edip Gurol and Harold P. Adams

Basic Concepts

Definition

Bleeding in the subarachnoid space (subarachnoid hemorrhage/SAH) can be caused by a number of pathologies. Blood can enter the subarachnoid space from arterial lesions located within the subarachnoid space, from an intracerebral hemorrhage that extravasates into the subarachnoid space, from bleeding that arises in ventricles, or from ruptured vessels in the subdural space, which can cause bleeding that extends through the outer arachnoid layer.

Background

Trauma is the most common cause of SAH. The most common etiology of nontraumatic SAH encountered by the internist is a ruptured aneurysm. Less commonly nonaneurysmal SAH, including isolated perimesencephalic SAH, may occur. These nontraumatic forms of SAH are medical emergencies that necessitate prompt recognition and specialized management and they are discussed subsequently. Traumatic subarachnoid hemorrhage (tSAH) occurs in most patients with a closed brain injury; its prognostic significance is unclear, its management is part of the general treatment of trauma, hence it is not included in this text.

The annual incidence of spontaneous SAH, adjusted for age and sex, according to the 1990 US Census was 9.7 per 100,000 (95% CI 7.5–12.0). African Americans and Hispanics may have a greater incidence of SAH than Whites [1]. SAH is relatively rare in the first three decades but the incidence progressively increases with age. Men are affected more frequently until

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the fifth decade of life after which women are at higher risk. The reported case-fatality rate for SAH varies between 32 and 67% (mean 51%). Fortunately, the case-fatality rate has decreased by 0.5% per year during the last three decades. A plausible explanation for this decrease is improved management of affected patients [2].

A ruptured intracranial aneurysm is the source of the bleeding in 80–85% of cases of nontraumatic SAH. The natural history of nontreated, recently ruptured aneurysm is horrendous; the risk of rebleeding within the first 2 weeks is estimated to be 20%. A number of neurological and medical complications also contribute to the very high risk of death or long-term disability. Interventions targeting the causative lesions and strategies to prevent and treat acute complications exist. These therapies may improve the outcome in the individual patient. However, use of these treatments is dependent upon early and accurate diagnosis of SAH. Failure to recognize SAH and to initiate the appropriate management emergently is a potential cause of litigation; primary care physicians, emergency room doctors and neurologists are at particular risk. Non-aneurysmal subarachnoid hemorrhage constitutes the remaining 15–20% of nontraumatic SAH patients, this group typically has a good prognosis [3] but the presence of an aneurysm must be ruled out with appropriate neurovascular imaging. As a result, these patients also need an emergency evaluation and early treatment that parallels that prescribed to patients with ruptured aneurysms.

Presenting Symptoms and Signs

Clinical Presentation

Generally, SAH is an acute and dramatic event presenting most commonly with a cataclysmal onset of an unusually severe headache. In addition nausea, vomiting, photophobia, neck stiffness, and focal neurologic symptoms related to mass effect or irritation from the hematoma (hemiparesis, hemisensory loss, aphasia) may appear. Transient or prolonged depression in the level of consciousness and seizures also may occur. The usual and typical symptoms and their reported frequencies are summarized in Table 6.1.

The literature abounds with reports of premonitory warnings, also called "sentinel bleeds" or "warning leaks" which are essentially milder forms of the symptoms and signs of a major SAH that occurs before the index event. The retrospective recollection of these warning signs is a medicolegal curiosity but their presence or absence does not have any impact on the diagnosis and management of SAH other than that physicians must be sensitive to these milder presentations of SAH. The diagnosis of SAH is often difficult in the situation of an alert, non-ill appearing patient complaining of a headache.

A more detailed review of the symptoms and signs associated with SAH is given here.

Table 6.1 Usual symptoms and their reported frequencies

– Headache (>90% of SAH patients): almost instantaneous in 50%; evolving in 2–60 s in 24%; crescendoing over 1–5 min in 19%
– Signs of meningeal irritation (up to 85%): Nausea, vomiting, photophobia, nuchal rigidity, chest pain, back pain, and radicular pain.
– Signs of increased intracranial pressure: blurring of vision, tinnitus, dizziness, nausea, and vomiting
– Changes in the level of consciousness (50%): prolonged coma (20%)
– Focal neurological manifestations (50–60%): Palsies of CN3, CN4, CN6, homonymous hemianopia, cortical blindness, hemiparesis, hemisensory loss, and aphasia
– Seizures (up to 25%)
– Fever
– Nausea and vomiting

Headache

Headache occurs in more than 90% of people with SAH [4] and is attributed to increased intracranial pressure and meningeal irritation. The classic headache due to SAH is precipitious in onset, severe, and continuous (thunderclap headache) which typically is described as "the worst headache of my life". These headaches are further described as agonizing, tremendous, awful, terrible, terrific, tearing, excruciating, crushing, unbearable, and a feeling "as if the head had burst" [5]. Patients also use other vivid terms to describe the acuteness of onset and the intensity: "I thought someone had hit me over the head", "all of a sudden", "bang", "my head just exploded". Vomiting and photophobia frequently accompany the headache. The pain can be felt across the forehead, the entire head, on the side of the aneurysm rupture, and into the neck and shoulders. Lateralization of the headache does not exclude the diagnosis of SAH as this can occur in up to 30% of patients [5]. Very localized headaches, restricted to the bifrontal region or vertex are rare [5]. Patients also may have eye, ear, face, or neck pain. Rupture of an aneurysm in the posterior circulation can cause severe nuchal and occipital pain. Blood that reaches the spinal subarachnoid space may cause pain in the thoracolumbar areas that may radiate down the legs. Chest pain has been reported. In a series of 42 patients with aneurysmal SAH, the onset of headache was described as almost instantaneous in 50%, evolving in 2–60 s in 24%, and crescendoing over 1–5 min in 19% [6]. A smaller percentage of the patients will describe a milder, gradually increasing headache. In rare instances, patients may not complain of any headache but some unusual sensation of acute onset in the head. The initial explosive headache may lessen in severity but may persist several days to 2–4 weeks. It is very rare for headache related to SAH to disappear in less than 2 h after onset. Continuing headache may suggest development of hydrocephalus whereas recurrent headache can be associated with rebleeding or delayed cerebral ischemia due to vasospasm. The differential diagnosis of the "thunderclap headache" which is commonly associated with SAH is given in the Table 6.2.

Table 6.2 The differential diagnosis of the "thunderclap headache" which is commonly associated with SAH

Subarachnoid hemorrhage
– Dural sinus thrombosis
– Cervicocephalic arterial dissection
– Spontaneous intracranial hypotension
– Pituitary apoplexy
– Acute hypertensive crisis
– Reversible cerebral vasoconstriction syndrome
– Head or neck infection
– Primary headache (no structural cause identified)
– Traumatic head and neck injury

Some patients describe transient blurring of vision at the onset of headache, which might be related to increased intracranial pressure; tinnitus, dizziness, and nausea have also been described.

Signs of Meningeal Irritation

When blood irritates the nuchal meninges, the cervical muscles contract resulting in neck stiffness. Meningeal irritation can also cause back pain and radicular symptoms. However, many patients do not have nuchal rigidity, especially early in the course of the illness. Stiff neck was reported to be present in 74% of the patients on the day of the aneurysm rupture, in 85% in second and third day, and again 75% on the fourth day [7]. A supple neck does not exclude SAH but many patients can have a presentation suggestive of meningitis with headache, stiff neck, nausea/vomiting, and low-grade fever.

Changes in the Level of Consciousness

Some disturbance of the level of consciousness occurs in 50% of SAH patients and the true incidence may even be higher as a number of such patients fail to reach the hospital after they bleed. Prolonged coma, as the initial presentation, occurs in 20% of SAH patients. An initial loss of consciousness that mimics syncope may be related to a transient interruption of cerebral blood flow caused by the sudden elevation in intracranial pressure from the hemorrhage. Among patients who regain consciousness, some complain of headache before they lost consciousness and almost all complain of significant headache after they awaken. The combination of sudden severe headache accompanied by loss of consciousness should prompt consideration of SAH. The depth of the coma is variable as well as its duration, which might last a few minutes to weeks. A case fatality as high as 85% was reported in patients whose initial period of

unconsciousness lasted more than an hour [8]. Persistent coma is more likely when there is focal intracranial hematoma with herniation, massive ventricular hemorrhage, massive SAH, or development of hydrocephalus.

Focal Neurological Manifestations

More than 40% of patients with SAH do not have localizing neurological deficits, thus absence of signs such as hemiparesis or aphasia does not exclude the diagnosis. When focal signs are present, they usually are related to massive hemorrhage, a hematoma compressing a cranial nerve, acute hydrocephalus or intracerebral hematoma. The signs point toward the source and location of the most extensive site of hemorrhage. The most common abnormalities involve the third, fourth, or sixth cranial nerves. In particular, the presence of an oculomotor nerve (III) palsy with pupil involvement in an alert patient with sudden severe headache points to a ruptured aneurysm of the posterior communicating or basilar artery. Homonymous hemianopia implies involvement of the optic tract; cortical blindness due to bilateral occipital lobe damage can also occur. Hemiparesis, hemisensory loss, and language problems depend on the location and extent of the hemorrhage. A detailed neurological exam should be obtained in each patient to document the existing deficits and clinical progression. This baseline assessment is important as patients might develop new deficits or worsening of the existing ones over the first 2 weeks due to rebleeding, delayed cerebral ischemia (vasospasm), medical complications, or hydrocephalus; any change in the neurological exam should prompt a search for a correctable cause. Focal deficits can also theoretically help in the localization of the underlying cause but this does not change the management, as patients need a full neurovascular evaluation (including all major cerebral arteries).

Seizures

Epileptic seizures occur at the time of hemorrhage in up to 25% of the patients [9, 10, 11]. A proportion of the patients who are unconscious upon presentation may have clinical evidence of intermittent seizures. Identification and proper treatment of the seizures is an important part of the medical management of SAH.

Fever

During the first day of a SAH, the temperature rarely exceeds 38.5°C (101.3°F) unless there is an ongoing infectious process. Thus, fever upon presentation should prompt one to consider alternative diagnoses (meningitis or other infections). Patients frequently have higher temperatures (38–39.0°C or higher)

after the second/third day, probably as the result of meningeal irritation or possibly due to hypothalamic dysfunction, which generally subside to normal over the next couple of days. When fever develops an intercurrent infection should be sought for and be treated appropriately.

Intraocular Hemorrhages and Papilledema

Intraocular hemorrhages may be (1) retinal (flame-shaped or punctate), (2) preretinal or subhyaloid (round bright red blobs that may change shape with altered patient position), or (3) vitreous (diffuse haziness or blackness obscuring fundal anatomy). Fundal hemorrhages may be retinal and preretinal [12, 13]. The presence of intraocular hemorrhages, which occurs in approximately 10–20% of patients, is associated with a worse prognosis [14]. Papilledema usually is not present within the first hours but may develop over the course of the first week after SAH. It is seen in about one sixth of patients with SAH and it appears to be secondary to blood accumulating in the optic nerve sheaths.

Etiologies (Table 6.3)

In SAH, the bleeding occurs primarily in the subarachnoid space. It may be generalized or localized as a subarachnoid hematoma. Bleeding from an aneurysm also may extend into the brain parenchyma, or enter the ventricular cavities. Nontraumatic SAH usually results from rupture of an aneurysm that most commonly arises on a branch of the circle of Willis. There is no compelling evidence supporting the view that physical or emotional stress can precipitate aneurysm rupture but SAH is reported to happen during or after strenuous exertion. Patients with acute onset of a headache suggesting SAH during physical activity, including sexual intercourse, should be fully evaluated for SAH. Nonaneurysmal causes of SAH are rupture of an arteriovenous malformation, bleeding diatheses or other medical conditions such as vasculitides. Coarctation of the aorta, polycystic kidney disease, fibromuscular dysplasia, moyamoya disease, cocaine use, sickle cell disease, Marfan syndrome, Ehlers–Danlos syndrome, and neurofibromatosis type I are reported to be associated with intracranial aneurysms and SAH. The prognosis and management issues can differ between etiologies of SAH.

Ruptured Saccular Aneurysm

Saccular (berry) aneurysms are the most common cause of SAH and they are distinguished from other types of intracerebral aneurysms, such as traumatic, dissecting, mycotic, and neoplastic aneurysms by their pathology, location, and

Table 6.3 Etiologies

1. Ruptured intracerebral aneurysm (80%)
Saccular (berry) aneurysms (by far the most common cause of SAH)
Nonsaccular aneurysms (dissecting, infective/inflammatory, fusiform/ dolichoectatic, and neoplastic types)
2. Isolated perimesencephalic SAH (10–15%)
3. Drugs
Anticoagulation with warfarin or heparin
Thrombolytic therapy (tissue plasminogen activator, streptokinase)
Cocaine and methamphetamine abuse
4. Coagulopathies
Hemophilia
Leukemia
Thrombocytopenia
Liver failure
5. Other non inflammatory vascular disease (rare)
Arteriovenous malformations
Dural arteriovenous fistulas
Moyamoya disease
6. Vasculitides
Isolated angiitis of the central nervous system
Behçet's disease
Polyarteritis nodosa
Wegener granulomatosis
Churg–Strauss syndrome
Borrelia burgdorferi-associated vasculitis
Temporal arteritis
Human immunodeficiency virus (HIV)-associated cerebral aneurysmal arteriopathy
7. Primary or metastatic tumors of the brain and its surroundings

appearance. Saccular aneurysms usually arise at major bifurcation points on the circle of Willis. They are characterized by a vascular wall lacking the normal muscular media and elastic lamina layers. While normal intracerebral vessels have a prominent muscular media layer, they have only one elastic lamina [15]. Saccular aneurysms retain the normal structure of the arterial wall but the aneurysmal wall becomes quite thin. The aneurysmal outpouching is usually connected to the artery by a narrow segment or neck. Saccular aneurysms usually arise at major bifurcation points on the circle of Willis. Approximately 25% of the patients have multiple aneurysms, which occur more frequently when there is a familial incidence of aneurysms [16]. Larger aneurysms have a higher risk of rupture, but most aneurysms that rupture are found to be smaller than 10 mm in diameter. The pathogenesis of saccular aneurysms and the cause of the subsequent rupture are essentially uncertain, both congenital and environmental factors have been implicated and most probably their interplay causes

the pathology in the individual patient. Major modifiable risk factors include cigarette smoking, hypertension, cocaine use, and heavy alcohol use (>2 drinks a day) [17, 18, 19, 20]. Patients with first-degree relatives with SAH are also at higher risk [17, 21]. The issue of risk factors for rupture will be explored in detail in Chapter 7, which will address long-term prevention.

Nonsaccular aneurysms include fusiform, dissecting, infective/inflammatory, and neoplastic types. Inflammatory/infective (mycotic) aneurysms are usually associated with subacute or acute infective endocarditis and less often with spread of infection from a contiguous site (i.e., osteomyelitis or meningitis). Causative microorganisms may be multiple and of low virulence, both bacteria and fungi may be responsible, the latter especially in immunocompromised patients and intravenous drug abusers. Unlike saccular aneurysms, infective/inflammatory aneurysms usually occupy distal branches of the arterial circulation. Infective endocarditis is a well-established cause of cardioembolism and therefore can cause cerebral infarctions but anticoagulation is contraindicated because of the known tendency to cause aneurysms and SAH. Starting aggressive treatment with appropriate antimicrobials as soon as this diagnosis is suspected is of paramount importance.

Dissecting aneurysms (arterial dissections) occur mostly in individuals between the ages of 25 and 45 years and can cause both infarcts and SAH. Rarely, in the intracranial posterior circulation, transmural dissection may result in SAH.

Fusiform (dolichoectatic) aneurysms result from enlargement and widening of an arterial segment along its length. These lesions are mostly seen in the geriatric population and are associated with complicated atherosclerosis. They rarely rupture to produce SAH.

Isolated Perimesencephalic SAH

In 10–15% (range 5–28%) of patients with SAH, no aneurysm or arteriovenous malformation is detected by angiography [22]. In the majority of these patients the locus of bleeding is identified to be anterior to the midbrain and pons (perimesencephalic), the leaking blood vessels being veins or capillaries around the midbrain [22, 23]. These hemorrhages have a better prognosis than aneurysmal hemorrhages even without any specific treatment, and rebleeding or delayed cerebral ischemia occurs very rarely [24, 25].

Arteriovenous Malformations (AVM)

Contrary to popular belief, AVMs are not a common cause of SAH. SAH was found in only 4% of ruptured AVM patients [26], with another 1% of ruptured AVM patients experiencing SAH in conjunction with an intracerebral hemorrhage (ICH).

Coagulopathies

Anticoagulation with warfarin or heparin may cause or aggravate SAH. Prolongation of the prothrombin time (PT) and activated partial thromboplastin time (aPTT) beyond the therapeutic range is the greatest risk factor for these patients [27]. Systemic anticoagulation with warfarin therapy has been associated with poor outcome after SAH [28]. Fibrinolytic therapy increasingly used for ischemic cerebral and myocardial events also may be associated with intracranial bleeding, including SAH. Stopping the inciting drug and correction of the coagulopathy should be performed. Corrective action may include use of vitamin K, protamine sulfate, fresh frozen plasma, ε-aminocaproic acid, cryoprecipitate, or factor VIIa.

Intracranial hemorrhage is the main cause of death in patients with hemophilia and 33–63% of the bleeds are SAH [29, 30]. Treatment again requires prompt replacement of antihemophilia factors to achieve hemostatic levels [31]. Leukemia, thrombocytopenia, and liver failure can all be associated with intracranial hemorrhages, including SAH, due to defects in platelet function or a deficiency of coagulation factors. First line blood tests including a CBC with differential, PT, aPTT, and liver function tests can help to quickly detect these conditions. Prompt treatment of the underlying condition should be undertaken to prevent rebleeding and worsening of the existing hemorrhage.

Vasculitides

Both multisystem and isolated central nervous system vasculitis may produce SAH. Among these are Behçet's disease [32, 33, 34], polyarteritis nodosa [35, 36, 37, 38, 39, 40], Wegener granulomatosis [41, 42, 43, 44], Churg–Strauss syndrome [45, 46], isolated angiitis of the CNS [47], *Borrelia burgdorferi*-associated vasculitis [48], giant cell arteritis [49, 50], and human immunodeficiency virus (HIV)-associated cerebral aneurysmal arteriopathy [51]. Cocaine and methamphetamine abuse may be complicated by subarachnoid hemorrhage, the causative mechanism is probably a combination of vasculitis and drug-induced hypertension [52, 53, 54, 55, 56, 57, 58, 59, 60, 61]. As a result, urine toxicological screening is warranted in patients with SAH who may have some risk for drug abuse.

Diagnostic Testing (Table 6.4)

SAH should be suspected in any patient presenting with the acute onset of an unusually severe headache that may be accompanied by nausea, vomiting, photophobia, neck stiffness, changes in level of consciousness, focal neurologic deficits, or seizures. Both the patient and witnesses should be interviewed to

Table 6.4 Diagnostic testing

1. Tests for confirmation of SAH
Computerized tomographic scan of the brain without contrast
Lumbar puncture (analysis from the last tube for cell count and differential, xanthochromia, protein, and glucose at a minimum)
2. Evaluation for underlying vascular or parenchymal lesion
CT Angiography
Brain magnetic resonance imaging (with and without contrast) +/– intracranial magnetic resonance angiography
Four-vessel digital subtraction cerebral angiography (DSA)
3. Other first line tests on admission
Complete blood count with differential
PT/INR, aPTT
Glucose, BUN, creatinine, Na, K, Cl, CO_2, Ca, P, Mg, AST, ALT, GGT, albumin, prealbumin
Chest X ray and 12 lead EKG
ESR, CRP, blood cultures, urinalysis, and urine cultures if any suspicion of infection
Peripheral blood smear if any suspicion for hematological problem
Urine toxicological screen if any suspicion for drug abuse
4. Tests for rare causes
ESR, CRP
ANA, VDRL
Hepatitis B and C serologies (association with polyarteritis nodosa)
Antineutrophil cytoplasmic autoantibodies (ANCA, both cytoplasmic and perinuclear): c-ANCA mostly in Wegener granulomatosis, p-ANCA usually in Churg–Strauss syndrome
Pathergy (skin prick) test (for Behcet's disease)
Presence of RBC casts on urinalysis (suggests glomerulonephritis)

help identify the mode of onset of headache, its features, the patient's activity level at the onset, the progression of symptoms and appearance of new symptoms or signs, past history of headaches and other relevant past medical history with an emphasis on conditions associated with an increased risk of cerebral bleeding. Even if the patient is fully awake at the time of evaluation, inquiry into any prior loss of consciousness should be specifically sought as its presence would be suggestive of a potentially ominous process like SAH and often would be an impetus for detailed testing, even in presentations otherwise less suggestive of SAH.

On a distressingly frequent basis, physicians miss the diagnosis of SAH, often with devastating consequences for the patient. Despite the well recognized clinical features in those patients who seek help, a delay in diagnosis occurs in many patients. In a series of 182 consecutive patients, 23% initially received another diagnosis [62] including flu, viremia/gastroenteritis, migraine, hypertensive crisis, neck trouble, brain tumor, meningitis, sinusitis, myocardial infarction, cerebral infarction, alcohol intoxication, inhalation of toxic fumes, head injury, otitis, delirium of unknown origin, vertigo, syncope, or malingering. The most common misdiagnoses in the primary care setting in patients with a chief complaint of headache are migraine, tension-type headache or benign

headache associated with exercise or intercourse. Knowledge of the clinical presentation of SAH and a high index of suspicion are the keys to correct identification and treatment of this condition.

Once SAH is suspected, a computerized tomography scan (CT scan) of the brain without contrast should be obtained promptly. The sensitivity of CT scans in detecting SAH is excellent initially but reduces over time. CT scans have a 98% sensitivity for confirming SAH within 12 h and 95% within 24 h, the sensitivity then decreases to 73% on day 3 [63, 64]. This high sensitivity is in the context of an experienced radiologist or neurologist reading the scan. CT scans showing SAH of various extents and at different locations are shown in Fig. 6.1. Lumbar puncture (LP) is needed when doubt exists and the CT does not show bleeding. Analysis of the cerebrospinal fluid (CSF) still is an effective test for diagnosis. Of note, when CT confirms the diagnosis of SAH, LP is best avoided

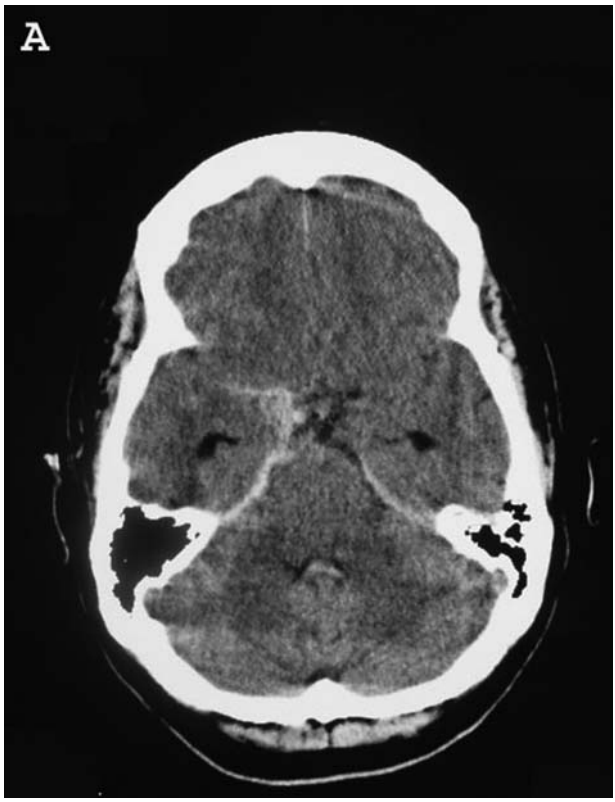
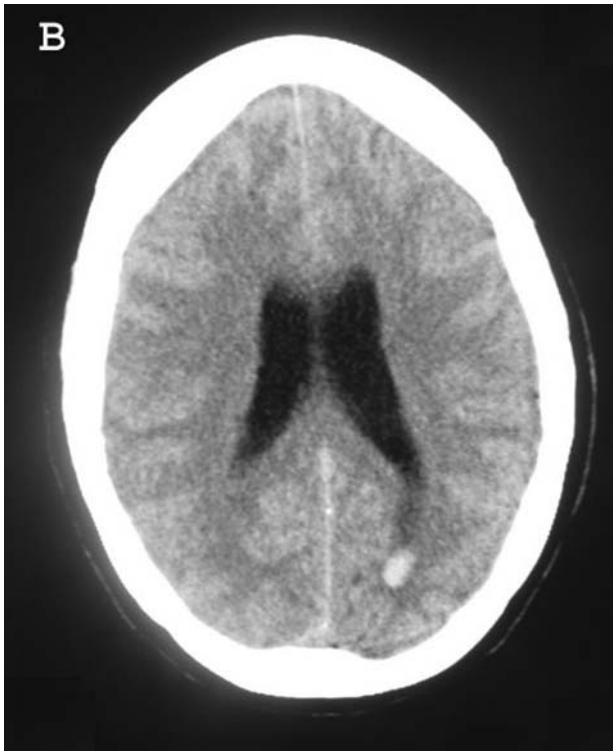


Fig. 6.1 Head CT showing SAH in the deep cisternae (**A**) and blood in the posterior part of the left lateral ventricle (**B**). DSA showing a large saccular aneurysm (*arrow* in **C**) and DSA obtained after successful endovascular coiling, showing obliteration of the same aneurysm (*arrow* in **D**)



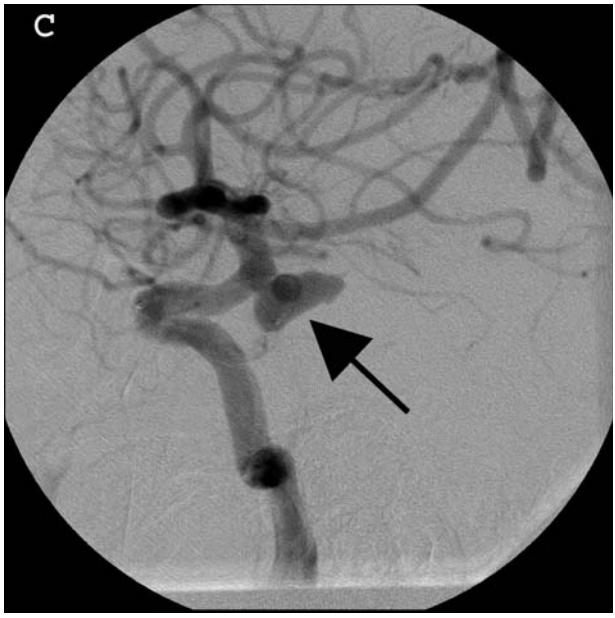


Fig. 6.1 (continued)

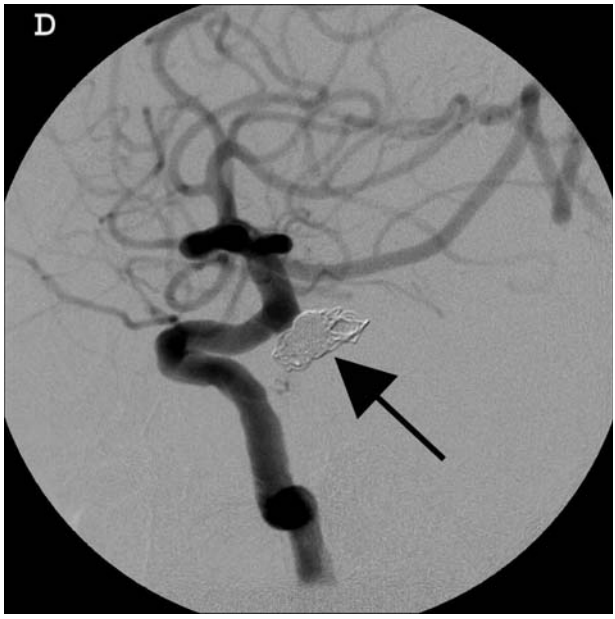


Fig. 6.1 (continued)

because it could potentially lower CSF pressure, increasing the pressure gradient across the aneurysm wall, possibly increasing the risk of rebleeding.

Once obtained, you may inspect the color of each CSF tube, against a white background, providing precious information to an experienced observer. CSF colored by blood from a SAH typically will not clear with analysis of each subsequent tube. The last tube obtained after a traumatic tap, on the other hand, would appear much lighter when compared to the first tube.

After this initial look, the CSF sample should be walked to the laboratory. CSF testing should include cell count, differential, xanthochromia, protein, and glucose; preferentially performed on the last tube of CSF obtained. After about 12 h, blood entering the CSF begins to break down and the released hemoglobin leads to the synthesis of bilirubin. Bilirubin in the CSF, examined for after centrifugation of the sample, causes a yellow appearance referred to as xanthochromia. There is an ongoing controversy about delaying the LP until about the 12th hour after onset of the event, so that the diagnosis can be made more securely, even if the tap was traumatic. The approach makes sense but it is not very practical as it can mean delaying the final diagnosis many hours after the patient's presentation to the hospital. The risk of rebleeding is highest during the first days, so such a delay may risk a recurrent SAH. As SAH is a medical emergency, we recommend the LPs in this setting to be performed by experienced physicians as soon as possible if they are needed for diagnosis. In a patient with a clinical picture suggestive of SAH, a negative brain CT and an LP

showing equivocal findings, one should proceed with vascular imaging with a presumption of SAH.

Once the diagnosis is confirmed either with brain CT or CSF analysis, the next step in diagnosis is an evaluation for aneurysm(s). As 12–31% of patients harbor multiple aneurysms, careful evaluation of all cerebral vessels is mandatory. Four-vessel digital subtraction cerebral angiography (DSA) has long been the gold standard for the diagnosis of cerebral aneurysms. CT angiography (CTA) is becoming a widely available, noninvasive means of assessing the intracranial circulation and its sensitivity and specificity are comparable to DSA [65]. CTA provides the advantage of three dimensional multiplanar reconstructions, which can be very useful for identifying the aneurysmal neck and distinguishing it from surrounding bony structures [66]. CTA is also fast and may be safely used in patients who have pacemakers or other equipment that would preclude MRI. In our center, experience with CTA has been quite positive and it is used as first line vascular imaging in patients suspected of having aneurysmal SAH. Patients with an initial negative imaging study should have a repeat vascular imaging study in 1–2 weeks after presentation. If the second study is also negative, brain magnetic resonance imaging (MRI) with magnetic resonance angiography (MRA) might help to find rarer causes of SAH such as an AVM. Brain MRA can also help to determine the size of an aneurysm, especially for partially thrombosed aneurysms.

Management

The management of SAH is multifaceted; clipping or coiling of the underlying aneurysm is needed to prevent rebleeding but close monitoring of the patient and prompt recognition and appropriate management of the complications are as important as treatment of the underlying lesion. These goals are best achieved in a specialized monitored setting, combining efforts of neurosurgery, interventional neuroradiology, neurology as well as nursing and allied teams familiar with the management of SAH patients. Access to advanced imaging modalities such as CT and/or MRI on a 7/24 basis is important. For these reasons, SAH patients, in the acute stage, are best transferred to facilities with these services available. Nevertheless, it is important for the primary care physician to be familiar with the major aspects of SAH management, since many patients may be diagnosed by them, and managed by them in the earlier stages. In addition, because some patients present with complications after the acute event, recognition of these complications, often by the primary care physician, is vital.

What follows is the general management, treatment of the underlying pathology, recognition and treatment of the complications of SAH. The early management as described here is mostly related to aneurysmal SAH (anSAH), which accounts for 80–85% of nontraumatic cases and which causes the most important morbidity and mortality. The most commonly used medications and their doses are given in Table 6.5.

Table 6.5 Most commonly used medications and doses

SAH precautions
"No TV, no radio, no phone calls, lights off, visitors limited to 10 min/h"
Prevention of vasospasm
– Nimodipine 60 mg PO/PNGT q4 h OR
– Nimodipine 30 mg PO q2 h as an alternative regimen in patients particularly susceptible to hypotension
– Intravenous normal saline at a rate of 120–150 ml/h
Analgesia
– Codeine 15–60 mg PO/PNGT q4–6 h
– Morphine 5–10 mg IM/IV q2–4 h
Sedation
– Phenobarbital 45–60 mg PO/PNGT/IV q6–8 h (not to exceed total of 180 mg over 24 h)
– Midazolam 0.5–2 mg IV slowly over >2 min, total 2.5–5 mg; dose must be individualized, it requires monitoring
Anticonvulsants
Continuous ECG and frequent blood pressure monitoring recommended for intravenous loading with phenytoin and fosphenytoin
– Phenytoin 15–20 mg/kg IV x1 for loading, maintenance dose phenytoin 100 mg PO/PNGT/IV q8 h (may need to be titrated according to blood phenytoin levels especially if there is a doubt about efficacy or toxicity)
– Fosphenytoin 15 mg/kg IM/IV x1 for loading, maintenance dose fosphenytoin 4–6 mg/kg IM/IV qDay (this total daily dose can be divided to TID) (may need to be titrated according to blood levels especially if there is a doubt about efficacy or toxicity)
– Levetiracetam 1,000 mg IV/ PO/PNGT x1 for loading on the first day; maintenance dose Levetiracetam 500–1500 mg IV/ PO/PNGT BID (generally well tolerated, no known drug interactions)
Antitussives
– Codeine 10–20 mg PO/PNGT q4–6 h
– Dextrometorphan 10–20 mg PO/PNGT q4 h)
Stool softeners
– Docusate sodium 100 mg PO/PNGT BID
– Bisacodyl 5–15 mg PO/PNGT QDay
Antiemetics
– Ondansetron 4 mg IV q6 h
Prevention of gastroduodenal ulcers and antiacids
– Proton pump inhibitors (omeprazole 20–40 mg PO/PNGT qDay, lansoprazole 30 mg PO/PNGT/IV qDay or BID)
– Maalox 30 cc PO/PNGT q4 h
Antihypertensives
Labetalol, followed by hydralazine both used on a PRN basis per institutional protocols to keep systolic blood pressure under 140–160 mmHg during the first few days (until 24 h after aneurysm is occluded). If these two fail to control the blood pressure or if diastolic BP is over 140 mmHg then IV nitroprusside infusion should be started and titrated to necessary BP in an ICU setting.

Table 6.5 (continued)

Prevention of deep venous thrombosis
– Graduated elastic compression (antiembolism) stockings and external pneumatic compression devices
Treatment of hyperglycemia
– using sliding scale insulin administration or intravenous insulin per institutional protocols
Others
– Supplementation with thiamine 100 mg IV/ PO/PNGT qDay and folic acid 1 mg PO/ PNGT/SQ/IM qDay (both to be used until nutrition is reestablished)

Any medical or iatrogenic condition that might increase the bleeding tendency should be aggressively treated. These conditions are discussed under Section Etiologies. Any anticoagulation should be aggressively reversed, platelets and factor deficiencies should be replaced as needed.

General Management

Patients should be admitted to a monitored bed in ideally a private room with low light, put at bedrest and frequent neurological checks should be ordered. They should be kept NPO until after the treatment of the aneurysm. The following ancillary maneuvers are aimed at decreasing the blood pressure surges that might increase the risk of rebleeding before the aneurysm is secured. In our institution, patients are put on SAH precautions that include: "No TV, no radio, no phone calls, lights off, and visitors limited to 10 min/h". Stool softeners (docusate sodium 100 mg PO BID, bisacodyl 5–15 mg PO qDay) should be started, Valsalva maneuver and rectal manipulation should be avoided. Antitussives (codeine 10–20 mg PO q4–6 h, dextrometorphan 10–20 mg PO q4 h) may be used as needed to minimize coughing. Mild sedation using low doses of phenobarbital (total of 90–180 mg over 24 h) or midazolam and analgesia using codeine (15–60 mg PO q4–6 h) or morphine improve patient comfort and can potentially help control hypertension. Excessive sedation should be avoided as it will hamper monitoring of neurological status. Steroids, anticoagulants, and antiplatelets should be avoided. Some centers prohibit the use of nicotine patch until the aneurysm is treated, because of its potential hypertensive effect. Other centers routinely treat all smokers with a transdermal nicotine patch, which may provide the added benefit of preventing agitation secondary to nicotine withdrawal [67, 68]. Graduated elastic compression (antiembolism) stockings and external pneumatic compression devices should be started to prevent deep venous thrombosis and subsequent pulmonary embolism. If invasive procedures such as endotracheal intubation are required, intravenous lidocaine administration is useful to blunt the autonomic response; in these patients good intensive care unit practices (aspiration

precautions, close monitoring of the respiratory, and metabolic parameters) are indeed required but their detailed discussion is beyond the scope of this chapter.

Concurrent medical conditions (infection, hyperglycemia, renal failure, heart disease) should be identified and appropriately managed. A recent study showed that a single incidence of hyperglycemia, fever, or anemia had an independent negative effect on outcome after SAH, even when traditional prognostic variables are controlled for such as severity of SAH by clinical examination or computed tomographic imaging tests, rebleeding, the occurrence of vasospasm-induced stroke, and age [69]. Hyperthermia in SAH patients may develop as a consequence of infection, may be related to blood breakdown in the subarachnoid space or may occur as a consequence of hypothalamic infarction or hemorrhage. Regardless of the time of onset, all patients with hyperthermia should have a full evaluation for potential sources of infection; both fever and its cause should be treated. There is compelling evidence suggesting that hyperglycemia is a predictor of poor outcome in SAH patients [69, 70, 71, 72, 73]. Treatment of hyperglycemia using sliding scale insulin administration or a continuous intravenous insulin infusion might be beneficial in terms of improving the outcome. Intravenous normal saline at a rate of 120–150 ml/h can potentially help decrease the risk of vasospasm and cerebral salt wasting. Supplementation with thiamine and folate can be very useful, especially in people at risk for vitamin deficiencies (alcoholism, post gastro-intestinal surgery). Proton pump inhibitors are used as a preventive measure against gastro-duodenal ulceration (Cushing's ulcers).

As seizures may occur in up to 25% of SAH patients and as they can be devastating in a patient with an untreated aneurysm, patients are loaded with phenytoin (15–20 mg/kg IV) after the diagnosis is made, then a maintenance dose is started orally or through a nasogastric tube. Nimodipine (60 mg PO/PNGT q4 h) is started as evidence suggests that it can reduce poor outcomes and the risk of delayed ischemic neurological deficits due to vasospasm [74]. In patients particularly susceptible to hypotension, an alternative regimen of nimodipine 30 mg PO q2 h can be used.

Appropriate blood pressure (BP) control is an important part of the management of SAH patient and the parameters change between the periods preceding and following the treatment of the aneurysm. The highest risk of rerupture of the aneurysm is within the first 48 h of the index event [75], while the risk of cerebral ischemia from vasospasm is rather low in the first 3 days after SAH. Most authorities therefore recommend keeping the systolic BP under 140–160 mmHg during the first few days, until after the aneurysm is either clipped or coiled. After this time blood pressures may be allowed to rise, or may even be pharmacologically increased if vasospasm is suspected. The first line treatment of elevated blood pressures is IV labetalol, followed by hydralazine; both used on a PRN basis per institutional protocols. If these two fail to control the blood pressure or if diastolic BP is over 140 mmHg then IV nitroprusside infusion should be started and titrated to the goal BP.

Treatment of the Cause of SAH

Together with the initiation of the general and specific measures mentioned earlier, definitive treatment of the aneurysm should be planned. The accepted treatment modalities are surgical clipping or endovascular coiling of the aneurysm. Microvascular neurosurgical clipping has been the definitive treatment for decades while endovascular coiling has become an alternative over the last 15 years [76]. A randomized international study comparing the relative efficacy and safety of coiling versus clipping in 2,143 patients with ruptured intracranial aneurysms potentially amenable to both treatment modalities showed that endovascular coiling was more likely to result in independent survival at 1 year compared to neurosurgical clipping [77, 78]. The risk of rebleeding was low but more common in the endovascular coiling arm, whereas the risk of epilepsy was substantially lower in the patients who underwent coiling. In the individual patient, factors such as age, general medical condition, location of the aneurysm and its relationship to adjacent vessels are considered in choosing the most appropriate treatment modality. Both procedures carry risks and both are operator dependent. In facilities where both options are available, the final decision is mostly based on the interplay among the patient, the neurosurgeon and the interventional neuroradiologist.

While the timing of the intervention is still a matter of debate, since rebleeding most commonly occurs during the first 48 h, early intervention is the preferred approach. Despite the logic of this approach, there is no strong clinical evidence to support early intervention. Quite often surgery is delayed until morning to allow for a well-rested team of surgeons, interventionalists, anesthesiologists, and nurses for these very delicate procedures.

Nevertheless, informing the neurosurgical team about the patient as soon as the diagnosis is made and arranging for admission of the patient to a facility equipped with the necessary staff and technology are important steps in the management of the patients with aneurysmal SAH.

In the rare cases of SAH due to an arteriovenous malformation, studies do not show significant risk of early rerupture, so early intervention is not warranted. Most cases of nonaneurysmal–nonlesional SAH have a fairly benign course but they deserve repeat parencyhmal (brain MRI with and without contrast) and vascular neuroimaging 2 weeks after the acute event in order to rule out any abnormality that might have been missed in the acute stage because of the surrounding hemorrhage or vasospasm. If another underlying cause (systemic or neurological) is detected as detailed under Section Etiologies, that should be treated accordingly.

Recognition and Management of Complications of SAH

Rebleeding

Rebleeding is most common during the first 24–48 h. The risk should be eliminated after successful treatment of the aneurysm. The incidence of rerupture may be as high as 30% in natural history studies and it carries a very

significant morbidity and mortality [79, 80]. All patients whose aneurysm has not been treated and who have worsening in the neurological status (new focal deficit, decrease in the level of consciousness) should have a repeat brain CT immediately to look for evidence of rebleeding. Most of the measures detailed earlier (treatment of the aneurysm, reversing of the bleeding tendency, controlling and preventing BP surges) are aimed at preventing rebleeding. Antifibrinolytics (ε-aminocaproic acid) were once fairly commonly used to decrease the risk of rebleeding, they are now considered in only very selective cases (when the intervention is delayed) as they are shown to increase the risk of vasospasm-mediated ischemia [7].

Vasospasm

Vasospasm is a transient pathology of the intracerebral arteries leading to the stenosis of the vessel lumen. It can present simply as an angiographic finding but it can cause delayed morbidity or death in about 30% of the patients because of cerebral ischemia/infarction [81]. Vasospasm is rather rare before the third day, peaks on days 9–14, and thereafter spontaneously resolves in surviving patients. The extent and location of blood in the subarachnoid space help predict the severity and location of vasospasm (more blood associated with higher risk) [82, 83]. For prevention, nimodipine and IV normal saline infusion should be instituted as soon as the diagnosis is made, as detailed under General Management.

Even in patients without evidence of vasospasm, the blood pressure parameters should be liberalized 24 h post surgery/coiling, lowering systolic BP only if it is 200 mmHg or above, regardless of treatment modality or of the presence of a second unruptured aneurysm. All patients should be kept euvolemic with a central venous pressure over 6 cm H_2O; crystalloids can be used to achieve this goal. Transcranial Doppler (TCD) is an established method of identifying vasospasm noninvasively and is performed daily after the hemorrhage in some centers. In patients with clinically suspected vasospasm, cerebral angiogram is the definitive method of confirming the diagnosis. This procedure also makes possible the performance of direct endovascular interventions for vasospasm such as angioplasty and stenting.

In patients with suspected vasospasm, medical management referred to as "triple H" therapy (hemodilution, hypervolemia, and hypertension) often is started. This therapy was shown to increase cerebral perfusion and reduce ischemia [84]. A hematocrit range of 30–35% is considered optimal in terms of establishing the balance between sustained oxygen carrying capacity and decreased viscosity. Hypervolemia involves the administration of crystalloids at a rate of 150–200 cc/h and, additionally, pressors (i.e., phenylephrine) can be used to increase blood pressure in an attempt to maximize cerebral blood flow. This approach is not without risks and should be used only in an intensive care unit setting.

Hydrocephalus

Hydrocephalus may be seen acutely or in more chronic stages as a result of factors such as obstruction of the CSF pathways or scarring of the arachnoid villi and requires appropriate management. It can present as an acute onset of stupor, prolonged coma, simple drowsiness or, in chronic forms, with gait difficulties. Diagnosis is made by identifying enlarged ventricles on head CT or MRI. Placement of an extraventricular drain can provide a means of both measuring intracranial pressure and of draining CSF to reduce it. Some patients require permanent drainage through a ventriculoperitoneal shunt.

Seizures

Seizures can complicate the clinical picture in up to 25% of cases and prophylaxis is recommended at the time of diagnosis. In patients with clinically mild SAH, anticonvulsants may be discontinued on post-op day 1. In more severe cases, they should be continued until day 15. They can then be stopped after an EEG is found to be free of epileptiform activity.

Cardiovascular Complications

During the first few hours after SAH, hypothalamic dysfunction can lead to cardiac dysrhythmias, due to excessive sympathetic stimulation. This can cause subendocardial ischemia, focal myocardial necrosis, EKG changes, worsening of cardiac indices, and pulmonary edema [85]. Blood pressure control should follow the parameters outlined in the 'General Measures' section. Beta-blocking agents might be the preferred agents since they have the added benefit of preventing ventricular tachycardias and other cardiac arrhythmias. Treatment of cardiopulmonary disorders is beyond the scope of this chapter. Treatment should be directed by an intensivist and the other specialists this physician wishes to consult.

Electrolyte Imbalances

Hyponatremia is the most common electrolyte disorder associated with SAH and may be due to the syndrome of inappropriate antidiuretic hormone production related to hypothalamic dysfunction or cerebral salt-wasting diuresis caused by an increase in circulating atrial natriuretic factor levels. It should be remembered that in the latter condition, because of the presence of true salt wasting, fluid restriction can increase the risk of vasospasm-related cerebral infarction and be associated with worse outcomes [86]. For salt wasting and

a sodium value of less than 135 mg/dl, salt tablets (max 3 gm TID) should be started until the sodium has been corrected. Treatment with fludrocortisone can decrease natriuresis and facilitate hypervolemia [87, 88]. Fludrocortisone 0.1 mg BID can be started in all patients post-operatively if the sodium is below 140 mg/dl (so long as there is no cardiac contraindication) and should be held for values above 140 mg/dl.

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Chapter 7
Subarachnoid Hemorrhage: Long-Term Complications and Prevention

Mahmut Edip Gurol and Harold P. Adams

Introduction

This chapter focuses on long-term sequelae among survivors of subarachnoid hemorrhage (SAH). It also describes screening and prevention strategies. Recurrent rupture of a previously treated or bleeding of a new aneurysm are dreaded complications after aneurysmal SAH because new intracranial bleeding has a high mortality rate. The other long-term complications related to SAH are usually related to the brain damage caused by the acute event. Nonetheless, some cognitive-behavioral consequences are commonly seen in SAH survivors and will be specifically addressed here. Normal pressure hydrocephalus (NPH) is a potential delayed complication. The need for long-term prophylactic treatment to prevent epileptic seizures after the acute event has also been a controversy and the existing evidence will be reviewed.

The recognition of SAH and of cerebral aneurysms among the public at large is facilitated by the relatively easy description of a rupturing balloon in a vessel wall near the brain resulting in a severe headache and a fatal course in many cases. The widespread publicity of the "centers of excellence" that provide treatment of aneurysms with relatively "painless techniques" has also raised public awareness and curiosity. Many internists are and will be asked by patients about the risk factors and prevalence of this condition, the best methods to prevent aneurysms from bleeding, and "How can I find out if I have one of these things?"

Studies of families in which one member has a cerebral aneurysm show an increased risk of aneurysm in first-degree relatives; so the concerns of patients' relatives need to be addressed and the internist should be aware of screening and prevention strategies. Important issues in prevention and screening will be addressed in the second and third parts of this chapter.

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Long-Term Outcome and Complications

Outcome in SAH

Repair of aneurysms after the occurrence of a SAH is the current standard of care. As a result, studies of the natural long-term history of patients with previously ruptured aneurysms, who have not been treated, are mainly from the 1960s or earlier. An average of 10% of SAH patients die before they reach the hospital (range 8–17%) [1, 2, 3, 4]. Studies that attempt to capture the natural history of aneurysmal SAH find that for every five cases, there will be one death by the end of the first day, two deaths by the end of the first week, three deaths by the end of the first 6 months, and four deaths after 20 years [5, 6, 7]. Some landmark studies provide data about the effect of interventions and modern management on case fatality and morbidity. Of 274 patients with a single intracranial aneurysm treated surgically between 1963 and 1970, the overall mortality was 37% [8]. Early medical management and delayed operation among 249 patients studied during the period 1974–1977 in the Cooperative Aneurysm Study (patients treated within 3 days of SAH and evaluated 90 days after aneurysm rupture), showed 36% mortality, 18% surviving with serious neurological sequelae, and 46% with a favorable outcome [9]. In the International Cooperative Study on the Timing of Aneurysm Surgery, where 83% of 3,521 patients underwent surgery between 1980 and 1983, the 6-month mortality was 26%; 58% having a full recovery [10, 11]. In the International Subarachnoid Aneurysm trial (enrollment between 1994 and 2002), 250 (23.5%) of 1,063 patients allocated to endovascular treatment were dead or dependent at 1 year, compared with 326 (30.9%) of 1,055 patients allocated to neurosurgical treatment [12]. It can be concluded that, at least in the context of clinical studies, there has been an improvement in outcomes after SAH over the last four decades but the prognosis is still dismal in many patients.

Long-Term or Delayed Complications

Knowledge of the potential long-term complications after a SAH is essential for successful outpatient management and patient education. We will address specific issues (aneurysm rerupture, hydrocephalus, epilepsy) as well as the larger categories of physical, intellectual, and behavioral disabilities resulting from brain injury at the time of SAH or acute/subacute complications.

Rebleeding

Rebleeding can occur from the site of the repaired aneurysm, from an existing aneurysm in a different location or from a newly discovered aneurysm. A new

type of headache, new severe headache, new focal neurological deficit, or change in the level of consciousness in a SAH survivor should be taken seriously. In such cases, an initial workup, including a repeat neurological exam and a head CT, should be performed. Expert opinion should be sought without delay if there is a suspicion of a new hemorrhage.

A long-term follow up study (up to 21 years) that included 364 patients who were not surgically treated, showed an annual rebleeding rate of 3.5% during the first decade for patients surviving the first 6 months, and 67% mortality associated with a late rebleed [13]. The authors of the study reviewed nine prior studies from the literature and calculated an average annual rebleeding rate of 2.6% (range 0.3–3.2%) [14]. Because of the success of surgical clipping and endovascular treatment, the long-term risk of bleeding among treated patients is much more benign. In the International Subarachnoid Aneurysm Trial (ISAT), the risk of rebleeding from a ruptured aneurysm after 1 year was two per 1,276 patient-years for those in the endovascular treatment arm and zero per 1,081 patient-years for patients in the neurosurgical treatment arm [15].

In another recent study, among a total of 1,010 SAH patients (711 surgically clipped, 299 treated with coil embolization), rerupture of the index aneurysm after 1 year occurred in one patient treated with coil embolization during 904 person-years of follow-up (annual rate 0.11%) and in no patients treated with surgical clipping during 2,666 person-years [16].

These recent reports of relatively low rates of aneurysmal rerupture in the long term are encouraging but they should not lead to the false belief that appropriately treated SAH patients do not rebleed. These data do not take into account bleeding from another aneurysm, either pre-existing or newly developed.

Hydrocephalus

Bleeding or inflammation can potentially cause scarring of the arachnoid granules with secondary disturbances in CSF absorption. This may lead to NPH in the chronic phase [17, 18]. The clinical features of NPH are gait difficulty (magnetic gait or gait apraxia), cognitive impairment (mainly subcortical type) and urinary incontinence. Brain CT and MRI will show ventricular enlargement, out of proportion to the degree of cortical atrophy, and may demonstrate transependymal CSF flow. If this condition is suspected, referral to a neurologist or neurosurgeon is indicated as the patient may benefit from a permanent ventricular shunt. This is best assessed by a specialist who may perform further testing such as a detailed neurocognitive evaluation and/or evalution of the effects of a high volume spinal tap.

Epilepsy

The long-term risk of epilepsy after SAH is estimated to be 10% (with a range of 7–25%) [19, 20, 21, 22]. Epilepsy is more frequent in patients with severe neurological sequelae. It is also more common in the setting of a subdural hematoma or cerebral infarction. Epilepsy is associated with poor functional recovery and quality of life [19, 20]. Unfortunately, the impact of long-term prophylaxis with antiepileptic medications among patients who have not had seizures is unknown. In patients with clinically mild SAH, anticonvulsants usually are discontinued approximately 3 days after surgery [23]. In more severe cases, the medication may be continued until day 15, they can then be stopped after finding an EEG free of epileptiform activity. If the EEG shows an epileptic focus (not just focal slowing), active epileptic discharges, and/or if the patient had a lobar hemorrhage, subdural hematoma, cerebral infarction, or a prior history of seizures, continuing the antiepileptic medication can be the safest approach. There are no data as to the optimal duration of therapy in patients who remain seizure free. It should be remembered that anticonvulsant medications are associated with potential toxic or idiosyncratic side effects [24]. Patients with recurrent seizures should indeed be treated with appropriate medications without hesitation. If there is a doubt about the need for treatment, optimal duration or choice of medication, a neurology referral might be reasonable.

Physical Impairments

Motor or sensory impairments can result from intracerebral bleeding secondary to the aneurysmal rupture, ischemia resulting from vasospasm, or the "trauma" of surgical procedures including clipping of the aneurysm. A sizeable percentage will have neurological sequelae that require rehabilitation. The timing and intensity of rehabilitation depend upon the patient's status and whether the aneurysm has been secured. In general, aggressive rehabilitation is not started until after the aneurysm is treated by surgery or endovascular occlusion. Physical therapy then should be started as early as 24–48 h after the aneurysm is occluded. The goal is to decrease the risk of complications and functional decline resulting from immobility. The intensity of the physical therapy should be tailored according to the patient's overall clinical condition. A team approach involving physical therapy, speech therapy, and occupational therapy specialists help the patient regain and sustain independence in daily activities. In addition, safety issues regarding swallowing, walking and functioning at home and work should be addressed.

Cognitive Impairments

Cognitive deficits in survivors of SAH can be caused by structural brain damage due to the SAH itself or accompanying intracerebral hematomas,

cerebral ischemia or hydrocephalus. Patients with pre-existing dementia (due to Alzheimer-type pathology, vascular causes, or others) are more vulnerable to worsening of their intellectual status after SAH. Metabolic or nutritional problems (electrolyte imbalances or vitamin deficiencies) can complicate the cognitive picture, so their prompt recognition and appropriate treatment are essential for maximum recovery. Overall, cognitive residuals are a leading cause of long-term morbidity after SAH. In some cases, the signs may be difficult to detect.

The largest prospective evaluation of neuropsychological function after SAH to date included a total of 1,001 patients who bled less than 15 days before surgery [25]. They were randomly assigned to intraoperative hypothermia (t = 33°C) or normothermia (37°C) during surgery. Testing, including the Benton visual retention, controlled oral word association, Rey–Osterrieth complex figure, grooved pegboard, and the trail making tests, was completed in a large percentage of patients approximately 3 months after surgery. Many patients showed impairment on at least one test, with global impairment present in 17–20% of patients (18–21% of survivors). This was true even among the patients with the best preoperative condition. There was no difference in the incidence of impairment between hypothermic and normothermic groups [25].

Global cerebral edema and left-sided infarction are reported to be important risk factors for overall cognitive dysfunction [26]; intracerebral and intraventricular hemorrhage (ICH and IVH) [27], hydrocephalus [27], delayed cerebral ischemia (DCI) or infarction [27, 28], and aneurysm location [28, 29] were implicated as risk factors for domain-specific cognitive dysfunction [30]. All types of cognitive deficits, including but not limited to memory impairment, executive dysfunction, attention deficits, aphasia, neglect, and other more subtle defects can be seen. Neuropsychological testing would help identify the cognitive domains involved, the neuropsychologist can also provide counseling and cognitive therapy. A speech therapy specialist also can provide expertise in dealing with language and swallowing impairments.

Behavioral and Occupational Issues

Behavioral problems can arise as a result of structural brain damage, as well as the psychological stress that most patients go through during the acute and more chronic phases; awareness of the physical disabilities also contribute to behavioral problems. A recent study [31] assessing behavioral and occupational consequences of SAH evaluated 610 patients who had been treated by aneurysm clipping after SAH between 1985 and 2001 and who resumed independent living (mean follow-up after SAH, 8.9 year). Of the employed patients, 26% stopped working and 24% worked shorter hours or had a position with less responsibility. On average, patients returned to work 9.4 months after discharge (range, 0–96 months). Seven percent of patients were divorced because of SAH-related problems. Fifty-nine percent of the patients reported changes in

personality, with the most commonly noted changes being increased irritability (37%) or emotionality (29%). Patients with SAH had a statistically significant higher mean depression score than the control population. Approximately 10% of the patients had a hospital anxiety and depression scale score in the range of a probable depressive or anxious state. Only 25% reported a complete recovery without psychosocial or neurological problems.

Patients with depression or other behavioral issues should be treated with appropriate pharmacological and behavioral interventions. It would be prudent to avoid medications that might potentially cause hypertensive attacks (i.e., MAO inhibitors).

Prevention

Modifiable risk factors for SAH are important both for primary and secondary prevention. The modification of the few identified risk factors are important parts of a healthy life style, so medical practitioners should recommend them to all patients. Identification and proper management of the medical conditions discussed in Chapter 6, that are reported to be associated with SAH can help prevent occurrence of SAH. Issues relating to aneurysm screening in some of these patients will be discussed in the last part of this chapter. We will also discuss the management of the aneurysms incidentally found on brain imaging in the light of available evidence.

Modifiable Risk Factors

Hypertension

Hypertension increased the risk of SAH by approximately 2.5-fold in longitudinal and case-control studies and was 30% more hazardous in women [32]. Thus, management of hypertension is important in preventing SAH just as with other types of cerebrovascular disease.

Smoking

The risk of SAH among people who smoke or who are former smokers is twice that for people who do not smoke. A history of smoking was associated with a 2.2- to 3.1-fold increase when compared with those who never smoked, and current smokers had a 2.2- to 3.1-fold increased risk when compared to the group of those who never smoked or formerly smoked, with the most pronounced associations in case-control studies [32]. Efforts to stop smoking should be part of the strategy to prevent SAH just as with other forms of stroke.

Excessive Alcohol Intake

Alcohol consumption in excess of 150 g/week (an average drink contains 12 g of alcohol) is associated with an approximately 2-fold increased risk of SAH in longitudinal and case-control studies, with a more hazardous effect in women [32]. In particular, there is an association of SAH with binge alcohol consumption. Limiting alcohol use should be recommended.

Other Potentially Modifiable Factors

The effects of hypercholesterolemia, diabetes, and the use of hormone replacement therapy on the development and rupture of SAH are rather uncertain. The most recent overview of 14 longitudinal and 23 case-control studies of risk factors for SAH showed trends implying these conditions as providing some protection from SAH [32]. It is possible that patients with diabetes and hypercholesterolemia have a high risk of dying from other causes, and therefore the chances of developing SAH might be smaller than in controls. Diabetes and hypercholesterolemia should still be treated appropriately according to current guidelines.

Management of Patients with Incidentally Found Aneurysm (Without a History of SAH)

With the advent of highly sensitive neuroimaging techniques (MRI/MRA, CT/CTA) incidental discovery of a brain aneurysm is becoming more common. The finding of an aneurysm causes anxiety for both the patient and the physician. Despite the growing body of information about the natural history of unruptured cerebral aneurysms, their management is still controversial. Treatment of an unruptured aneurysm is far from a risk-free procedure. Thus, factors such as potential predictors of rupture in a particular patient, accessibility of the aneurysm, skills of the available interventionalist or neurosurgeon, the age of the patient, and the patient's willingness to pursue intervention should be considered when making a recommendation.

The International Study of Unruptured Intracranial Aneurysms (ISUIA) provides robust data about the natural history of these lesions in patients without a history of SAH. In this study, aneurysm size was the single best predictor of future rupture with posterior circulation location also conferring greater risk of rupture [33, 34]. According to their first publication (based on retrospectively identified patients) the rupture rate was less than 0.1% per year, in patients with unruptured intracranial aneurysms of less than 10 mm diameter [34]. Aneurysms with a diameter 10 mm or larger ruptured at a rate of 1% per year. Giant aneurysms (>25 mm in diameter) had a rate of rupture of

approximately 6% in the first year [34]. The ISUIA investigators recently reported natural history data from a *prospective* cohort involving 1,077 patients with unruptured aneurysms without prior SAH (with a mean follow-up of 4.1 years) [33]. Rupture rates and predictors of future rupture followed the same patterns as with the retrospective ISUIA cohort [34], but the rupture rates for the prospective cohort were higher (than those for the retrospective cohort) for unruptured aneurysms 7 mm or greater in diameter [33]. Patients with a prior SAH from an aneurysm also had a higher risk of bleeding from a second, incidental aneurysm.

A family history of aneurysmal SAH is associated with an increased risk of rupture. The presence of other comorbid states should be carefully evaluated in an attempt to find potentially treatable conditions (infectious, inflammatory, or vasculitic diseases) as well as to assess the risk of periprocedural intervention directed to the aneurysm.

Patients with an incidentally discovered unruptured intracranial aneurysm should be referred to a specialist (neurologist, neurosurgeon, or interventional neuroradiologist) with special expertise in the management of aneurysms and SAH, who can engage the patient in a full discussion of the risks of this condition and potential treatments.

Genetic Issues

Evidence showing the importance of genetic factors in the pathogenesis of SAH and intracranial aneurysms continues to increase. The first-degree relatives (parent, sibling, or child) of patients with these conditions have up to seven times greater risk than the general population for having a SAH or intracranial aneurysm [35, 36, 37, 38, 39]. About 10% of patients with aneurysmal SAH have a first- or second-degree relative with SAH or unruptured intracranial aneurysms [35, 36, 39, 40, 41, 42]. Having an affected sibling is associated with a greater risk of having an aneurysm than having an affected parent or child [35, 43, 44]. A family history of aneurysmal SAH is associated with increased risk of rupture. Having more than one affected relative is associated with a higher chance of having an aneurysm and is associated with a greater life-time risk of SAH in the individual [35, 44]. As the presence of a positive family history is the most important (albeit not the most common) identifiable risk factor for aneurysmal SAH, decisions regarding screening and treatment in these people are even more critical than in any other population at risk. Expert advice should generally be sought in these cases. Aneurysmal SAH is probably caused by an interaction of genetic and environmental factors so that the mode of inheritance is complex (not of the simple mendelian type). Further identification of genes or inheritance patterns may improve advice regarding screening and treatment in the future.

Aneurysm Screening in Primary and Secondary Prevention

The noninvasive screening methods are computerized tomography angiography (CTA) and magnetic resonance angiography (MRA). Both techniques may miss very small aneurysms, but these are the lesions that are typically not treated even if they are detected.

Nevertheless, the finding of an asymptomatic aneurysm in itself does not solve the problem. The treatment modalities discussed in Chapter 6 carry risks; the information that the person has an aneurysm can result in problems with driving privileges and insurance issues. This information is also a huge emotional burden for the patients and their families who would need to cope with this for the rest of their lives. Indeed, the results of centers with different levels of expertise and intervening on lesions of different complexity would vary but overall, the risk of complications from treatment of unruptured aneurysms can be estimated around 5% for death or persisting impairment in activities of daily living, and 10% for persisting cognitive deficits or reduced quality of life [45]. In general, the risk of rupture of small aneurysms (<7 mm) is low based on data from ISUIA, especially if they are in the anterior circulation [33]. In the absence of a family history, these small aneurysms can probably be followed with repeat noninvasive imaging. For larger aneurysms, and in the presence of a positive family history, there is not enough data to make general statements about the appropriateness of intervention. In all cases, the decision about screening should be made only after an adequate discussion with the patient regarding potential risks and benefits. Again, liberal use of experts in this regard is recommended. Some specific situations are discussed below.

Screening for Aneurysms in the Early Phase After SAH

Most patients undergo at least one digital subtraction angiography (ideally a four vessel exam) during the initial workup for SAH or at follow up. CTA and MRA are the noninvasive methods of obtaining similar information. As 12–31% of patients harbor multiple aneurysms, careful evaluation of all cerebral vessels is mandatory. If an aneurysm is not found on early neuroimaging, a repeat exam in 2–3 weeks is warranted as an existing aneurysm can be missed due to the presence of vasospasm.

Screening for Newly Formed Aneurysms Late After SAH

Patients who have had an aneurysmal SAH have a risk both of aneurysm recurrence and of new aneurysm formation. The Dutch ASTRA group

reported follow-up CT angiography on 610 patients 1–15 years after surgical clipping of a ruptured aneurysm, finding that 16% of patients had developed new aneurysms [46]. While this might seem significant, according to a Markov decision model, screening of individuals with a previous SAH only slightly increased life-expectancy while at the same time, it reduced quality of life and increased costs [47]. For now, the identification of patients with a high risk for new aneurysm formation and rupture is not possible on evidence-based grounds, so repeated neurovascular imaging in long-term follow up is not routinely recommended except in those (especially women) with an initial episode at very young age and multiple aneurysms at time of the initial SAH [47].

Screening for Aneurysms in First-Degree Relatives of SAH Patients

Individuals with two or more affected first-degree relatives should be screened for this condition starting around 20 years of age, with a subsequent exam in 5 years if the first evaluation was negative. Repeating the screening (CTA or DSA) in 5 years showed a newly developed aneurysm in 7% of such individuals [48]. In identical twins with SAH occurring in one of the twins, the other may need to be screened. Screening may not be advised if the life expectancy of the individual is already short because of other medical conditions.

To prevent one episode of fatal SAH, 300 individuals with only one affected first-degree relative would need to be screened, based on the current evidence [45]. In general, screening is not recommended if only one relative has had a SAH. If such an individual requests screening, recommendations should be made after a thorough discussion of the evidence. If the affected relative was younger than 40 years of age at the time of SAH, if he/she had multiple aneurysms or if the individual is very anxious about SAH, screening may be reasonable.

Screening for Aneurysms in Patients who have a Medical Condition Known to be Associated with SAH

Patients with autosomal dominant polycystic kidney disease are at high risk of aneurysmal SAH (relative risk 4.4) and therefore should be screened for intracranial aneurysms [45]. Cerebral aneurysms have also been associated with Ehlers–Danlos syndrome type IV, but because the fragility of the vessel wall substantially increases the risks of treatment in this condition, these patients are not typically advised to have screening [45, 49, 50].

Recommendations for General Follow up After SAH

For the internist who manages a patient discharged after SAH without significant ongoing problems, a reasonable follow-up plan would be an evaluation of the patient in 1 month, then again in 3 months and if no significant issues develop, to repeat evaluations every 6 months three times before resuming regular annual visits. The potential cause(s) of the SAH in the particular patient should be revisited (see Section Etiologies in Chapter 6). Treatment of hypertension, cessation of smoking, and avoidance of heavy alcohol use are important in both primary and secondary prevention. Follow-up imaging of the repaired aneurysm is typically ordered by the neurosurgery or interventional neuroradiology teams according to institutional guidelines.

The internist, with the help of neuropsychology, speech therapy, physical therapy, and occupational therapy specialists, should address cognitive, behavioral, and physical sequelae from SAH. If there are concerns regarding seizure prophylaxis/management and diagnosis of hydrocephalus, appropriate testing and referral to neurology should be obtained.

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Part I
Special Topics

Chapter 8
Ischemic Stroke in Young Adults

Eric McDade and Steven Kittner

Introduction

The prevalence of cerebrovascular disease is more than twice that of multiple sclerosis (MS) in adults aged 18–44 [1]. Almost 120,000 women and 105,000 men in the US under age 45 have suffered a stroke [2]. Consequently, those involved with the primary care of adults will be caring for young adults with strokes. In the following sections, we will provide the reader with a means of approaching and diagnosing the cause of ischemic stroke in young adults.

The Approach to the Young Patient with Possible Ischemic Stroke

Mimics of Ischemic Stroke

In approaching the young patient with stroke, one must consider that several conditions can mimic ischemic stroke including seizures, MS, tumors, and infections. The abrupt and temporary motor, sensory and cognitive affects of seizures, as well as a focal, post-ictal paralysis can commonly mimic cerebral ischemia. However, the time to resolution of symptoms, presence of aura or premonitions as well as the presence of "positive" symptoms such as convulsions and paresthesias and lack of typical MRI evidence of ischemia can often discern between seizures and stroke. MS may also mimic stroke, in that it presents with focal neurological dysfunction and may be associated with an abnormal brain MRI. A history of optic neuritis and evidence for spinal cord involvement might help to make the diagnosis of MS, and make stroke less likely. Some neuroimaging features are particularly characteristic of early MS, such as ovoid lesions in the periventricular white matter with the major axes perpendicular to the ventricular surface. Abnormalities of the corpus callosum,

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U-fibers, and optic nerves, may also allow for the differentiation of MS from cerebrovascular disease [3]. Often it is necessary to evaluate for both ischemic stroke and MS and longitudinal follow-up may be needed to establish the diagnosis. Tumor and, rarely, CNS infection may also present with stroke-like symptoms but are accurately established as non-ischemic events with appropriate work up.

Considerations for the Young Patient with Proven Ischemic Stroke

The history can often provide important clues to the diagnosis of ischemic stroke. If a thorough history cannot be provided by the patient, it is paramount that others be located to provide necessary details. The following aspects of the history, symptoms, and signs are important in an accurate diagnosis.

- Cerebral venous thrombosis (CVT) should be considered in the patients with a new onset headache and focal signs, particularly in the presence of seizures or mental status changes. The headache is usually subacute (more than 48 h but less than 30 days), but can rarely be sudden in onset [4].
- Vascular risk factors and systemic disease remain important in young as well as older patients [5, 6]. Young adults with multiple vascular risk factors are at high risk for premature stroke, either large artery extra- or intracranial vessels or small vessel/lacunar disease. Systemic diseases such as thrombotic thrombocytopenic purpura or sickle cell disease are proximate causes and have specific treatments. Conditions such as systemic lupus erythematosis (SLE) and AIDS confer an increased risk of stroke but still require further investigations.
- Family history of early arterial events or venous events at any age is particularly important in the evaluation of early onset stroke. Early thrombotic events in the arterial circulation can be a clue to inherited atherogenic risk factors or monogenic causes of stroke. Specific monogenetic conditions are associated with small vessel disease (CADASIL), arterial dissection (Marfan's syndrome, Ehlers–Danlos Type IV), or large or small vessel disease (Fabry disease, pseudoxanthoma elasticum, neurofibromatosis type I). These and other genetic conditions are uncommon but should be considered when the etiology of the stroke is unknown, particularly in the presence of a family history, or when there is a distinctive clinical phenotype, such as recurrent dissection or severe small vessel disease without risk factors, see Table 8.1 [7, 8, 9]. Venous thrombotic events can be an important clue to an inherited hypercoagulable state and may raise suspicion for paradoxical embolism or CVT.
- Head or neck trauma in the past 6 months, including chiropractic manipulation of the neck, can be a clue to cervical artery dissection. However, since

Table 8.1 Common Mendelian disorders of Stroke

	History		System-based findings				
Disease type	Patient and family history	Age of onset, predilection	General	Nervous system	Associated abnormal findings and laboratory tests	Inheritance and chromosomal location	Ancillary diagnostic tests
Large arterial disease							
Homocystinuria OMIM: 236200	• Seizures • Arterial and venous thrombotic events • Osteoporosis • PVD • Psychiatric disorders	• Occasional failure to thrive in infancy • High risk of thrombotic events in childhood	• Marfanoid habitus – tall, thin body • Myopia • Ectopia lentis • MVP • MI • Livedo reticularis • Foot deformities – high arched feet • Arachnodactly	• Cognitive impairment – mental retardation • Seizures • Myelopathy and neuropathy are less common	• Homocystine is elevated in blood, CSF and urine; • Methionine elevated in blood and urine	• AR, 21q22.3	• Urine/serum homocystine • Urine/serum methionine
Familial hypercholesterolemia (Type II-a) OMIM: 143890	• Early MI • PVD • Hereditary dyslipedmia	• CAD after 30 years in heterozygotes, childhood in homozygotes	• Corneal arcus (by third decade) • Xanthelasma • Bruit – atherosclerosis • CAD • Tendon xanthomas – (Achilles common)		• Serum: elevated LDL, elevated cholesterol	• AD, 19p13.2	• Fasting lipid panel
Tangier disease (familial HDL deficiency, Type I) OMIM: 205400	• Extremity pain • Asymmetric sensory deficits or abnormalities	• Infancy or childhood with pharyngeal findings	• Adenopathy • Orange tonsils – cholesterol laden • Hepotospleno-megaly	• Facial diplegia • Weak intrinsic hand muscles • Asymetric Polyneuropathy – motor and sensory, deficit of pain/temp.	• Serum: low HDL, low LDL, low cholesterol, elevated triglycerides, low phospholipids, abnormal	• AR, 9q22-q31	• Fasting lipid panel • Denervation apparent on EMG

Table 8.1 (continued)

Disease type	History		System-based findings		Associated abnormal findings and laboratory tests	Inheritance and chromosomal location	Ancillary diagnostic tests
	Patient and family history	Age of onset, predilection	General	Nervous system			
	• Hereditary dyslipidemia • Early MI				chylomicron remnants		
Small vessel disease							
CADASIL – Cerebral autosomol dominant; subcortical infarcts and leukoencephaly OMIM: 125310	• Migraines – with prolonged aura • Familial hemiplegic migraine • Early onset dementia • Manic episodes • Depression • Seizures	• Early adulthood • Migraines by age 30 • First stroke by age 45	• Lumbar spondylosis	• Cognitive impairment • Pseudobulbar palsy and dementia • Progressive motor disability	• MRI with multiple subcortical infarcts, both clinically evident and silent	• AD, 19p13.2-p13.1 Notch 3 gene	• MRI
Fabry disease OMIM: 301500	• Anhidrosis • Periodic fever • Lancinating pain in hands and feet – often initial symptom, heat or exercise may induce • Cardiomegaly with MI • Arthritis	• Children and young adults with paresthesias • Stroke occurs in adults	• Retarded growth • Corneal opacity • Crystalline deposits in conjunctiva • Cardiomegaly • MI • Renal disease • Telangiectasias • Angiokeratomas – with primary locations on lower abdomen, scrotum, upper thigh	• Neuropathy – limb paresthesias • Autonomic dysfunction • Pain episodes induced by exercise • Seizures	• Proteinuria • Lipid laden macrophages in bone marrow	• X-linked, Xq21.33-q22 • Complete form in males • Incomplete form in female carriers	

Table 8.1 (continued)

Disease type	History		System-based findings		Associated abnormal findings and laboratory tests	Inheritance and chromosomal location	Ancillary diagnostic tests
	Patient and family history	Age of onset, predilection	General	Nervous system			
Hematologic Diseases							
Sickle Cell disease OMIM: 603903	• Acute pain crisis with physical exertion • Unexplained fevers • Abdominal, bone, and chest pain • Large or small vessel occlussive disease • Intracerebral epidural or subdural hemmorhages • Subarachnoid hemorrhages	• Black children	• Slow growth • Jaundice • Proliferative retinopathy • Acute chest syndrome • Asplenia – autosplenectomy • Hand foot syndrome with: swollen joints, short middle finger, short second toe, non-healing ulcers		• Aplastic crisis induced with Parvo B-19 virus	• AR, 11p15.5 • Missense mutation, valine for glutamte in position 6 of beta hemoglobin chain	• Follow-up with transcranial doppler studies recommended
Protein C deficiency OMIM: 176860 Protein S deficiency OMIM: 176880	• DVT • Recurrent thrombotic events • Warfarin induced skin necrosis • Purpura fulminalis neonatalis	• Young adults • Occasional late onset with homozygosity with Protein C deficiency	• Pulmonary embolism • Intraabdominal venous thrombosis • Superficial thrombophlebitis	• Cerebral arterial and venous thrombosis	• Vitamin K antagonists may worsen • Acquired deficiencies may occur with pregnancy, liver disease, DIC, oral contraceptive use, warfarin use, and following surgery	• Protien C – AD, 2q13-q14 • Protien S – AD, 3p11.1-q11.2	• Protein function test • No heparin for greater than 72 h

Table 8.1 (continued)

	History		System-based findings				
Disease type	Patient and family history	Age of onset, predilection	General	Nervous system	Associated abnormal findings and laboratory tests	Inheritance and chromosomal location	Ancillary diagnostic tests
Factor V Leiden mutation OMIM: 227400	• Cerebral venous thrombosis • DVT	• Young adults		• Cerebral venous thrombosis	• Prolonged bleeding time • Prolonged clotting time • Prolonged one–stage prothrombin time, corrected by rabbit plasma	• AR, 1q23 • Point mutation G to A nucleotide 1691R506Q protien mutation, glutamine for arginine at residue 506	• Protein function test • No heparin for greater than 72 h • Preferably off warfarin
Mitochondria Based Disease							
MELAS – mitochondrial encephalopathy lactic acidosis and stroke OMIM:540000	• Seizures – Grand Mal • Episodic vomiting • Visual disturbances • Episodic migraines • Deafness • Maternally inherited diabetes	• Infancy – failure to thrive • Children or young adults – stroke	• Short stature – children • Opthalmoplegia • Pigmentary retinal degeneration • Cardiomyopathy • Cardiac conduction defects • Progressive renal dysfunction	• Seizures • Myoclonus • Dementia • Weakness – reduced muscle mass • Deafness	• Elevated serum lactic acid and pyruvic acid; • Ragged Red fibers on muscle biopsy; • Progressive renal dysfunction • MRI – multifocal infarcts in non vascular distribution	• Mitochondrial • Defect in transfer RNA for leucine	• Serum lactic and pyruvic acid levels elevated at rest, markedly increase with exercise • Muscle biopsy
Connective tissue disorders							
Ehlers-Danlos Syndrome (Type IV) OMIM: 130050	• Cerebral aneurysms • Arterial dissections	• Typically death by age 40–50 years secondary to dissecting aneurysms		• Cerebral hemorrhage	• Premature delivery because of cervical insufficiency or membrane fragility	• AD, 2q31 • Collagen III, alpha-1 gene – COL3A1	• Echocardiogram

Table 8.1 (continued)

Disease type	History		System-based findings		Associated abnormal findings and laboratory tests	Inheritance and chromosomal location	Ancillary diagnostic tests
	Patient and family history	Age of onset, predilection	General	Nervous system			
	• Easy bruising – vascular fragility • Excessive scarring s/p surgery						
Marfan syndrome OMIM: 154700	• Cerebral aneurysms • Internal carotid artery dissection • Premature arthritis	• Typically death by age 40–50 years secondary to dissecting aneurysms		• Cerebral hemorrhage	• Dilated aortic root • Coarctation of aorta	• AD, 15q21.1 • Fibrillin 1 gene	• Protien based – immunohistochem-isrty • Echocardiogram
Fibromuscular dysplasia OMIM: 135580	• Headaches • Myocardial infarction • Tinnitus and/or vertigo • Transient retinal or cerebral ischemia • Dissection – carotid aneurysms • SAH	• Female > Male • Typically middle aged females • White > Blacks		• Cerebral hemorrhage	• MRA – "String of beads" in carotid arteries at cervical levels C1 and C2	• AD, location unknown	• Carotid doppler ultrasound

Table 8.1 (continued)

	History		System-based findings				
Disease type	Patient and family history	Age of onset, predilection	General	Nervous system	Associated abnormal findings and laboratory tests	Inheritance and chromosomal location	Ancillary diagnostic tests
Pseudoxanthoma elasticum	• HTN			• Cerebral hemorrhage	• Females – estrogen, pregnacy, puberty may increase skin lesions	• AD and AR forms, 16p13.1	
AD Form OMIM: 177850 AR Form OMIM: 264800	• Angina – CAD, MI • Gradual vision loss • Epistaxis • Hematuria • Arterial dissections • GI Hemorrhages • PVD						

Adapted from Ref. [7].

Abbreviations: ASD – atrial septal defect, CAD – coronary artery disease, CHF – congestive heart failure, DVT – deep venous thrombosis, FMD – fibromuscular dysplasia, GI – gastrointestinal, HDL – high density lipoprotein, HTN – hypertension, MI – myocardial infarction, MVP – mitral valve prolapse, PVD – peripheral vascular disease, SAH – subarachnoid hemorrhage, VSD – ventricular septal defect.

most dissections are spontaneous, the absence of a trauma history does not substantially lessen the probability of this diagnosis.

- Drug abuse within the past 24 h, particularly cocaine, is associated with stroke but should not preclude further evaluation. A toxicology screen is mandatory on admission for all early onset stroke patients. Additionally, inquiry should be made for weight loss supplements as sympathomimetic drugs can be associated with vasculitis [10].
- The 6 weeks post-partum is a time of increased risk of both arterial stroke and CVT [11].

Examination of the patient should include careful attention to the cardiovascular system, skin, and eye. An ophthalmologic consultation may be useful because many systemic diseases associated with stroke have ocular manifestations.

Overview of Causes of Ischemic Stroke in Young Adults [6]

Of 428 first ischemic stroke patients 15–44 years of age presenting to all acute care hospitals in the Baltimore–Washington area, 42% had a probable cause, 27% had a possible cause, and 31% had no identified cause. Figure 8.1 shows the distribution of etiologies for the 178 cases with a probable cause. Cardioembolism was the largest category, constituting 37% of those with a probable cause, with endocarditis, cardiomyopathy, and valvular heart disease being most common. Lacunar stroke or small vessel disease without the presence of another probable etiology constituted 24%. It should be noted that lacunar stroke as a category is descriptive rather than being a "smoking gun" cause. A miscellaneous category of hematologic and other disorders constituted 21%,

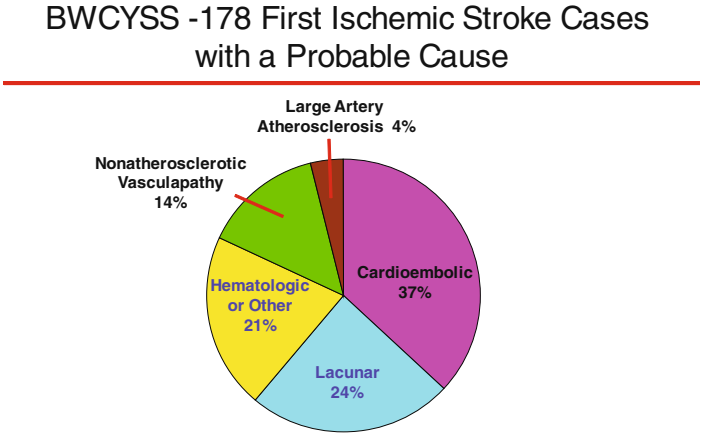

Fig. 8.1 Percent Distribution of Probable Causes in the Baltimore-Washington Cooperative Young Stroke Study. Adapted from Ref. [6]

including sickle cell disease, thrombotic thrombocytopenic purpura, SLE, and iatrogenic causes among others. Large artery atherosclerosis constituted only 4% of cases with these patients tending towards the upper end of the age range and having multiple vascular risk factors. In contrast, nonatherosclerotic vasculopathy, constituted 14% of cases with carotid dissection representing the majority of these cases and vasculitis less commonly.

Special Topics

Patent Foramen Ovale (PFO)

The prevalence of PFO by TEE in the general population is approximately 20% [12]. PFO and especially PFO with atrial septal aneurysm (ASA) are associated with stroke in young adults [13] with the presumed mechanism of "paradoxical" transcardiac arterial embolization of venous thrombi. Although the association is clear, there are limited clinical trial data to guide management. An American Academy of Neurology Consensus statement in 2004 concluded that the evidence is insufficient to determine if warfarin or aspirin is superior in preventing recurrent stroke or death or to evaluate the efficacy of surgical or endovascular closure [22]. Current treatment options consist of medical treatment with aspirin or warfarin with or without surgical or transcatheter closure. Randomized clinical trials comparing medical management to transcatheter closure are ongoing and are expected to be reported shortly. Pending additional randomized clinical trial evidence, we discuss our recommendations for workup and treatment of patients with PFO and stroke.

The diagnosis of PFO can be difficult and the management of early-onset cryptogenic stroke in association with PFO is controversial [15]. Clinical diagnosis of a right-to-left shunt is most commonly accomplished using an air-contrast or "bubble" echocardiogram, wherein the agitated saline is injected into the venous system and provocative maneuvers that increase right-sided cardiac pressures are performed, such as cough or valsalva. Transthoracic echocardiography (TTE) has only a 50–75% sensitivity compared to transesophageal echocardiography (TEE) [16, 17].

TEE may be falsely negative for a variety of reasons, especially lack of an adequate valsalva due to oropharyngeal instrumentation for the procedure and patient sedation [18]. False positive TEE tests are also rarely possible [18]. If the clinical setting is strongly suspicious for a cardioembolic stroke or if an ASA is found, a negative TEE can be followed by an air contrast transcranial Doppler for microemboli detection at a specialized center. In the presence of a right-to-left intracardiac shunt, microbubbles are insonated in the middle cerebral artery, usually within three cardiac cycles of the injection.

Although paradoxical embolism is the putative cause of stroke in the setting of PFO, an embolic source is rarely identified. Nonetheless, if a PFO is

identified in a young patient with cryptogenic stroke, lower extremity venous doppler studies are indicated because a venous source of embolism would mandate short-term anticoagulation for prevention of pulmonary embolism and it also increases confidence in the diagnosis of paradoxical embolism as the stroke mechanism. If the venous doppler study is normal, then pelvic vein MR venograms should be performed. This test is available at many MRI imaging centers. Cramer et al. found that 20% of patients with cryptogenic stroke had "high probability MRV" for pelvic vein thrombosis compared to 4% with stroke of determined origin [19]. Additionally, in those patients rated as a high probability of having a pelvic vein thrombosis, PFO was identified in 61% of cryptogenic stroke patients compared to 19% of those with identified cause.

If no obvious systemic embolic source is identified, we recommend a hypercoagulable work be performed as some studies, though not all, have found an increased prevalence of inherited thrombophilia [20, 21]. The presence of a venous prothrombotic state would increase diagnostic confidence that paradoxical embolism is the pathogenic mechanism. Please refer to the section on hypercoagulable state regarding appropriate work up.

There is currently no consensus regarding management of cryptogenic stroke in the presence of a PFO. The 4-year recurrent stroke risk in aspirin-treated patients less than age 55 with cryptogenic stroke who have a PFO and an ASA has been estimated to be near 15% compared to 2–4% for patients without PFO or with PFO only [14]. Current stroke prevention options consist of medical treatment with aspirin or warfarin and surgical or transcatheter closure. An American Academy of Neurology Consensus statement in 2004 concluded that the evidence is insufficient to determine if warfarin or aspirin is superior in preventing recurrent stroke or death or to evaluate the efficacy of surgical or endovascular closure [22]. Clinical trials comparing medical management to transcatheter closure are ongoing and are expected to be reported shortly. Warfarin should be considered particularly in the presence of PFO with ASA, large PFO, PFO with venous thrombosis or thrombophilia, and recurrent thrombosis while on maximal antiplatelet agents. A high flow left-to-right shunt due to an atrial septal defect other than a PFO may mandate closure for cardiac reasons.

Dissection of the Carotid or Vertebral Arteries

Dissection is a common cause of stroke in young adults, accounting for approximately 15% of cases. The vast majority are spontaneous dissections, although dissection is also associated with major trauma such as motor vehicle accidents or minor trauma such as roller coaster rides and chiropractic manipulation. Dissection should be suspected in any patient with Horner's syndrome (carotid artery) or with symptoms of cerebral or retinal ischemia, particularly with associated head or neck pain. Carotid duplex is of very limited value in

detecting dissection. MR imaging of the neck and head with axial fat suppressed T1-weighted sequences can detect small hematomas in cervical vessels that can be missed with MR, CT, or conventional angiography. MR angiography may identify tapering or occlusion of the carotid artery, generally several centimeters distal to the bifurcation, or of the vertebral artery, generally during its course through the bony transverse foramina of C6–C2 or the subsequent C1 atlas loop before it enters the skull [23]. In cases where arterial dissection is strongly suspected but there is an absence of MR evidence of dissection, CT angiography or catheter angiography may detect evidence of a small pseudoaneurysm, which may be the only clue that dissection has occurred [24].

In most cases of dissection, no specific cause is identified. However, a detailed family history may suggest a monogenetic cause of stroke. Table 8.1 provides clues to these conditions that should be sought in the history and examination in the setting of dissection. For those patients with evidence of an inherited condition contributing to the dissection, genetic counseling should be available prior to additional testing to confirm a monogenetic cause of stroke.

Prognosis of extracranial cervical artery dissection is generally good, while intracranial dissection is often associated with a poor outcome. The risk of recurrence is 2% in the first month, falls to 1% per year in the following decade and is higher in patients with a family history of dissection [25, 26]. The risk of rupture from a pseudoaneurysm is exceedingly rare; conservative management is generally indicated [27] .

Prevention of recurrent stroke due to dissection is controversial and usually involves anticoagulation or antiplatelet agents. Historically, acute anticoagulation with heparin has been advocated, followed by warfarin administration with an INR goal of 2.0–3.0 for 3–6 months, unless the infarct was large or there was intracranial extension of the dissection. In recent years, based on increasing evidence of the risks of acute anticoagulation and lack of corresponding benefit in other non-cardioembolic stroke settings, anticoagulation has been increasingly questioned by the stroke community, and many stroke specialists use antiplatelets as first-line therapy [28, 29]. Surgical or transcatheter management is rarely needed and is generally considered only in those who continue to have symptoms on medical therapy.

All patients should be informed of reasonable restrictions including avoiding heavy lifting, chiropractic neck manipulation, roller coaster riding, and participation contact sports. Patients should be educated not only about the signs and symptoms of cerebral ischemia, but also be taught to recognize the symptoms and significance of a newly occurring Horner's syndrome.

Hypercoagulable Disorders

Currently, there is much debate surrounding the association of prothrombotic conditions with arterial ischemic stroke and, particularly, regarding the role of

anticoagulation for these conditions [30]. The strength of association between these conditions and ischemic stroke is relatively weak suggesting that these conditions may be contributory risk factors, like hypertension, but not a sufficient cause, like atrial fibrillation or carotid stenosis [31]. There are no long-term observational or randomized follow-up studies comparing outcome for patients treated with warfarin versus antiplatelet medications. Thus, the optimal management of a patient, young or old, with ischemic stroke and a prothrombotic state is unknown. It is the authors' opinion that a "shot-gun" approach to the search for a prothrombotic state in every young stroke patient should be avoided as it may lead to unnecessary cost, confusion, false-positives test results, and potentially serious medical complications associated with anticoagulation.

Testing for prothrombotic states is recommended in the setting of arterial stroke in a young person if there is: (1) family history of arterial or venous thrombotic events at a young age, such as less than age 60, (2) a PFO or other right-to-left intracardiac shunt is diagnosed during evaluation, (3) prior arterial or venous thrombotic events, or (4) a history of recurrent miscarriages before ten weeks of gestation or one miscarriage after ten weeks of gestation or early term deliveries before 34 weeks gestation. Additionally, a history of thrombocytopenia or livedo reticularis should lead to testing for antiphospholipid antibodies. All patients with CVT should have a comprehensive screen for hypercoagulable states. False positive results for hypercoagulable conditions may occur in the setting of acute stroke. For this reason, if abnormalities are found during the acute period, repeat testing after 1 month should be done for confirmation. However, since testing is not valid on warfarin, testing should be done before anticoagulation is started or after anticoagulation has been stopped. These caveats do not apply to gene-based tests for mutations.

The hypercoagulable states can be divided into heritable and acquired conditions (see Table 8.2). Heritable hypercoagulable states that have been linked to venous thrombosis include: deficiencies of protein C, protein S, and antithrombin III; activated protein C resistance associated with factor V Leiden mutation; prothrombin 20210A mutation; and disorders of fibrinogen. However, their association with ischemic stroke is not nearly as strong or consistent. Thrombotic events likely represent an interaction between genetic predisposition and modifiable exposures, such as smoking, hormone use, and other traditional atherosclerotic risk factors [32]. Although moderate hyperhomocysteinemia is generally acquired secondary to nutritional deficiencies, markedly elevated levels can rarely occur on a genetic basis and can be associated with both venous and arterial thrombosis. High dose B vitamin replacement may lower homocysteine levels in this setting.

There are currently no evidence-based data regarding the antithrombotic treatment of stroke in the setting of an inherited thrombophilia. The 2006 American Stroke Association guidelines for prevention of recurrent stroke state that "In the absence of venous thrombosis, long-term anticoagulation or antiplatelet therapy is reasonable" and "patients with a history of recurrent

Table 8.2 Hypercoagulable conditions associated with stroke

Inherited conditions:
• Sickle cell disease and trait
• Prothombin 20210A gene mutation[a]
• Antithrombin III deficiency[a]
• Factor V Leiden[a]
• Protein C deficiency[a]
• Protein S deficiency[a]
Acquired conditions:
• Antiphospholipid antibody syndrome[a,b]
• Heparin-induced thrombocytopenia and thrombosis[a]
• Myeloproliferative disorders[a]
• Thrombotic thrombocytopenic purpura[a]
Additional blood disorders associated with stroke:
• Secondary polycythemia
• Disseminated intravascular coagulation
• Malignancy
• Nephrotic syndrome
• Hyperhomocysteinemia
• Paroxysmal nocturnal hemoglobinuria
• Hypereosinophilic syndrome
• Hyperfibrinogenemia
• Thrombocythemia

[a]Those conditions associated with known predisposition to coagulopathy.
[b]Antiphospholipid antibodies rarely inherited.
Adapted from Levine SR. Hypercoagulable states and stroke: A selective review. CNS Spect 2005; 10(7):567–578.

thrombotic events may be considered for long-term anticoagulation [33].” The authors generally consider long-term anticoagulation for those patients with repeated thrombotic events.

There are a number of acquired coagulopathies associated with cerebral ischemic events (see Table 8.2) with the antiphospholipid antibodies being one of the most common. Antiphospholipid antibodies are a heterogeneous group of antibodies, which include anticardiolipin (aCL) antibodies, antibodies to beta-2-glycoprotein-1, and lupus anticoagulant (LAC). Although there is more evidence for an association of antiphospholipid antibodies and arterial ischemic stroke than for other hypercoagulable states, the epidemiologic association is a weak one and by no means a “smoking gun” [34, 35]. The presence of these antibodies should not be considered the ‘cause’ of a stroke, but rather a predisposing factor and other etiologies should be pursued.

There are limited data on the benefit of anticoagulation in patients with ischemic stroke and antiphospholipid antibodies. A substudy of the Warfarin vs. Aspirin Recurrent Stroke Study (WARSS) identified patients with aCL antibodies and/or LAC and found that the presence of antiphospholipid

Table 8.3 Features of the antiphospholipid antibody syndrome (APS)

Clinical features:
• Deep vein thrombosis
• Arterial thrombosis
• Livedo reticularis
• Miscarriages
• Libman sacks/ verucous endocarditis
Laboratory features:
• Prolonged aPTT
• False positive VDRL
• Thrombocytopenia
• Hemolytic anemia
• Positive ANA
• Evidence of anticardiolipin antibodies or lupus anticoagulant (LAC)

antibodies did not predict an increased risk of thrombotic events over 2 years or the response to aspirin or warfarin therapy [36]. The 2006 American Stroke Association guidelines [33] for prevention of recurrent stroke state that antiplatelet therapy is reasonable in cases of cryptogenic ischemic stroke or TIA associated with antiphospholipid antibodies and that warfarin therapy with an INR of 2.0–3.0 is reasonable in cases that meet criteria for antiphospholipid antibody syndrome with venous and arterial occlusive disease in multiple organs, miscarriages, and livedo reticularis (Table 8.3). It is also the authors' practice to institute anticoagulation if a patient suffers a second arterial or venous event while on antiplatelet therapy. It should be noted that LA, but not aCL antibodies, may affect INR; if INR fluctuates, other monitoring methods should be considered [37].

For further information on the prothrombotic state and cerebral ischemia, please refer to Chapter 10 of this text.

CNS Vasculitis [38, 39]

Vasculitis, whether primary or secondary, is implicated in a small minority of young stroke patients. It is important to consider as a cause of stroke since it has a specific treatment other than antiplatelet agents. Vasculitis should be considered in the presence of multisystem rheumatologic conditions, such as SLE (although stroke in SLE generally is due to non-vasculitic mechanisms). Westergren sedimentation rate and C-reactive protein are useful screens for vasculitis, although it should be recognized that isolated CNS vasulitis will not have laboratory evidence of systemic inflammation. Vaculitis should be considered in patients with stroke in multiple vascular distributions or in patients with bihemispheric signs such as changes in intellectual function or level of consciousness, particularly in association with headache. In patients with suspected

vasculitis, MRI with and without gadolinium enhancement should be performed; cerebral vasculitis with an entirely normal MRI is rare, although the abnormalities can be subtle. An ophthalmologic consultation to look for signs of ocular inflammation should be obtained. A lumbar puncture should be done with cytology, oligoclonal bands and IgG index, varicella zoster virus (VZV) DNA by PCR and anti-VZV IgG antibody by enzyme immunoassay [40], as well as glucose, protein, cell counts, cryptococcal antigen, VDRL.

Laboratory tests should search for evidence of other organ involvement, including urinalysis, CPK, renal function (BUN and Cr), hepatic enzymes (alkaline phosphatase, SGOT, SGPT) and also include complete blood count with differential, erythrocyte sedimentation rate, CRP, FTA, antinuclear antibody, extractable nuclear antigens, serum complements (C3, C4, and CH 50), rheumatoid factor, SSA and SSB, hepatitis B antigen and antibody, cryoglobulins, and antineutrophil cytoplasmic antibodies titer. Other studies, such as immunoelectrophoresis, HIV titer, lyme titer, blood and urine toxicology screen, immune complex assays, and urine vanillylmandelic acid and 5-hydroxyindoleacetic acid levels may be needed in individual patients, depending on the clinical presentation.

Patients with suspected vasculitis should be referred to tertiary care referral centers for definitive diagnosis and treatment. Further diagnostic testing generally includes a four vessel catheter angiogram. A brain biopsy is often indicated because immunosuppressive treatment for vasculitis has a high risk of morbidity and mortality, because angiographic findings may be nonspecific for vasculitis (e.g., intracranial atherosclerosis or vasospasm) and because true vasculitis may be secondary to an infection. Empiric treatment with steroids should be avoided until infection is excluded with a reasonable degree of confidence. Treatment may also preclude definitive diagnosis by modifying CSF and brain biopsy findings. Once the diagnosis is confirmed, treatment is generally initiated with high dose steroids and cyclophosphamide. Cyclophosphamide takes longer to work but lessens the need for steroids and their attendant complications. In addition, high dose steroids alone are not adequate treatment for isolated intracranial vasculitis.

Cerebral Venous Thrombosis [41]

An important cause of stroke that is often associated with a prothrombotic state is CVT. This is a distinct cerebrovascular event that account for 0.5% of all strokes [41] and involves thrombosis of the cerebral veins and sinuses leading to both local edema with venous hemorrhage and subsequent ischemic brain damage. Obstruction of the cerebral venous system may lead to an increase in intracranial pressure and, if severe enough, cerebral herniation.

Clinically CVT may present in a number of ways but headache is the most common and may be associated with new seizures, focal neurological deficits,

encephalopathy and decreased level of arousal. CVT should be considered in any young adult with a headache and focal neurological symptoms.

The current gold standard for diagnosis of CVT is the combination of MRI to visualise the thrombosed vessel and magnetic resonance venography to detect the non-visualisation of the same vessel. T2* susceptibility-weighted imaging sequences should be included with the MRI, as it is more sensitive than other MRI sequences or MRV for detecting cortical vein thromboses [41]. Additionally, CT-venogram is a promising technique where available. Rarely will a cerebral angiogram with a venous phase be necessary.

Any thrombophilia (Table 8.2) may be associated with CVT. The etiology of CVT is typically multifactorial, with a recent series showing 44% of cases to have more than one contributing cause [42]. Therefore, even if a risk factor such as recent surgery, infection, pregnancy and puerperium are present, further attempts should be made to identify congenital thrombophilias as well as hyperhomocysteinemia. Testing should be repeated in following cessation of anticoagulation as a prothrombotic risk factor or direct cause can be identified in up to 85% of cases of CVT [43].

Although there is some controversy as to the optimal treatment of CVT, anticoagulation is widely used as first line therapy for symptomatic CVT [44]. Typically intravenous heparin is started in the acute phase. The presence of intracerebral hemorrhage is not considered to be a contraindication to anticoagulation. Endovascular treatment with catheter delivered thrombolytics is generally reserved for patients deteriorating on heparin therapy. Other acute therapy may include anticonvulsants when there is a parenchymal lesion or seizures on presentation. Rarely, if there is increased intracranial pressure causing non-obstructive hydrocephalus, aggressive measures, including neurosurgical intervention, may be required. After the acute period, patients are converted to warfarin for 3–6 months with an INR goal of 2–3. If an underlying coagulopathy is identified then longer, even lifelong, anticoagulation is recommended, depending on individual circumstances. Serial visual field testing in the months after CVT is necessary to monitor for visual loss due to increased intracranial pressure.

Stroke in Pregnancy and the Puerperium

Although the risk of ischemic stroke, CVT, intracerebral hemorrhage, and subarachnoid hemorrhage is increased during the peripartum and postpartum periods [11, 45, 46], pregnancy should be considered a predisposing factor similar to hypertension or diabetes, rather than the cause of a given stroke. The approach to stroke during pregnancy and the postpartum period should be similar to the approach to stroke in the non-pregnant young adults, but there are additional considerations in the diagnostic approach and therapeutic approach.

Head CT is reasonably safe in pregnancy if the uterus is shielded. The dose of radiation to the uterus from a routine head CT (< 1 mrad) is significantly less than that necessary to cause harm to the fetus [47]. Although there is not documented risk of MRI in pregnancy from human studies, there remains concern regarding the effects of MRI during organogenesis in the first trimester [48] While radiologists have become more comfortable with the use of MRI during the second and third trimesters, use during the first trimester should be restricted to situations where the benefit to the mother outweighs the potential risk [49] . Gadolinium contrast should be avoided as it crosses the placenta and has unknown effects on development.

There are several causes of stroke that deserve special consideration in the pregnant or post-partum patient. Pre-eclampsia/eclampsia is the most common pregnancy-specific etiology for ischemic stroke, reported to account for 24–47% of nonhemorrhagic stroke occurring during pregnancy and the post-partum period [50, 11]. Recent evidence from imaging and follow-up studies demonstrates most patients with eclampsia and stroke-like syndromes have reversible deficits which show T2 hyperintensities, but not restricted diffusion, suggesting that vasogenic edema and not infarction is the cause of the T2 hyperintensities [51]. Patients with restricted diffusion on MRI scan and irreversible deficits can be confidently diagnosed with stroke. Care must be taken to distinguish CVT from eclampsia since these two conditions can share the symptoms of new headache, focal neurological changes, and seizures. Other conditions requiring particular consideration in the pregnant or post-partum woman are peripartum cardiomyopathy, postpartum cerebral angiopathy, pituitary apoplexy, choriocarcinoma, and amniotic fluid or air embolism.

There is presently no consensus on the treatment of acute ischemic stroke during pregnancy. The exclusion of pregnant women from most stroke trials, as well as increased concern over bleeding complications and risk to the fetus has led most clinicians to take a conservative approach. There are case reports of the successful use of intravenous and intraarterial thrombolytics for acute stroke during pregnancy but complications have occurred and the risks and benefits to mother and fetus must be carefully weighed [52].

Available evidence suggests that low dose (less than 150 mg/day) aspirin during the second and third trimesters is safe for both mother and fetus [53]. The safety of low dose aspirin use during the first trimester is uncertain due to the lack of data from large studies and a balancing of risks and benefits with patient involvement is essential. Nevertheless, with this caveat in mind, low-dose aspirin may be considered for prevention of recurrent ischemic stroke in women of childbearing ages and in the first trimester. Warfarin is teratogenic and the safety of other antiplatelet agents, including clopidigrel and dipyridamole, has not been determined. Although aspirin use for stroke prevention during breastfeeding has not been systematically studied, available evidence suggests that low-dose aspirin is safe for the infant [54].

There is no evidence at this time to recommend avoidance of further pregnancies unless the etiology of the stroke is known and is known to have an increased risk for recurrence in the setting of pregnancy [55].

Migraine and Stroke

Please see Chapter 9 for a discussion of the association of headache and stroke and the treatment of headaches in those suffering from stroke. A recent review of migraine and stroke by Drs. Bousser and Welch [56] is also highly recommended.

Intracranial Hemorrhage

Spontaneous intracranial hemorrhages, although less common than ischemic infarction, compromises a significant number of strokes in the young adult ranging from 0.7 to 40% of total strokes [57]; with intracerebral hemorrhages (bleeding into the brain parenchyma) occurring more often than subarachnoid hemorrhages. Regardless of age, subarachnoid hemorrhages are most often due to aneurysms. In young patients, the most common causes of intracerebral hemorrhage include vascular malformations, aneurysms and hypertension, either acute or chronic. Additional important causes include bleeding diatheses, trauma, bleeding secondary to CVT and intracranial tumors, and hemorrhage secondary to drugs of abuse, particularly cocaine and amphetamines, or over-the-counter sympathomimetics [58]. A toxicology screen for drugs of abuse should be obtained at the admission of any young patient with hemorrhagic (or ischemic) stroke. Additionally, it is important to realize that a hemorrhage may occur in the setting of an ischemic infarct (a hemorrhagic conversion). This most often occurs with a cardioembolic source, both infective and non-infective.

If the cause of the intracerebral hemorrhage is not apparent on initial evaluation, further diagnostic tests should be pursued after resolution of the blood, including MRI, with and without gadolinium contrast, and CT or conventional catheter angiography.

For additional information on intracranial hemorrhages, the reader is referred to **Chapters 4–7**.

Bulleted Summary

- Consider ischemic stroke mimics: seizure, MS, tumor, infection, cerebral venous thrombosis (CVT).
- Comprehensive history including not only vascular risk factors and systemic disease, but also detailed family history, trauma, drug abuse, pregnancy, and headache history.

- Careful examination with attention not only to the cardiovascular system, but also to the skin. Ophthalmologic consultation is useful because many systemic diseases associated with stroke have ocular manifestations.
- Team approach is useful involving not just neurology but often cardiology, rheumatology, ophthalmology and sometimes dermatology, hematology, and genetic specialists.
- Causes of stroke in young adults are more varied compared to older onset stroke and some points deserve emphasis:
  - Less than 50% of cases will have a probable cause identified.
  - Endocarditis is the single most common cause and should always be considered.
  - Monogenetic causes are more common than in older adults, but still are very rare.
  - Carotid and vertebral dissection are important causes of stroke in young adults and will not be detected by carotid duplex.
  - Patent foramen ovale (PFO), particularly with atrial septal aneurysm (ASA), is an important risk factor for stroke in young adults, though there is no evidence-based optimal treatment. Ongoing clinical trials may provide guidance in the management of PFO-associated stroke.
  - Although migraine, especially migraine with aura, is associated with an increased risk for stroke, migrainous stroke is a diagnosis of exclusion and is very rare.
- Initial evaluation should consist of:
  - Basic admission labs: CBC and differential, chemistry profile including liver function tests, PT/PTT, lipid panel, ESR, CRP, HgA1C, urine and blood toxicology screen, ANA, FTA, homocysteine (on ice and spun within 3 h), urinalysis, EKG, CXR, and low index of suspicion for blood cultures. In appropriate clinical context, add HCG, sickle screen, Lyme test, and HIV test.
  - MRI brain; MRA head and neck
  - Transthoracic echo with bubble study (TTE)
- If cause not apparent, secondary tests should consist of:
  - CT angiogram to look for evidence of dissection, including pseudoaneurysms.
  - Transesophageal echo with bubble study to exclude PFO and ASA.
  - Antiphospholipid antibodies: anticardiolipin antibodies, Anti-ß2-glycoprotein I antibodies, lupus anticoagulant by two methods, such as Russell venom viper method and hexagonal phase phospholipid method
  - If CVT or PFO or other clinical indication such as personal or family history of venous thrombosis, pursue further hypercoagulable workup, including fibrinogen, Factor V Leiden and Prothrombin Gene G20210A mutations, Protein C and S (free and total), Antithrombin 3, Factor 12 (low levels), Factors 8, 9, 11 (high levels), and APC resistance.

- If historical or other clinical suspicion of vasculitis, pursue more extensive vasculitis evaluation, including ophthalmologic examination, LP and catheter angiography. Tests to consider are serum ACE level, serum complement (C3, C4, and CH 50), rheumatoid factor, SSA and SSB, hepatitis B antigen and antibody, Hepatitis C antibody, cryoglobulins, and antineutrophil cytoplasmic antibodies titer, HIV titer, and Lyme titer. Other studies, such as immunoelectrophoresis, immune complex assays, and urine vanillylmandelic acid, and 5-hydroxyindoleacetic acid levels may be needed in individual patients, depending on the clinical presentation. LP should include cytology, oligoclonal bands and IgG index, varicella zoster virus (VZV) DNA by PCR and anti-VZV IgG antibody by enzyme immunoassay, as well as glucose, protein, cell counts, cryptococcal antigen, VDRL. Definitive diagnosis should be reserved for tertiary care centers and brain biopsy should be considered before immunosuppressive therapy is initiated.

- Treat contributing risk factors aggressively, including cessation of smoking and exogenous estrogen, treatment of hypertension, diabetes mellitus, and hyperhomocysteinemia. Statin use should be strongly considered unless LDL < 70 mg/dl.
- In stroke patient with migraine, consider lower threshold for migraine prophylaxis and avoid use of serotonin agonists such as triptans and ergot alkaloids.
- Strong evidence is lacking that anticoagulation is indicated for long-term treatment of most hypercoagulable states.

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Chapter 9
Headache and Stroke

John W. Cole

Introduction

Headaches are a common manifestation of central nervous system disease, including stroke, and are particularly common in the setting of hemorrhagic stroke. Therefore all clinicians, office or hospital-based, must be able to recognize when a headache may be benign or the symptom of a more concerning neurological disorder. The aim of this chapter is to provide the reader with clinical guidelines for the general diagnosis and evaluation of headache, with special emphasis on stroke-related headache.

Headache Epidemiology

Headache accounts for approximately 2–4% of all emergency department (ED) visits with one large review [1] placing that figure at 2.2%. Most headaches (about 95%) have benign causes while few (~5%), are caused by "must not miss" diagnoses (that is, diseases that are treatable but that can result in serious harm or death). Table 9.1 lists these "must not miss" diagnoses; some of which are definitively vascular-related diagnoses. A subset of these diagnoses, meningitis, and subarachnoid hemorrhage (SAH), for example, should also not be missed or the diagnoses delayed, as such situations often serve as the basis for malpractice lawsuits. Given both time and resource utilization pressures, physicians should have a logical, practical and accurate approach to distinguish between the "concerning" versus "benign" headache patient. There are three well-established tools to make this critical distinction – the history, the physical examination, and certain diagnostic tests.

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Table 9.1 "Must not miss" causes of headache

Vascular related
Stroke (ischemic or hemorrhagic)
Subarachnoid hemorrhage (SAH)
Cerebral venous sinus thrombosis
Dissection of cranio-cervical arteries
Giant cell (temporal) arteritis
Other etiologies
Meningitis and encephalitis
Hypertensive encephalopathy
Idiopathic intracranial hypertension
Spontaneous intracranial hypotension
Acute angle closure glaucoma
Intracranial mass (tumor, abscess, hematoma, colloid cyst)
Carbon monoxide poisoning
Pituitary apoplexy

Some General Considerations: Evaluation and Workup

When evaluating a patient with headache, the clinician should understand that head and neck pain does not localize particularly well, and as such, patterns of referred pain can be quite misleading. As examples, the extravasation of subarachnoid blood can cause vasospasm with pain far from the site of the hemorrhage, while a carotid dissection originating in the lower neck may cause pain behind the ear. In general, head pain results from tension, traction, distention, dilation, or inflammation of the pain sensitive structures external to the skull, portions of the dura, and the blood vessels of the head and neck. However, each of these mechanisms is likely mediated by a final common cellular pathway that results in pain. With this in mind, favorable response to analgesics or even the more specific "anti-migraine" agents such as triptans, should not be used to judge the cause of an individual headache. Therefore, when evaluating the headache patient, it is important for clinicians to have some rudimentary knowledge regarding the relationships between head and neck anatomy and the structures capable of conveying pain. These structures can be classified as intracranial or extracranial as listed in Table 9.2 (adapted from [2]).

Evaluation

All headache patients warrant a thorough history, physical, and neurological examination. A useful mnemonic to help identify patients of concern during the initial evaluation is *first*, *worst*, *cursed*, *burst*, and *fifty-first*. This mnemonic applies to patients presenting with their first significant headache; the worst headache of their life; cursed – a headache with associated symptoms or signs

Table 9.2 Pain-sensitive structures in the head and neck

Extracranial	Intracranial
Scalp	Periosteum
Scalp muscles	Cranial nerves
Skull	Meninges
Carotid and vertebral arteries	Meningeal arteries and dural sinuses
Paranasal sinuses	Proximal intracranial arteries
Eyes and orbits	Sphenoid sinus
Mouth, teeth, and pharynx	Thalamic nuclei
Ears	Brainstem pain-modulating centers
Cervical spine and ligaments	
Cervical muscles	

such as fever or exam findings; burst – a headache that reaches maximal severity at onset; and, fifty-first – those patients 50 years or older of age presenting with their first severe headache. This simple mnemonic allows one to easily identify headache patients of concern and further highlights the need for a thorough, expedited evaluation, and workup. One's suspicion for secondary causes of headache is also raised if the headache qualities and pattern do not easily fit those of a primary headache disorder.

History: All headache patients, both those with and those without pre-existing headache syndromes, must have their history of present illness thoroughly reviewed. It is important to include questions regarding recent falls, trauma (head or other), motor vehicle accidents, neck chiropractic manipulation, and whiplash injury. Key elements of the headache history must include questions regarding headache onset, severity, quality, and associated symptoms (nausea and vomiting, diplopia, seizures, or syncope). Other important questions/considerations are detailed in Table 9.3.

Physical Examination: As stated a thorough physical and neurological exam should be performed on all headache patients. Table 9.4 describes presenting signs that warrant further workup and would be considered atypical in the "standard or benign" headache patient.

Workup

Further workup is indicated for patients who have worrisome features on the history or physical exam. Determining who should undergo further testing is often a matter of experience and judgment. At a minimum, brain imaging and a lumbar puncture (LP) must be considered.

Brain Imaging: A brain CT must be considered for all headache patients, and contrast may be included depending upon the differential diagnosis. At this time, CT scanning is widely available, extremely rapid, with an unenhanced scan posing minimal risk to the patient. Follow-up to obtain the official

Table 9.3 Important questions and considerations to assess in the headache patient

Questions	Considerations if response is 'yes'
Do you have recurrent disabling headaches?	Possible migraine or cluster headaches.
Did your headaches begin or increase in the last 3 months?	Mass lesion or other new cause of headaches.
Do you have to take medication for headaches more than three times a week?	Frequent medication use may be causing rebound headaches.
Is this headache different in quality or pattern than any you have had before?	Possible new underlying secondary cause.
Where is the pain located?	Note if ipsilateral or contralateral to an exam deficit or finding.
Is this the worst headache you have ever experienced?	Consider SAH.
Are there any associated symptoms with the headache, such as nausea, vomiting, or stiff neck?	Infection; meningitis; subarachnoid bleed; migraine.
Was there some form of physical exertion temporally related to this headache?	Blood pressure related; ruptured aneurysm.
Have you taken any medications for this headache?	Medications are masking degree of pain/problem.
Do headaches occur with exertion, coitus, coughing, or sneezing?	Increased intracranial pressure; aneurysm.
Do your headaches tend to be seasonal?	Sinusitis related.
Is the headache related to your menstrual cycle?	Migraine headaches.
Is there a family history of similar headaches?	Migraine headaches.
Have you had a recent head injury or infection?	Post-traumatic headaches or abscess.
Do you grind your teeth during sleep?	Temporomandibular joint (TMJ) disorder.

Table 9.4 Concerning signs in a headache patient

Decreased alertness, cognition, or memory
Worsening headache under observation
Nuchal rigidity or other signs of meningeal irritation
Focal neurological signs including:
• Progressive visual or neurological changes with associated headache
• Asymmetry of pupillary response or other cranial nerve findings
• Paralysis or weakness, especially if asymmetric
• Ataxia or loss of coordination
• Sensory loss or paresthesias
• Deep tendon reflexes/Babinski response – unilateral or bilateral

neuroradiological interpretation is important since other physicians may miss subtle findings. Some tumors and abscesses will not be apparent on a non-contrast scan, although most masses large enough to cause a significant headache will be evident.

A non-contrast CT scan is extremely sensitive for acute intra-parenchymal blood and highly sensitive for subarachnoid blood (~92%) [3], but small or

older bleeds may not be visible. Other important limitations include the following:

- Timing – sensitivity to detect blood decays rapidly with time. One large study evaluating aneurysmal SAH demonstrated that 92% of the CT scans were positive on the day of rupture, but this percentage declined to 86% 1 day later, 76% 2 days later, and 58% 5 days later [4].
- Size bias – small volume warning bleeds are more easily missed.
- Technical factors – thick cuts and the quality of the scanner can influence detection.
- Hematocrit – values less than 30% can lead to a negative scan in the setting of an actual SAH.

In general, MRI is superior to CT, especially in evaluating ischemic stroke, small arteriovenous malformations (AVMs), neoplasms, infections, and pathology at the cervico-medullary junction or in the posterior fossa. When MRI is not available, consider transfer to a tertiary center or performance of a CT with infusion of intravenous contrast. Additionally, either MRA or CTA of the head and neck are required when evaluating for vascular dissection, aneurysms or large-vessel occlusive disease.

Lumbar puncture: Since no radiological tests are 100% sensitive in defining the pathological processes, a critical role remains for the LP. This is especially true in the setting of a history and physical suggestive of SAH; here a negative CT requires a LP. CSF should be evaluated for deviations from its normal appearance and the normal values of protein (15–45 mg/dl), glucose (50–80 mg/dl), WBC (0–5 cells), RBC (0 cells), as well as a measure of the opening pressure (80–180 mmH_2O).

Normal CSF has an appearance consistent with water: clear and colorless. Because blood often leaks into the CSF, from a punctured vein during the LP process, it is sometimes difficult to know whether RBCs found in the CSF are due to the LP process or are from a SAH. The best way to distinguish RBCs related to intracranial bleeding is examination of the centrifuged supernatant CSF for xanthochromia (yellow color) [5]. If more than 6 h have passed since the time of a SAH, RBC breakdown causes this yellow discoloration. Although xanthochromia can be confirmed visually, it is identified and quantified more accurately in the laboratory. While xanthochromia can be produced by spillover from a very high serum bilirubin level (i.e., >15 mg/dL), patients with severe hyperbilirubinemia usually have been identified prior to the LP (e.g., jaundice, known liver disease). With this exception, the presence of xanthochromia in a freshly spun specimen is evidence of preexisting blood in the subarachnoid space. It is also important to note that an extremely high CSF protein level, as seen in an LP below a complete spinal block, can also render the fluid xanthochromic, though without RBCs. Xanthochromia can persist up to several weeks following a SAH. Thus, it has greater diagnostic sensitivity than a CT scan of the head without contrast, especially if the SAH has occurred more than 3–4 days prior to presentation. Patients with aneurysmal leaks

(i.e., sentinel hemorrhages) may present days/weeks after headache onset, increasing the likelihood of a false-negative head CT scan [5].

Finally, it is also important to note that if a mass lesion (tumor, ICH, or other) is seen on brain imaging or a situation exists that predisposes to a herniation syndrome (i.e., brain shift seen on CT, papilledema indicating elevated intracranial pressure on ophthalmologic exam) an LP should be avoided and neurological consultation should be requested.

Other workup considerations: Measurement of the erythrocyte sedimentation rate (ESR) can help diagnose giant cell arteritis. Tonometry can rule in acute narrow angle closure glaucoma. In addition, carboxyhemoglobin levels are useful when carbon monoxide poisoning is a possibility; consider this during the winter months coinciding with increased use of space heaters in enclosed spaces. Brain MRV can be used to evaluate for cerebral venous thrombosis which often presents with headache, seizures, and papilledema (secondary to intracranial hypertension). Bilateral brain hemorrhages can be seen in the setting of a cerebral venous thrombosis involving the superior sagittal sinus.

Headache as a Symptom of Stroke

Hemorrhagic Stroke

Hemorrhagic stroke (as discussed in Chapters 4–7) is classified on the basis of location of the hemorrhage. Classifications include: (1) SAH consistent with aneurysm rupture, (2) intraparenchymal hemorrhage (ICH) consistent with an AVM or hypertensive hemorrhage, or (3) intraventricular bleeding due to an extension of an ICH. All forms of hemorrhagic stroke can present with headache.

SAH typically presents with severe headache, although some patients may not describe it as the worst headache of their life. Neck stiffness, altered mental state, and focal neurological signs are common but may be absent. A brief mental status evaluation is worthwhile, because altered sensorium may be the only sign of neurological compromise. CT of the brain usually reveals blood in subarachnoid cisterns. However, in the appropriate clinical setting (first, worst, cursed, burst, and fifty-first), a normal scan must be followed by LP to completely rule out SAH.

Some patients suffer from a more insidious entity, the so-called sentinel or warning headache, in which a severe acute headache occurs shortly before aneurysmal rupture. Between 20 and 50% of patients with documented SAH report a distinct, unusually severe headache in the days or weeks before the index episode of bleeding [6]. The mechanism of such headaches is still poorly understood. Several theories exist as to what causes a sentinel headache including: (1) a small, undetected leakage of blood (with arachnoid irritation) from a berry aneurysm, (2) expansion of the aneurysm, with pain resulting from

stretching of pain fibers in the arterial wall, and (3) expansion of the aneurysm leading to irritation the meninges [2]. The sentinel headache is thought to be a warning of an impending SAH. Interestingly, a number of cases have been reported in which sudden acute headache ("thunderclap headache") occurred in patients with normal cerebrospinal fluid (CSF) who were found later to have an unruptured berry aneurysm [2, 7].

While acute severe headaches can occur due to ruptured AVMs, unruptured AVMs can present with various types of headache, including recurrent severe migraine [2, 8]. In addition, AVM patients may present with seizure and occasionally with transient neurologic symptoms, the cause of which is not clear. CT/CTA and MRI/MRA scans are helpful in identifying AVMs.

Headache is a common manifestation of hypertensive ICH. There are six primary locations of hypertensive ICH including the: (1) putamen, (2) caudate, (3) thalamus, (4) subcortical cerebral lobe, (5) cerebellum, and (6) brainstem. Each location differs in clinical presentation and headache severity, which typically relates to the size of the hemorrhage, concomitant intracranial pressure increase, and relationship to pain-sensitive structures of the head and neck.

Headache, usually sudden, is also a frequent manifestation of pituitary apoplexy and pituitary hemorrhage.

Ischemic Stroke

Pathologies affecting the carotid and/or vertebral arteries often present with head and neck pain. Given the function of these arteries of supplying blood to the brain, these same pathological processes can cause ischemic stroke via embolic and thrombotic mechanisms. Spontaneous or traumatic dissections are important examples that should be diagnosed early to reduce the possibility of brain infarction. Presenting symptoms of a carotid dissection may include pain in the neck, face, or head; *Horner's syndrome* (which in its complete form involves the triad of ipsilateral miosis (constricted pupil), partial ptosis, and anhidrosis [loss of hemifacial sweating]); and transient or persistent focal neurologic deficits. Carotidynia (a syndrome of recurring pain in the jaw, neck, or lower face) is thought by some investigators to be a migraine variant, although in certain cases it may represent undiagnosed carotid artery disease (e.g., dissection). Vertebral artery dissection may lead to posterior neck pain and disruption of the posterior circulation. The latter may cause transient or persistent vertigo, nausea with or without emesis, balance problems (cerebellum), vision loss (occipital lobe involvement), abnormal eye movement (cerebellum or brainstem nuclei) or crossed sensory/motor symptoms with the face affected ipsilaterally and arm/leg contralaterally to the brainstem lesion.

The most common form of arteritis affecting cerebral blood vessels is giant cell (temporal) arteritis [2], which was first described in 1890 [9]. Pain is almost always a symptom because of the high-pain sensitivity of temporal and other scalp arteries.

This condition generally affects only persons older than 60 years and must be diagnosed early to prevent visual loss, which can result from inflammation of ophthalmic arteries. Jaw pain during chewing (i.e., jaw claudication) is pathognomonic, and the ESR is almost always high. Polymyalgia rheumatica often accompanies giant cell arteritis, and temporal arteries are often tender. If there are no symptoms to suggest polymyalgia rheumatica, with a normal ESR and physical exam, yet with a suspicion for giant cell arteritis, temporal artery biopsy should be strongly considered. If suspicion of giant cell arteritis is high, corticosteroid treatment can be started before biopsy to prevent visual consequences. Histologic findings usually are not affected by a few days of treatment [2].

Cerebral arteritides due to systemic lupus erythematosus, rheumatoid arthritis, polyarteritis nodosa, or primary arteritis of the central nervous system (PACNS) (i.e., granulomatous angiitis) also produce headaches, and in most cases they are caused by diffuse vascular inflammation [2]. Diagnosis can be difficult, often requiring cerebral angiography, which may show a "sausage-like beading" of the cerebral blood vessels. LP may also be helpful in these diagnoses primarily to detect an elevated protein and/or cell count.

Headache as a Risk Factor for Stroke

Approximately 50% of ischemic stroke patients present at the time of their stroke with some form of headache. While the causal role between the various headache types and risk of stroke remains difficult to accurately identify, there is considerable evidence indicating that migraine headache may be an independent risk factor for ischemic stroke, principally among oral contraceptive (OC) users and younger adults [10, 11, 12, 13].

Migraines are often associated with aura. An aura is a transient neurological symptom or deficit that may present as a visual, sensory (including smell), cognitive or motor disturbance before or during a migraine attack, usually lasting less than 60 min. The cause appears to be a phenomenon called cortical spreading depression. To evaluate the potential contribution of migraine to ischemic stroke, it is first worthwhile to consider the broad range of symptoms that can be associated with migraines. Migraine headaches with aura can be associated with positive visual phenomena (bright lights, scintillations, fortification spectra, visual distortions, etc.), but may also be associated with negative visual phenomena (scotomas, hemianopsias). They may cause paresthesias of the face, hemibody, or a smaller portion of the body. While they are not known to induce movements or tremors – they can induce weakness in an extremity or half of the body. In particular, basilar artery migraine (BAM) and hemiplegic migraine, may lead to sustained periods of weakness. Given migraines' broad range of neurological symptomatology and their close similarity to known stroke symptoms, it becomes easy to imagine that these two phenomena could be interrelated or confused with one another.

Based upon the inherent complexity of these disorders, the exact risk relationship between migraine and ischemic stroke has proven difficult to ascertain. Given the vast number of migraine patients, the likelihood that a few will also suffer ischemic strokes by chance is not surprising. Similarly, given the vast number of ischemic strokes, it is not surprising that some of these individuals will be migraine sufferers. However, adding strength to a possible causal relationship is the finding that patients who repeatedly experience neurological deficits with their migraines do have a higher risk of stroke. One large study pooled data from 11 case-control studies and three cohort studies, demonstrating that migrainuers have more than double the risk of ischemic stroke (relative risk 2.16, 95% confidence interval 1.89–2.48) [14]. The risk was greater in people who had migraine with aura than in those without aura, and was about eightfold greater in users of OCs than in those not using them. Please see Chapter 3, for a more detailed discussion regarding OCs use and stroke risk.

Migraine could have a causal association with stroke either because migraine or one of its subphenotypes confers a predisposition to stroke remote from migraine events or because stroke may occur as a direct consequence of a migraine event, as in migrainous infarction [15, 16]. A spurious association between migraine and stroke could occur if cerebral ischemia with migraine, either transient or resulting in stroke, were misdiagnosed as migraine with aura [15, 16, 17, 18, 19].

Migraine and stroke share several similar risk factors, including hypertension [20] and PFO [21, 22] and there is evidence of a familial basis to both [23, 24, 25, 26]. Some evidence indicates that the increased risk of stroke associated with migraine may not be uniform across all migraine or stroke subgroups. For example, the association between migraine and ischemic stroke is reported to be stronger for strokes occurring among younger (i.e., less than 50 years) compared to older individuals and for women compared to men [10, 11, 12, 15, 26, 27, 28]. Recent evidence further suggests that migraine with aura may elevate risk for stroke more than migraine without aura, [29, 30, 31] and, as mentioned earlier, some, [13, 27, 32] but not all, [31, 33] studies suggest that the association between migraine and stroke may be elevated among women who smoke or use OCs [15].

The effect of migraine frequency, lifetime duration of migraine, and time of migraine onset on stroke risk is also unclear [15]. An association between higher frequency (more than 12 per year) and longer duration of migraine (more than 12 years) with ischemic stroke with has been reported in at least one study, [33] and an association of higher migraine frequency with subclinical infarcts has been reported in another [28].

The contribution of patent foramen ovale (PFO) to the risk of migraine-associated ischemic stroke is also not fully established. PFO has been shown to be a risk factor for young-onset stroke [34] and is more common among migraineurs (especially those with aura) compared to non-migraineurs, [35] however, prior epidemiologic studies of migraine and stroke have lacked information about PFO [15].

A recent study [15] evaluated migraine associated stroke using a case-control sample of young (ages 15–49 years) female stroke patients who were classified as no migraine, probable migraine without visual aura, or probable migraine with visual aura (PMVA). Women with PMVA had 1.5 greater odds of ischemic stroke (95% CI, 1.1–2.0) compared to those without migraine. The relative risk was highest in those with no history of hypertension, diabetes, or myocardial infarction compared to women with no migraine. Women with PMVA who were current cigarette smokers and current users of OCs had a 7.0-fold higher risk of stroke (95% CI, 1.3–22.8) than did women with PMVA who were non-smokers and non-OC users. Women with onset of PMVA within the previous year had 6.9-fold higher risk of stroke (95% CI, 2.3–21.2) compared to women with no history of migraine. Hence, the authors concluded that PMVA was associated with an increased relative risk of stroke, particularly among women without other medical conditions associated with stroke. Behavioral risk factors, specifically smoking and OC use, markedly increased the risk of stroke in those with PMVA, as did recent onset of PMVA [15].

Concluding this section, the causal role between various headache types and risk of stroke remains difficult to accurately define, however, there is considerable evidence indicating that migraine headache may be an independent risk factor for ischemic stroke, particularly among OC users and younger adults. Furthermore, stroke risk is particularly high among smoking female migraineurs using OCs. Therefore, it is strongly recommended that female migrainuers taking OCs be advised not to smoke.

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Chapter 10
Hypercoagulable States and Stroke

A.G. Vaishnav

Introduction

The term *hypercoagulable state* refers to a predisposition to clinical thrombotic events. Hematologic abnormalities lead to thromboses in the cerebral vasculature, causing ischemic cerebrovascular events. These can be arterial ischemic strokes or more commonly, venous strokes (cerebral venous thromboses). However, the majority of patients with ischemic cerebrovascular events do not have a well-defined hematological abnormality.

Most hypercoagulable states cause cerebral venous thromboses. Antiphospholipid antibody (aPL) syndrome and sickle cell disease (SCD) also predispose to cerebral arterial strokes. The aim of this article is to highlight the significance of these factors in stroke, to assess their impact on long-term prognosis, and to outline an approach to the patient with stroke for evaluation of hemostatic abnormalities. The specific factors discussed in this article include:

1) Factor V Leiden (i.e., resistance to activated protein C [APC])
2) Prothrombin G 20210A mutation
3) Deficiencies of proteins C and S and antithrombin III
4) Sickle cell anemia
5) aPL syndrome.
6) Hyperhomocystinemia

Pathophysiology

Hemostasis means prevention of blood loss. Hemostasis is provided by an interaction of normal vessel responses, platelet plug formation, and activation of the coagulation cascade. The coagulation cascade involves activation of

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blood coagulation factors with formation of prothrombin activator, which catalyzes the conversion of prothrombin to thrombin. Thrombin acts as an enzyme to convert fibrinogen into fibrin fibers that enmesh platelets, blood cells, and plasma to form a clot.

Counteracting hemostasis are normal vascular endothelial cells, which inhibit platelet adhesion and aggregation, and proteins such as thrombomodulin. Thrombomodulin activates protein C, which in turn activates protein S; together, these two factors play a role in inactivating factors V and VIII. Antithrombin III also plays a role in inactivating factor X and thrombin, thus inhibiting thrombosis. In this way, interactions among multiple plasma proteins, protein C, protein S, resistance to APC, antithrombin III and normal vascular endothelial cells form an important barrier to thrombosis.

Factors that accelerate the hemostatic mechanism or inhibit mechanisms that counteract hemostasis contribute to an increased state of hypercoagulability and thereby play an etiological role in strokes.

Presenting Signs and Symptoms

No specific clinical signs differentiate stroke secondary to hypercoagulable states from other causes of both arterial and venous strokes. A high index of suspicion is necessary when stroke occurs in individuals under 45 years of age with no traditional risk factors for stroke and also in young stoke patients whose medical history includes recurrent miscarriages, venous thrombosis, a family history of thrombosis, and lupus-like clinical features (e.g., arthralgias, skin lesions). Abnormal findings on routine screening coagulation tests (aPTT) should also raise a red flag.

Patients may have an acute focal neurological deficit, as in an arterial stroke, or they may have headache, nausea, vomiting and/or seizures when they have cerebral venous thrombosis. It should also be emphasized that cerebral venous thrombosis can present with intracerebral hemorrhage.

Associated characteristics may point towards a particular hypercoagulable state. These characteristics, which include livedo reticularis (Sneddon's syndrome) [1, 2], Raynaud's phenomenon (Sneddon's syndrome), or Marfanoid habitus (hyperhomocysteinemia), may be detected on clinical exam. However, a high index of suspicion and appropriate laboratory testing is necessary to detect a hypercoagulable state that has caused a stroke.

Etiology

Causes can be divided into primary and secondary. Primary hypercoagulable disorders are discussed here with a brief mention of secondary causes of hypercoagulable states. Treatment of the underlying secondary causes leads to reversal of the hypercoagulable state.

Primary Hypercoagulable States

Hereditary Hypercoagulable Disorders

- Factor V Leiden mutation: This is the most common hereditary hypercoagulable disorder associated with cerebral venous thrombosis [3, 4, 5]. There is scant evidence of its association with arterial strokes. It is caused by a mutation that makes Factor V resistant to inactivation by activated Protein C (APC resistance). APC resistance can also be induced by pregnancy and estrogen.
- Antithrombin III, Protein C, and Protein S deficiency: These conditions are relatively rare [3], but they are a more potent cause of cerebral venous thrombosis than Factor V Leiden. There is no evidence of their association with arterial strokes. Antithrombin III, Protein C, and Protein S levels can also be reduced by liver disease, oral anticoagulant therapy, and disseminated intravenous coagulation. Protein S is also decreased by pregnancy and estrogen therapy.
- Prothrombin gene mutation (G20210A): This mutation occurs in approximately 2–5% of individuals and in itself is a weak procoagulant in its action [6].

Other hereditary hypercoagulable disorders include dysfibrinogenemias (very rare) and hyperhomocysteinemia (described later). Hyperhomocysteinemia is associated with both arterial and venous thrombosis.

Antiphospholipid Antibody (aPL) Syndrome

Antiphospholipids (aPLs) have been associated with both arterial and venous strokes [7, 8]. The two major types of clinically relevant aPLs are anticardiolipin antibodies (aCLs), which require the presence of serum cofactor beta-2 glycoprotein for binding, and lupus anticoagulant (LA), which may not require the presence of beta-2 glycoprotein. About 70% of patients with aPS have both aCL and LA.

Antiphospholipid antibody syndrome (APS) is defined as the presence of both thrombosis or recurrent, unexplained fetal loss and aCLs (IgG or IgM) of medium to high titres or LA on at least two occasions at least 8 weeks apart [9]. Patients with primary APS do not have systemic lupus erythematosus (SLE) or any other underlying autoimmune disorders.

Patients with aPLs suffer from both venous and arterial strokes. The risk of recurrence is significantly higher in subjects with a high level of IgG aCL antibody, those with LA, and those subjects who have high titres of aCL with SLE [10, 11].

It is also noted that the association weakens with aging between aPLs and vascular disease which may be related to changes in risk factors.

Cerebrovascular symptoms associated with aPS include amaurosis fugax, occlusion of retinal arteries and veins, transient ischemic events of the brain, thrombosis of cerebral arteries and veins, and dementia.

Sickle Cell Disease (SCD)

Subjects with SCD experience recurrent vascular events in part due to an increase in blood viscosity. Viscosity increases because the solubility of deoxyhemoglobin S is lower than that of normal hemoglobin. In addition, due to complicated interactions between sickle cells and the endothelium, there is progressive segmental narrowing of the distal internal carotid artery, portions of the Circle of Willis and proximal branches of the major intracranial vessels. Symptoms usually occur in early childhood, with the highest rate of brain infarctions occurring at this age, but persons may live into early or middle adulthood before manifesting adverse effects [12, 13].

Hyperhomocystinemia

Observational studies have shown a positive association between serum concentration of homocysteine and risk of stroke, independent of other stroke risk factors [14, 15]. However, evidence is stronger in retrospective studies than prospective studies, which may suggest reverse causality bias. Homocysteine can be lowered by folic acid, Vitamin B_{12}, and Vitamin B_6 [16].

Hyperhomocystinemia is caused by several inborn errors of metabolism that impair cystathione β-synthase (CBS) and several other enzyme systems important for methionine metabolism [17]. These errors are autosomal recessive traits, and patients homozygous for CBS deficiency often have atherosclerosis and thromboembolic complications. A mutation in methylenetetrahydrofolate reductase (MTHFR) in the folate pathway has also been correlated with increase in plasma homocysteine.

Secondary Hypercoagulable States

Certain diseases/causes lead to hypercoagulable states that are reversed on resolution of the underlying disease or cause. Common secondary hypercoagulable states are seen in:

1) Pregnancy
2) Liver diseases
3) Malignancy
4) Nephrotic syndrome
5) Disseminated intravascular coagulation
6) Drugs, specifically heparin (heparin-induced thrombocytopenia-II)
7) Estrogen–progestin
8) Infections
9) Autoimmune diseases
10) Hemodialysis/plasmapheresis
11) Myeloproliferative disease

Diagnostic Testing

Testing for specific hypercoagulable disorders requires a high index of suspicion. Most tests are done by means of a simple blood sample, though in select cases other diagnostic modalities are recommended.

Blood work to diagnose a hypercoagulable state does not preclude the routine work up of any stroke patient: neuroimaging (brain CT scan and MRI), neurosonology (carotid ultrasound and transcranial Doppler), echocardiogram, and basic blood tests including a routine hemogram, prothrombin time (PT), partial thromboplastin time (aPTT), and a fasting lipid profile.

There are also a couple of important points to be noted before ordering a work-up for hypercoagulable state. Use of anticoagulation can affect results of aCL, LA, protein C, protein S, and antithrombin III. Also, results should be repeated in 4–8 weeks to exclude false positives that may be related to an acute phase reaction (Table 10.1).

Prothrombin Time (PT)

PT is used to diagnose deficiencies or inhibitors of factors I, II, V, VII, and X. It also is used to monitor warfarin therapy and screen for vitamin K deficiency. It usually is expressed in terms of a standardized international normalized ratio (INR).

Partial Thromboplastin Time (aPTT)

aPTT is used to diagnose deficiencies or inhibitors of factors VIII, IX, XI, and XII and to diagnose a deficiency of von Willebrand factor. It also is used to monitor heparin therapy and as a screening test for LA.

Antiphospholipids (aPLs)

Two antibodies are routinely measured: aCLs and LA. They should be tested in all patients with suspected hypercoagulability. These include patients with stroke who have a history of thrombocytopenia, fetal loss, and recurrent venous

Table 10.1 Indications for hypercoagulable workup

Young individual with stroke (absence of risk factors)
Family history of thrombosis in a young individual with stroke
History of DVT/recurrent miscarriages in a young individual with stroke
Abnormal routine screening tests (aPTT)
Associated characteristics: livedo reticularis, Raynaud's phenomenon, Marfanoid habitus, arthralgias in a young stroke individual

thrombosis. aPLs are associated with both arterial and venous strokes. aCL antibodies (IgG and IgM) are expressed as GPL Units/ml. Higher IgG titres (>40 GPL units/ml) are more strongly associated with a risk of recurrent events. Risk of recurrent events is also higher in patients with SLE and presence of aCL antibodies [9].

LA is expressed as positive and negative. LA tends to be positive in patients with a primary hypercoagulable state whereas aCL, although highly sensitive, is not very specific and so is also positive in secondary hypercoagulable states [18].

Protein C

This activity is measured as U/ml. It is used to screen for a primary protein C deficiency or to diagnose protein C deficiency secondary to dysproteinemia. To confirm protein C deficiency, and to differentiate it from dysproteinemia, the protein C antigen is measured.

Protein S

Activity is measured by a functional assay. Both the total Protein S and free Protein S functional assays are performed because the free assay is a more reliable marker for hypercoagulability. To confirm protein S deficiency, and to differentiate it from dysproteinemia, the protein S antigen is measured.

Antithrombin III

This is also measured as U/ml**.** Antithrombin III deficiency is noted following acute thrombotic events, surgery, liver disease, nephrotic syndrome, DIC, heparin therapy, l-asparaginase therapy, pregnancy and with oral contraceptives. It is recommended to repeat the level in 4–6 weeks if a deficiency was initially found in the setting of an acute thrombotic event, pregnancy, or warfarin use.

Genetic Test for Factor V Leiden and Prothrombin G20210A Mutation

Resistance to APC is the most common inherited risk factor for thrombosis and the commonest cause (95%) of APC resistance is Factor V Leiden mutation, which can be easily be detected. Homozygous forms of Factor V Leiden mutation are much more prone to thrombosis than a heterozygous mutation. One can also measure APC resistance as a screening for Factor V Leiden mutation.

Homocysteine

The homocysteine level is usually measured by high-performance liquid chromatography (HPLC) with fluorescence detection. Hyperhomocystinemia is associated with arterial and venous thrombosis. Elevated homocysteine levels are encountered in the elderly; in patients with nutritional deficiency of vitamins B_6, B_{12}, or folate; and in renal insufficiency and other disorders.

Hemoglobin Electrophoresis

This test enables detection of hemoglobin SS and SC, both of which are risk factors for arterial strokes. The test should be ordered in African Americans and others whose ethnicity puts them at particular risk of sickle cell anemia (Table 10.2).

Treatment

Treatment for the secondary hypercoagulable states is directed towards the condition leading to the hypercoagulable state. However, treatment of primary hypercoagulable states in the setting of stroke is controversial.

Hereditary Hypercoagulable Disorders

Treatment decisions are driven by weighing risks (of thrombotic events and adverse effects related to treatments) versus benefits. Unfortunately, there have been no randomized trials to determine the effects of various treatments in

Table 10.2 Hypercoagulable states: investigations

Routine hemogram, PT, and aPTT
Lupus anticoagulant (LA)
Anti-cardiolipin antibody (aCL)
Protein C[a]
Protein S[a]
Antithrombin III[a]
Factor V Leiden mutation[a]
Prothrombin G 20210a mutation[a]
Homocysteine
Hemoglobin electrophoresis[b]

[a]Associated with venous events only.
[b]African American, Asian population.

patients with inherited hypercoagulable states. In the absence of such data, there are two guiding principles:

- Patients with a deficiency of Antithrombin III, Protein C or Protein S have a higher predisposition to thrombotic events than those with Factor V Leiden or prothrombin G20210 A mutation [3].
- The duration of anticoagulation for the prevention of recurrent events should be shorter if the thrombotic event is provoked by a major transient risk factor such as surgery or infection.

For patients with a deficiency of antithrombin III, Protein C or Protein S, prolonged anticoagulation with a goal INR between 2.0 and 3.0 is recommended if the thrombotic event is unprovoked. If the thrombotic event occurs in the setting of a transient risk factor (surgery, infection), then anticoagulation for up to 6 months is recommended [3].

For patients with Factor V Leiden or prothrombin G 20210A mutation, there is no convincing evidence that prolonged anticoagulation is needed. A short course of anticoagulation (from 6 months to 2 years) based on risk factors is recommended.

It is important to aggressively treat other modifiable risk factors of stroke in patients who have a hypercoagulable state.

Antiphospholipid Antibody (aPL) Syndrome

Results of the APASS (The Antiphospholipid Antibodies and Stroke Study) showed that there was no difference in recurrent events between aspirin and warfarin (INR, 1.4–2.8) in patients with ischemic stroke who had positive aCL or LA [19]. It is important to emphasize that the APASS study did not look specifically at APS. Also, a high INR-producing dose of warfarin was not used in the APASS. A prior study also showed that warfarin at moderate-intensity doses is equally as effective as warfarin at high-intensity doses in patients with APS [20]. A study using patients who specifically have APS would be ideal. It is important to note that the risk of recurrent thrombosis was increased in patients who had both aCL and LA. Thus, presently there is no significant difference between aspirin and warfarin for the prevention of recurrent strokes and they are equally effective based on the limited evidence available (APASS).

Sickle Cell Disease

Patients with SCD and stroke are treated with antiplatelet agents and treatment is towards the underlying disease process. Other methods of treatment that are

advocated include blood transfusion and hydroxyurea. Bone marrow transplantation is remains experimental.

The Stroke Prevention Trial in Sickle Cell Anemia (STOP) was a randomized trial to evaluate whether chronic transfusion could prevent initial stroke in children with sickle-cell anemia at high risk, as determined by transcranial Doppler (TCD) [21, 22]. The trial demonstrated a large benefit of transfusion and therefore children with SCD should be regularly evaluated with a transcranial Doppler.

Hyperhomocysteinemia

Hyperhomocysteinemia is treated with vitamin supplementation, usually folic acid, cobalamin (Vitamin B-12) and pyridoxine (Vitamin B-6). The Vitamin in Stroke Prevention trial (VISP) was undertaken to determine whether high doses of folic acid, Vitamin B-6 and Vitamin B-12 reduce the risk of recurrent stroke over a 2-year period compared to low doses of these vitamins [23]. Results of the VISP trial did not show a significant benefit of higher doses over lower doses. However, it did show that there was a persistent and graded association between total homocysteine and outcomes, irrespective of the treatment group. A larger study with high baseline homocysteine levels and longer follow up may help resolve the issue. We await the completion of the ongoing VITATOPS trial which may address certain issues unanswered by the VISP trial [24].

Brief Summary

- Hypercoagulable state refers to a predisposition for clinical thrombotic events
- Etiology can be primary or secondary
- Primary causes include deficiencies of Protein C, Protein S, and antithrombin III, factor V Leiden and prothrombin G20210A mutation, SCD and antiphospholipid antibody syndrome. Association with hyperhomocysteinemia remains debatable.
- It should be considered in young stroke patients or with patients with a strong family history of thrombotic events
- Venous strokes (cerebral venous thrombosis) are more common
- Antiphospholipid antibody syndrome and SCD can cause arterial ischemic strokes
- Treatment is controversial for primary hypercoagulable states and is mainly directed at the underlying cause for secondary hypercoagulable states (Table 10.3).

Table 10.3 Hypercoagulable states and stroke: treatment

Protein C, S, and antithrombin III deficiency: Provoked event: 6 months warfarin (INR 2.0–3.0)
Protein C, S, and antithrombin III deficiency: unprovoked: 2–5 years warfarin (INR 2.0–3.0)
Factor V Leiden (homozygous): 6 months (2 years ?)
Factor V Leiden (heterozygous): antiplatelet agent
Higher titres of aCL, LA (4–6 weeks after stroke) and aCL with LA: 5 years warfarin (INR 2.0–3.0)
SCD: blood transfusion to decrease Hb S (TCD referral)
Hyperhomocysteinemia: folic acid 2 mg, vitamin B_6 25 mg, and vitamin B_{12} 500 μg

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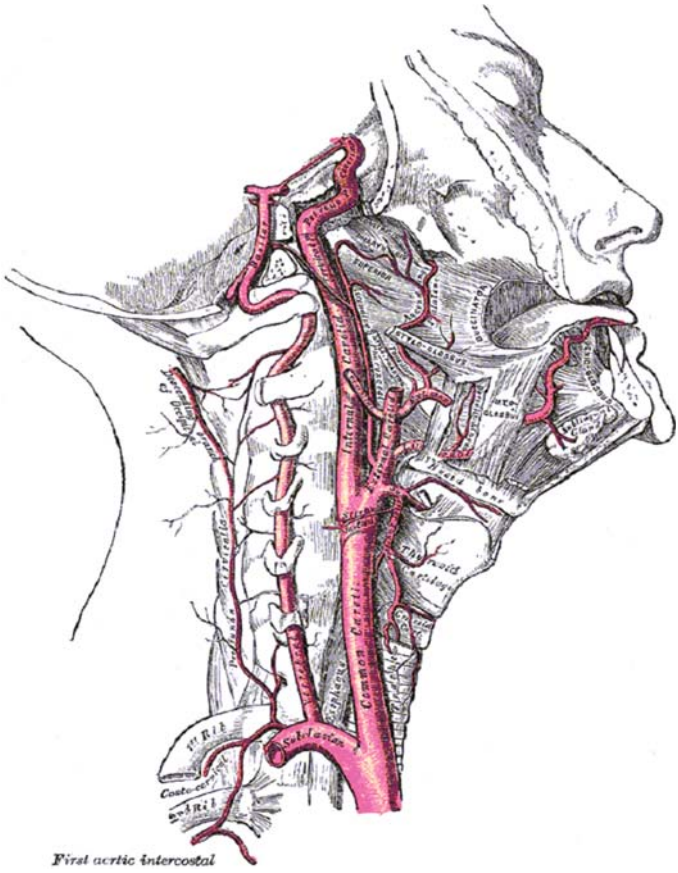
Chapter 11
Carotid Artery Stenosis

Marcella Wozniak and Karen Yarbrough



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Cerebral Vasculature and Stroke Location

The brain receives blood from two internal carotid arteries and two vertebral arteries. The majority of the blood flow to the brain is supplied by the internal carotid arteries. The internal carotid arteries supply blood to the retina and to the frontal, parietal, insular, and lateral temporal lobes of the brain. Carotid artery narrowing, referred to as stenosis, is responsible for about 10–15% of all ischemic strokes. Symptoms of ischemic stroke due to carotid artery stenosis or occlusion include: (1) weakness and numbness on the side of the body opposite the stenosis, (2) visual loss in one eye on the same side as the carotid stenosis, (3) aphasia (usually occurs with left internal carotid stenosis), and (4) gaze preference (the patient prefers to look towards the stenotic carotid artery but can look to the opposite side with encouragement).

The vertebral arteries supply blood to the brainstem, cerebellum and usually the occipital lobes, thalamus and medial temporal lobes. Strokes in these locations are generally not caused by carotid artery disease. Stroke symptoms due to vertebral artery disease include vertigo, double vision, ataxia (unsteady gait without weakness), weakness or sensory loss of all four limbs, coma, and total inability to move the eyes to one direction (see Table 11.1).

Table 11.1 Symptoms and stroke/TIA location

Cerebral artery	Ischemic stroke symptoms
• Right internal carotid artery (RICA)	• Left-sided weakness and/or sensory loss • Left homonymous hemianopsia (loss of the same visual field in both eyes) or quadrantanopsia (loss of vision in one fourth of the same visual field in both eyes) • Right gaze preference: gazes to the right but can look left • Cannot draw interlocking pentagon or a clock face • Denies obvious weakness on the left (neglect/inattention) • Vision loss in right eye only
• Left internal carotid artery (LICA)	• Right-sided weakness and/or sensory loss • Right homonymous hemianopsia (loss of the same visual fields in both eyes) or quadrantanopsia (loss of vision in one fourth of the same visual field in both eyes) • Left gaze preference: gazes to left, but can look right • Aphasia: inability to understand or produce language • Vision loss in left eye only
• Vertebral and Basilar arteries	• Ataxia: unsteady gait • Double vision • Dysarthria: slurred speech with normal production and comprehension of speech • Loss of sensation on one side of the face and the opposite side of the body (crossed sensory loss) • Quadriparesis: paralysis of all limbs • Coma

To determine if a TIA or stroke is due to carotid versus vertebral artery stenosis, consider the presenting symptoms, neurological examination findings, and brain imaging results. In patients with atypical symptoms, consultation with a neurologist may be required to confirm which vascular territory has been affected and if the stroke is likely due to carotid stenosis. Atrial fibrillation (AF) and narrowing of small intracranial vessels may also cause ischemic stroke. A stroke with an unknown cause is referred to as a cryptogenic stroke and accounts for 30–40% of all ischemic strokes [1] (see Table 11.1).

Methods of Carotid Evaluation

Bedside Auscultation for Carotid Bruit

The disordered and rapid flow of blood through a narrowed carotid artery will sometimes result in a bruit which can be detected by auscultation. However, not all critical stenoses of the carotid artery result in a bruit. Bruits can be observed in patients with normal carotid arteries, and murmurs transmitted from the heart can be confused with bruit. In patients with 70–99% stenosis on a carotid angiogram, the presence of a carotid artery bruits had only moderate sensitivity (63–76%) and specificity (61–76%) for clinically significant stenosis [2]. A recent review of the utility of auscultation for carotid bruit indicates its usefulness is very limited as it neither excludes significant carotid disease if it is absent nor indicates carotid disease if it is present [3].

Carotid Artery Ultrasonography

Carotid artery Doppler is an ultrasound test which estimates the speed of blood flowing in the internal, external, and common carotid arteries in the neck. As the artery is narrowed, blood flows faster. Carotid Doppler uses the increased speed to estimate the degree of narrowing. This is usually reported as a range of narrowing (i.e., <50%, 50–70%, 70–99%). Duplex ultrasound includes two-dimensional imaging of the artery to determine its structure and plaque morphology.

Limitations, Benefits, and Risks: While ultrasound can only predict a range of narrowing and is not as precise as an arteriogram, the ability of carotid Doppler ultrasound to detect carotid artery stenosis and normal arteries can approach >90% in experienced labs [4, 5, 6, 7]. Given its low risk, this makes it an ideal screening test for carotid stenosis. Ultrasound may not work well if the carotid arteries are located behind the bones of the jaw and the origins of the internal carotid arteries cannot be visualized sufficiently. Heavy deposits of calcium in plaque located in the carotid artery may limit penetration of ultrasound waves and can make even the most stenotic areas invisible to it. It is best to use a lab

which performs regular quality control and compares the results of their Doppler studies with results of cerebral angiograms. Organizations such as The Intersocietal Commission for the Accreditation of Vascular Laboratories have recommended standards for laboratory quality (www.icavl.org).

Magnetic Resonance Angiography

Magnetic resonance angiography (MRA) is a radiological test using the effects of perturbations of magnetic waves on tissues to create images of arteries.

Limitations, Benefits, and Risks: Cervical and cranial imaging with MRA can be quite effective in revealing extracranial and intracranial carotid pathology. Good quality images require the most up-to-date hardware and software. The ability to detect carotid artery stenosis and normal arteries can approach >90% sensitivity in good quality studies with experienced interpreters [4, 5, 6, 7]. Unfortunately, some patients become quite claustrophobic and agitated during MRA testing and may require sedation prior to testing. Even a small amount of patient motion during MRA testing can result in poor images which will be inaccurate. Patients often request "open" or "accessible" MRIs due to claustrophobia. As with the more typical "tube" configuration MRI, the quality of study from accessible MRIs can be variable depending on hardware and software used. Sometimes a contrast agent, gadolinium, is given to improve the accuracy of the test. Gadolinium is administered through an intravenous line. Although reactions to gadolinium are rare, patients with reduced creatinine clearance can develop a rare but fatal fibrosis after gadolinium use [8, 9]. Some patients cannot be safely exposed to high-magnetic fields of the MRA. For example, patients with pacemaker and implanted defibrillator can generally not undergo MRA.

Computerized Tomographic Angiogram (CTA)

A CTA requires an injection of intravenous radio-opaque contrast followed by a spiral CT scan. The contrast material is similar to that used for cerebral arteriogram. CTA allows for the detection of stenotic lesions and occlusions.

Limitations, Benefits, and Risks: This procedure is less risky than a cerebral angiogram because there is no canalization of arteries. There remains, however, a risk of allergic reaction to the contrast and the development of renal insufficiency. CTA testing is less likely to be affected by patient motion than MRI. With CTA, the ability to detect carotid artery stenosis or occlusion can approach >90% sensitivity in good quality centers with experienced interpreters [5].

Cerebral Angiography

Cerebral angiography (also known as an arteriography) is the "gold standard" for assessing the presence and degree of carotid stenosis [4, 5, 6, 7]. This is an invasive test which begins with the placement of a catheter in the femoral artery, which is then advanced to the level of the aortic arch or carotid or vertebral arteries. Radio-opaque contrast material is directly injected into the artery, and X-rays detect the flow of contrast through the arteries. The risks of this procedure are generally low (<2% for serious complications) when the test is performed by experienced interventionalists. Serious complications include TIA or stroke during the procedure, anaphylactic reaction to the contrast material, arterial dissection, and renal insufficiency. More common complications include mild allergic reaction to the contrast agent (rash, itching), formation of hematoma at the puncture site, and headache during the procedure.

Since there are finite risks with invasive cerebral angiogram, some advocate utilizing the other less invasive procedures to evaluate the carotid arteries, often an MRA or CTA and carotid duplex imaging are performed and the results compared. When two or more non-invasive diagnostic tests yield the same (or similar) degree of carotid stenosis, cerebral arteriogram may not be required. When non-invasive test results are incongruent in determining the degree of carotid stenosis, cerebral arteriogram may be necessary prior to surgical intervention. This strategy, however, has not been rigorously examined in clinical trials.

Screening for Asymptomatic Carotid Stenosis

Several guidelines, based on extensive reviews of the literature, do not recommend routine screening of the carotid arteries for patients who have never had a TIA or stroke. [10, 11, 12] Non-invasive screening for carotid artery stenosis is not 100% accurate. Some patients with stenosis will be missed, and even worse, some patients with minor stenosis may be exposed to risk from a needless procedure.

Timing of Carotid Artery Imaging for Symptomatic Carotid Artery Disease

The patient with symptomatic carotid artery disease should have urgent imaging for carotid artery stenosis within 24–48 h of first presenting with symptoms, since the risk of recurrent stroke within 90 days is from 8 to 20% [13, 14, 15, 16, 17, 18]. The two most important clinical predicators of stroke in the patient with carotid disease are the degree of stenosis and a history of previous TIA or stroke. Other features such as plaque morphology, various demographic

characteristics, and the presence of contralateral carotid disease may affect prognosis but are clearly less important [4].

Carotid Stenosis: Medical, Surgical, and Endovascular Management

Several large research trials have provided evidence-based guidelines for the treatment of carotid stenosis, including recommendations for: (1) medical therapy, (2) carotid endarterectomy (CEA), and (3) endovascular angioplasty and stent placement. Details of stroke clinical trials are reviewed and published in practice guidelines by the American Heart Association, American Academy of Neurology, and American College of Chest Physicians [12, 13, 14, 15, 16, 17, 19, 20, 21, 22, 23, 24, 25].

Medical Therapy

CEA surgery is not indicated in the patient with carotid stenosis of less than 50%. Instead, the patient with carotid artery stenosis of less than 50%, with a TIA or non-disabling stroke, should be treated with aggressive medical therapy. This includes management of known stroke risks factors including: hypertension, cigarette smoking, dyslipidemia, diabetes mellitus, obesity, and other modifiable risk factors. Antithrombotic therapy should also be instituted. It is important to know that 20% of newly diagnosed TIA and stroke patients have undiagnosed cardiovascular disease. Indeed, atherosclerosis is a systemic disease which can affect many areas of the body. Aggressive measures instituted to prevent its progression will decrease the risk of stroke, myocardial infarction, and the development of peripheral vascular disease and aortic aneurysms. The American Heart Association has developed consensus guidelines to assist the provider in identifying target treatment goals [12, 25] (these can be viewed online at http://stroke.ahajournals.org/cgi/content/full/37/2/577).

Antithrombotic Therapy for Stroke and TIA Prevention: Carotid Artery Disease

All patients with carotid artery disease without evidence of atrial fibrillation should be placed on antiplatelets for stroke and TIA. There is strong evidence that daily antiplatelet therapy rather than anticoagulation should be used for stroke prevention in the patient with carotid artery disease [12, 20]. Current AHA consensus guidelines state that aspirin, Aggrenox ^{TM} (combination of

aspirin and extended release dipyridamole) and clopidogrel are all acceptable options for secondary prevention of stroke [12]. Aspirin can be used for stroke prevention in the dosage range from 50 to 325 mg daily. Aggrenox™ is suggested instead of aspirin alone. Clopidogrel can also be considered instead of aspirin alone and is recommended for the patient with aspirin sensitivity. The addition of clopidogrel to aspirin for routine stroke prevention is not recommended as clinical trials have demonstrated an increased risk of bleeding. The patient requiring CEA or endovascular angiography with stent should be treated with antiplatelet therapy pre- and post-operatively.

When the patient has atrial fibrillation and carotid artery stenosis, anticoagulation is the antithrombotic treatment choice for stroke prevention. The patient should be managed with warfarin therapy with an INR goal of 2.5 [12, 20]. If a patient requires surgery or an endovascular surgical procedure, the patient may need to stop warfarin therapy. A pre- and post-operative antithrombotic management plan for stroke prevention will need to be clearly communicated to the patient, primary care provider, and the surgeon.

Carotid Endarterectomy

Carotid endarterectomy (CEA) has been proven to decrease stroke risk in patients with high-grade carotid stenosis [12, 26, 23, 27, 24]. A variety of surgical techniques exist to open and extract carotid plaque. No particular technique has been proven better than another. The surgery is made easier by the relatively easy accessibility of the carotid arteries to surgical manipulation. Rates of complications from endarterectomy have varied widely. Regardless of the exact technique, the training and skill of the surgeon used seems to be the most important factor in keeping operative mortality and morbidity (stroke and death) low. All consensus recommendations specify using a surgeon who documents surgical mortality and morbidity of less than 6% for CEA in patients with recent TIA or stroke and $<3\%$ for patients with asymptomatic carotid narrowing [12, 23, 24, 26, 27, 28].

Secondary analysis of clinical trials has suggested certain patients have a greater benefit from CEA. Older men seemed to have an increased benefit from CEA because women had a higher rate of complications [26]. Patients who had a CEA in the first 2 weeks after a TIA or minor non-disabling stroke had the most benefit [4, 12, 17, 26]. Patients with limited life expectancy due to other medical problems ($<$ 5 years) may not live long enough for the benefit of preventing future stroke to outweigh the risk of stroke or death during the CEA [24] Whether or not surgical intervention is indicated, all patients with carotid stenosis should be managed with aggressive medical therapy for primary and secondary prevention of TIA and stroke.

Several large randomized trials demonstrated that CEA significantly reduces the risk of stroke in patients with symptomatic carotid stenosis. Patients with

TIA or non-disabling stroke due to carotid artery stenosis >50% should receive aggressive medical therapy and will likely benefit from CEA. The risk of recurrent TIA or ischemic stroke in patients with a 51–69% carotid artery stenosis and a recent TIA or non-disabling stroke was reduced if CEA was performed [10, 24, 27, 28, 29]. Patients with severe carotid stenosis, defined as 70–99%, had the best risk/benefit ratio when provided surgical intervention with CEA. The risk of stroke in the 2 years following a TIA or stroke is about 27% following a diagnosis of severe carotid stenosis when the patient is only medically managed. When the patient is treated with both aggressive medical management and CEA, the rate of stroke was decreased to about 9% [24, 27, 28, 29].

Patients with TIA or non-disabling stroke due to complete occlusion of the carotid artery are best treated with aggressive medical therapy. Once the carotid artery is *completely closed*, it is generally not possible to reopen the internal carotid artery with either surgical or endovascular intervention. Non-invasive testing, especially carotid ultrasound and MRA, may be inaccurate in distinguishing severe carotid stenosis from complete occlusion. Non-invasive imaging repeated several weeks following a study with the finding of total carotid artery occlusion will sometimes reveal that the previously "closed" artery is now open. Since the internal carotid artery will not typically "re-open" once it is completely occluded, this scenario usually represents a case where non-invasive imaging did not distinguish a severely narrowed artery from an occluded one. A cerebral angiogram may be required to verify the presence of a total carotid artery occlusion and thus confirm that there is no option for surgical management. Surgical therapy to bypass the internal carotid artery (EC-IC bypass) by implanting a branch of the external carotid artery into the arteries at the base of the brain is not routinely recommended [12]. A clinical trial is underway to test this procedure in carefully selected patients (COSS – Carotid Occlusion Surgery Study, http://dmchost.public-health.uiowa.edu/coss/home.asp).

Endovascular Angioplasty and Stenting

Coronary artery angioplasty and stenting have become an important part of the management of coronary artery disease. Some have assumed that carotid artery stenting will similarly become the therapy of choice for carotid artery stenosis. However, there are significant differences between coronary and carotid arteries. Endovascular therapy such as angioplasty and stenting can cause the formation of emboli that travel distally. In the brain, even very small emboli can lead to a disabling stroke that paralyzes one side of the patient. In coronary arteries, the loss of small amounts of myocardium because of distal emboli is well tolerated.

Endovascular interventions, including carotid artery angioplasty and stent placement, have been less well studied than CEA for management of carotid stenosis. Non-randomized clinical trials have shown that carotid stenting can be

done in patients judged inappropriate for CEA [12, 30]. The patient with significant cardiac or pulmonary disease may be a high-risk surgical candidate and can be considered for carotid stenting. Other patients who may be better candidates for carotid stenting include those with a history of cervical radiation, those who have previously undergone a CEA and are now experiencing recurrent arterial narrowing, or those with an ICA takeoff located high in the neck, making surgical access difficult [12].

Complication rates for endovascular angioplasty and stenting are very dependent on the expertise of the physician and available technology. In the future, as newer endovascular technologies are developed, randomized trials will be needed to re-assess the role of carotid artery angioplasty and stenting in the routine management of carotid artery stenosis. Randomized clinical trials are needed to confirm that carotid artery stenting is non-inferior to CEA. A recent study reported early termination of a large randomized trial after carotid artery stenting was found to have a 3× higher rate of complications in the first 30 days compared with CEA [31]. Preliminary results of another large clinical trial comparing carotid artery stenting and CEA revealed slightly more complications in the stenting group at 30 days [32]. This trial continues to measure complications and recurrent stroke rates at endpoints beyond 30 days.

Patient Education

Although stroke is the third leading cause of death in the United States, many people do not know the symptoms of TIA or stroke [13, 34]. Often patients with TIA ignore their symptoms and are mistakenly reassured because they spontaneously got better. As most TIA and stroke symptoms are painless, patients may be less concerned with stroke versus heart attack symptoms. Patients must be taught the signs and symptoms of TIA and stroke and to immediately seek medical care as these symptoms warn of a dramatic increase in stroke risk. Patients need to know that the risk of stroke, heart attack, and sudden death increases dramatically even after a brief TIA.

The occurrence of carotid artery narrowing should signal the patient and doctor to set aggressive secondary stroke prevention goals. Patient need to be taught that high blood pressure, cigarette smoking, high cholesterol, diabetes, and obesity are risk factors that increase their risk of heart disease and stroke. Multiple resources exist for patients and their families that teach how to decrease stroke risk. The National Institutes of Health (http://www.ninds.nih.gov/disorders/stroke/stroke.htm) and the Centers for Disease Control (http://0-www.cdc.gov.mill1.sjlibrary.org/stroke/) maintain internet sites containing information on stroke, stroke risk factors, and lifestyle modifications, and they list other organizations that provide information regarding stroke, stroke treatment and prevention. For patients without access or expertise in use of the Internet, these same sources can provide written materials.

Brief Summary

- Carotid artery stenosis accounts for 10–15% of all ischemic strokes.
- Symptoms due to carotid stenosis include weakness and/or numbness on one side, aphasia, and visual loss in one eye. Neurological symptoms of vertigo, double vision, memory loss, and syncope are not attributable to carotid artery stenosis.
- Proven medical therapies for the secondary prevention of stroke due to carotid stenosis should include the use of antithrombotics, control of hypertension and hyperlipidemia, and smoking cessation interventions. Additionally, control of blood sugar, weight management strategies, and implementation of a daily aerobic exercise routine may also reduce risk of future stroke.
- Carotid endarterectomy (CEA) is not indicated for carotid artery stenosis $<50\%$.
- For the patient who experienced a TIA or mild stroke due to severe (70–99%) carotid stenosis, the risk of stroke over the next 2 years is approximately 26%. In patient's with an acceptable surgical risk, a CEA performed by an experienced surgeon with a $<6\%$ rate of CEA complications is recommended.
- For the patient who experienced a TIA or mild stroke due to moderate (50–69%) carotid stenosis, the risk of stroke over the next 5 years is approximately 22%. In patient's with an acceptable surgical risk, a CEA performed by an experienced surgeon with a $<6\%$ rate of CEA complications is recommended. Men may benefit more than women with similar moderate stenosis.
- Since the risk of stroke is highest in the days following the initial TIA or minor stroke, CEA should be performed in a timely manner.
- For the patient who has never had a TIA or ischemic stroke but has an incidental finding of carotid artery stenosis of 60–99%, ischemic stroke risk is very low. Aggressive primary stroke prevention interventions should be utilized. CEA may be considered in selected patients. CEA complication rates must be $<3\%$ for asymptomatic patients to benefit.
- Once an internal carotid artery is completely occluded, aggressive medical therapy is the recommended treatment to decrease stroke risk. Currently there is no proven surgical or endovascular treatment to decreased risk of stroke from a carotid artery occlusion.
- Current evidence-based medical practice limits carotid artery endovascular treatment (angioplasty and stenting) to patients who are at high risk for surgery.
- For symptomatic patients, carotid endarterectomy should be performed in surgical centers with a perioperative complication rate (all strokes and death) of less than 6%. The rate of complications can vary greatly between practitioners.

- For asymptomatic patients, carotid endarterectomy should be performed in surgical centers with a perioperative complication rate (all strokes and death) of less than 3%. The rate of complications can vary greatly between practitioners.

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Chapter 12
Cerebral Venous Thrombosis

W. Alvin McElveen

Introduction

Compared to cerebral infarctions from arterial sources, cerebral venous infarctions are less common. The ratio of venous strokes to arterial stroke is reported as 1:62.5. Newer techniques in cerebral imaging such as magnetic resonance venography and computerized tomographic venography may alter the incidence of diagnosed cerebral venous thrombosis (CVT) as less severe cases may be diagnosed with these noninvasive measures.

Venous Sinus Anatomy

One of the difficulties in diagnosing CVT is the wide variability in symptoms. Multiple anastomotic channels may result in poor demarcation of venous drainage territories leading to symptoms that are less predictable than those seen in arterial occlusions. Symptoms may be nonspecific with a broad range of presentations and with severity ranging from mild to life-threatening. Therefore, a high index of suspicion is needed to diagnose the condition early and institute appropriate treatment. Knowledge of the cerebral venous anatomy is also required to understand the presenting symptoms of CVT.

The venous sinuses may be divided into the superficial and deep sinus systems; although, anastomotic veins connect the two systems. The superficial system begins with the superficial cerebral veins which empty into the superior sagittal sinus which runs in the parasagittal area. Bridging veins drain the cortex, cross the subarachnoid space and open into the superior sagittal sinus. This system collects blood from the convexities and medial surface of the hemispheres. The superior sagittal sinus terminates in the confluence of sinuses.

Also considered part of the superficial sinus system are the inferior cerebral veins which drain the basilar portions of the brain and ventral portion of the

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lateral brain empty into the basilar sinuses. The superficial middle cerebral vein drains the middle portion of the superficial system. It drains anteriorly into the cavernous sinus and posteriorly into the transverse sinus via the Vein of Labbe. It is connected to the superior sagittal sinus by the Vein of Trolard.

The deep cerebral white matter and basal ganglia drain centrally into the deep venous system via subependymal veins including septal, thalamostriate, internal cerebral veins, basilar vein of Rosenthal and vein of Galen. Septal veins drain the frontal horns and join to form the internal cerebral veins. The paired internal cerebral veins on each side receive blood from the thalamostriate veins and then join with the basilar vein of Rosenthal to form the vein of Galen. The vein of Galen curves around the splenium and joins the inferior sagittal sinus to form the straight sinus. The straight sinus then terminates in the confluence of sinuses. The majority of blood draining the brain leaves the confluence of sinuses via the transverse (or lateral) sinuses. The transverse sinus then leaves the tentorium to become the sigmoid sinus. It then traverses the jugular foramen to be drained by the jugular vein.

The cavernous sinus lies on either side of the sphenoid bone. It is the only sinus in the body through which other blood vessels run. The cavernous sinus contains the carotid artery and abducens nerve. The lateral walls contain the oculomotor and trochlear nerves as well as the first and second division of the maxillary nerve. Veins draining into the cavernous sinus include the superficial middle cerebral vein, the ophthalmic vein, and sphenoparietal sinus. The cavernous sinus drains posteriorly into superficial and inferior petrosal sinuses which empty into the transverse sinus and jugular foramen, respectively. Details of the venous sinus flow can be seen on the schematic of the venous sinus system depicted in Fig. 12.1.

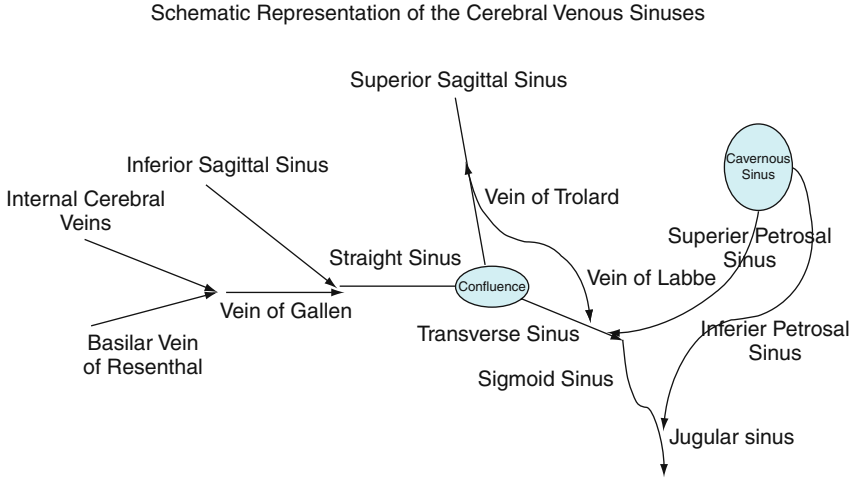

Fig. 12.1 Schematic representation of major cerebral venous sinuses

Clinical Syndromes

The onset of symptoms may be slow and insidious rather than rapid, as seen in arterial strokes. They may be rapid, however, if associated with hemorrhage or infection. Some symptoms such as headache, nausea, and vomiting are not specific to a single sinus thrombosis, and indeed, they are not specific for CVT. Thunderclap headache is usually a symptom of subarachnoid hemorrhage, but may also be seen with venous sinus thrombosis. The headache has no specific character and may be the earliest as well as only symptom of venous thrombosis. Headaches may also be positional and resemble low CSF pressure headaches.

Lateral Sinus Thrombosis

Lateral sinus thrombosis is often associated with mastoiditis or ear infections. Patients may present with severe headache and diplopia secondary to increased intracranial pressure causing a VI nerve palsy. Papilledema may be present. This is also a clinical picture of pseudotumor cerebri (idiopathic intracranial hypertension) and there may be overlap between the two conditions. In fact, using a technique called auto-triggered elliptic-centric-ordered three-dimensional gadolinium-enhanced MR venography, Farb et al. [1] found that 27 of 29 patients with idiopathic intracranial hypertension had bilateral sinovenous stenosis; this was seen in only 4 of 59 control subjects.

Cavernous sinus thrombosis may occur with obstruction of the ophthalmic veins resulting in proptosis and ipsilateral sinus thrombosis. As several cranial nerves course through the cavernous sinuses, patents may develop disorders of oculomotor movement as well. These findings include ptosis, sluggish pupillary reaction, and eye movement paralysis. The first division of the trigeminal nerve may also be involved causing numbness of the ipsilateral forehead.

Sagittal Sinus Thrombosis

Sagittal sinus thrombosis may result in increased intracranial pressure and edema of the scalp and forehead. Thrombosis of the tributary veins may lead to seizures, hemiplegia, aphasia, or hemianopsia. Lower extremity paresis may result from venous infarction of the parasagittal motor strip.

Deep Venous Thrombosis

The deep venous system consists of the straight sinus, the vein of Galen, the internal cerebral veins and basal vein. Marked thrombosis in this system results in coma, abnormal eye movements and pupillary dysfunction due to ischemia of

the diencephalon. Decerebrate posturing also may occur. Partial syndromes can occur with the spectrum of findings dependent on the degree of venous congestion. Thalamic lesions, often bilateral, can occur secondary to occlusion of the internal cerebral veins. Hemorrhagic lesions are seen with more pronounced venous occlusion. Patients may therefore present with headache and hemiparesis. The deep venous system also drains the periventricular white matter, the corpus callosum, the hippocampus, the limbic system, the visual cortex, and the cerebellum. Headaches, seizures, hemianopsia, ataxia, and speech disturbances may therefore be seen with thrombosis of these venous channels.

Etiologies

CVT is often seen as a complication of other medical conditions that must be identified. These are summarized in Table 12.1. Oral contraceptives and pregnancy have been linked to venous thrombosis and may be responsible for a slight increase in the incidence of cerebral vein thrombosis in women compared to men. In addition, the incidence in women appears greater in the 20–35 year age group. The puerperium period is a vulnerable time for CVT occurrence. Risk factors may also be seen in combination such as an increased risk of CVT with the use of oral contraceptives in women with a prothrombin gene mutation.

Hypercoaguable states are associated with the antiphospholipid syndrome, protein S deficiency, protein C deficiency, antithrombin III deficiency, lupus anticoagulant, and the Leiden factor V mutation.

Inflammatory and infectious etiologies should also be considered. Crohn's disease and ulcerative colitis have been linked to CVT. In addition, corticosteroids have also increased the risk of venous thrombosis, but may be used in the treatment of inflammatory bowel diseases. Infection of the paranasal sinuses may also spread to the cerebral venous sinuses leading to septic cerebral venous phlebitis. The frontal sinus is the most common location with development of subdural empyema in addition to septic sinus thrombosis.

Hematological conditions such as thrombotic thrombocytopenia purpura, sickle cell disease, paroxysmal nocturnal hemoglobinuria, and polycythemia may be risk factors to the development of CVT. Collagen vascular diseases such as Behcet's, systemic lupus erythematosis, and Wegener's granulomatosis are mentioned as etiologies for development of CVT.

Other medical conditions including hepatic cirrhosis, nephrotic syndrome, dehydration, and sarcoidosis are linked to increased risk of CVT. Neoplasms such as carcinoma, lymphoma, and leukemia may also be associated with hypercoagulability, and therefore be associated with CVT.

In addition to oral contraceptives and corticosteroid use, other medications such as epsilon aminocaproic acid and l-aspartate are associated with increased incidence of CVT.

Table 12.1 Medical conditions associated with cerebral venous thrombosis

I. Hematalogical conditions
A.Thrombotic thrombocytopenia purpura
B. Sickle cell anemia
C. Paroxysmal nocturnal hemoglobinuria
D.Polycythemia
E. Protein S deficiency, protein C deficiency, Leiden factor V mutation, antithrombin III deficiency, lupus anticoagulant, antiphospholipids and cardiolipin syndromes
II. Inflammatory conditions
A. Collagen vascular diseases
1. Wegener's granulomatosis
2.Systemic lupus erythematosis
3 Behcet's
B. Crohn's and ulcerative colitis
C. Paranasal sinus infections
III Medications
A.Oral contraceptives
B. Epsilon aminocaproic Acid
C. Corticosteroids
D. l-Aspartate
IV Other medical conditions
A. Sarcoidosis
B. Nephrotic syndrome
C. Hepatic cirrhosis
D. Dehydration
E. Neoplasm
F. Pregnancy

Diagnostic Procedures

The clinical suspicion of venous sinus thrombosis should be raised if CT or MRI imaging procedures shows an infarct pattern that does not correspond to an arterial distribution. A contrast enhanced CT brain scan may show loss of flow in the sagittal sinus in a finding known as the empty delta sign. In addition a recent change in headache pattern or a thunderclap headache may clinically be the major presenting symptom. Loss of flow void in venous channels on MRI should raise suspicion. In addition the use of ECHO planar T2* sequence may be helpful as a hemorrhagic venous infarct may be more easily demonstrated. The sinus itself may show susceptibility effect within the thrombosed sinus. Diffusion weighted imaging may show subtle areas of infarct, but are quite variable in patients with venous thrombosis.

MR venography has become an important method in the visualization of CVT. Single slice phase contrast angiography is the sequence of choice in making the diagnosis. However, flow gaps in the transverse sinus may be seen in 31% of normal individuals and should not be mistaken for thrombosis. The nondominant transverse sinus is the affected sinus in 90% of individuals with

this anatomical variant. Abnormal intraluminal signal compatible with clot is helpful in making this differentiation.

CT angiography (CTA) with attention to the venous phase is also helpful in demonstrating venous sinus thrombosis, but all procedures may have difficulty in separating thrombosis from anatomical variant if intraluminal clot cannot be demonstrated. Computerized subtraction techniques may improve detail with CTA. Separation of venous from arterial flow may also be difficult with CTA while MR venography sequences show only venous structures.

In some patients conventional angiography with prolonged filming to look at the venous phase may be necessary. Although this procedure is invasive and carries a small risk, it should be considered in those patients with suspicious symptoms and findings in which MR venogram or CT angiogram are not diagnostic. Dilated tortuous venous channels leading away from an absent sinus is supportive of venous thrombosis. This procedure also demonstrates direction of flow, which may be helpful if there appears to be loss of flow in a major sinus. If the flow in a tributary vein is reversed, this may be indicative of loss of blood flow in the sinus (Fig. 12.2).

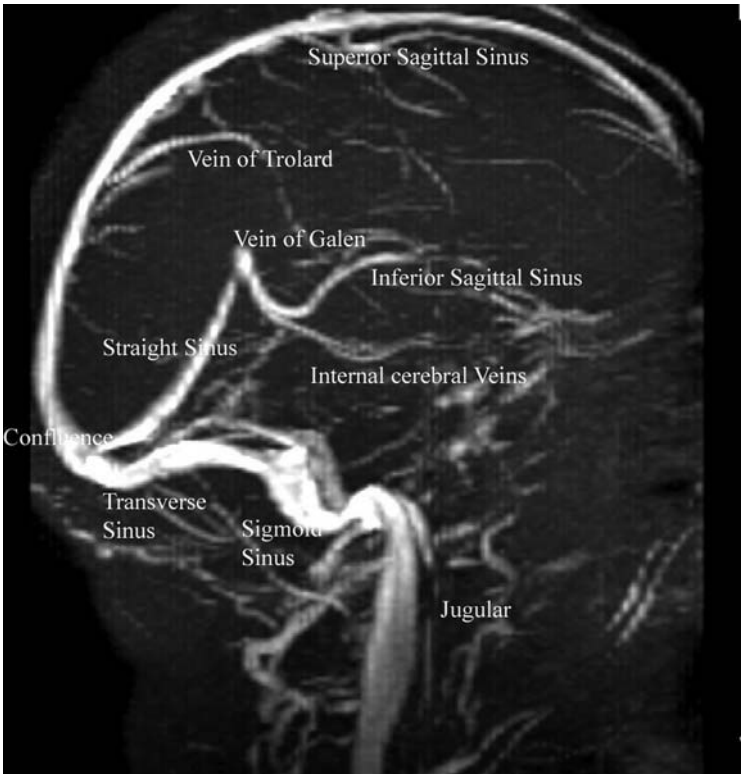

Fig. 12.2 Lateral view of MR venogram of cerebral sinuses

Laboratory studies may be helpful in the determination of cerebral vein thrombosis. D-dimer values may be elevated in screening patients with acute venous sinus thrombosis. The value is positively correlated with the extent of thrombosis and negatively correlated with the duration of thrombosis. If a high suspicion for cerebral vein thrombosis exists, a normal d-dimer does not eliminate the need for more specific imaging studies such as MR venography.

Investigating Potential Etiologies – What tests to order?

Blood cultures should be obtained as venous thrombosis may be seen with sepsis or acute sinusitis. CBC may be helpful as leukocytosis may indicate an infectious etiology. Polycythemia may also be present as a causative condition. If heparin is being used, monitoring the platelet count is important.

Antiphospholipid and anticardiolipin antibodies should be obtained to evaluate for hypercoaguable states. These antibodies may be seen with seen with collagen vascular diseases so ANA and sedimentation rate should also be considered. The Beta2 glycoprotein antibody is a highly specific indicator of the antiphospholipid syndrome. Other hypercoaguable conditions to be considered include protein S, protein C, antithrombin III, lupus anticoagulant, and Leiden factor V. These values cannot be evaluated if the patient is on anticoagulant therapy.

Urine protein may be elevated in nephrotic syndrome. Liver function studies should be evaluated to exclude cirrhosis. Hemoglobin electrophoresis or sickle

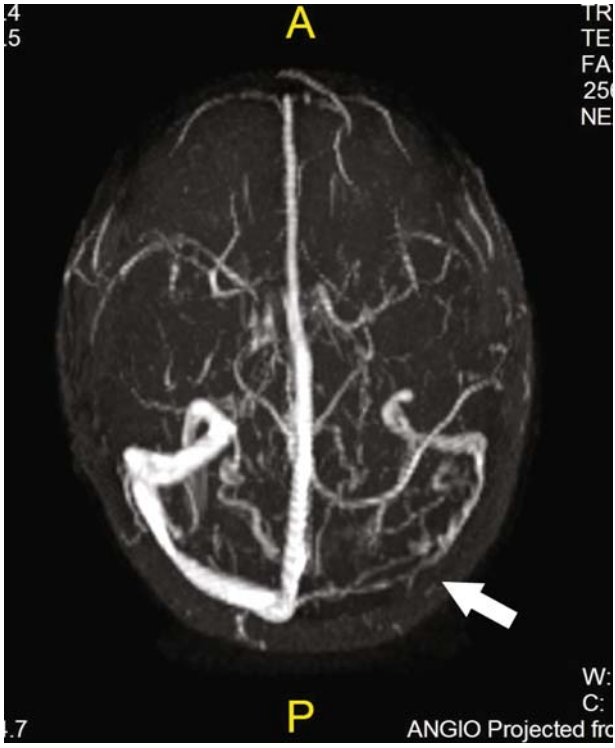

Fig. 12.3 Arrow indicates thrombosis of left transverse sinus in patient with Beta2 glycoprotein elevation

cell preparation should be obtained in individuals of African descent as sickle cell anemia may be an associated condition.

Lumbar puncture may be indicated to look for basilar meningitis as an associated infectious process. However, CT scan or MRI should be used to exclude a large hemispheric lesion or posterior fossa lesion prior to performing the procedure. In the past unilateral compression of the jugular vein was utilized to demonstrate elevation of CSF pressure and hence occlusion of the contralateral transverse sinus. However, concern over precipitation of herniation has led to abandonment of this procedure since there are more specific noninvasive methods to determine CVT (Fig. 12.3).

Treatment Options

Specific therapy for CVT involves anticoagulant therapy. Use of anticoagulation has been debated among neurologists secondary to the fear of causing or worsening cerebral hemorrhage. Anticoagulation helps to prevent propagation of clotting in the venous system and allows recanalization so that the venous pressure normalizes. A Cochrane Review [2] published in 2002 sited two small trials involving 79 patients. One trial (20 patients) examined the efficacy of intravenous, adjusted dose unfractionated heparin. The other trial (59 patients) examined high dose, body weight adjusted, subcutaneous, low-molecular weight heparin (Nadroparin). Anticoagulant therapy was associated with a pooled relative risk of death of 0.33 (95% CI, 0.08–1.21) and of death or dependency of 0.46 (95% CI, 0.16–1.31). No new symptomatic intracerebral hemorrhages were observed. Based upon the limited evidence available, anticoagulant treatment for cerebral sinus thrombosis appeared to be safe and was associated with a potentially important reduction in the risk of death or dependency; though the finding did not reach statistical significance.

Long-term anticoagulation with warfarin is usually recommended with proven CVT. Treatment is generally continued for 4–6 months. If a hypercoaguable state is discovered, permanent anticoagulation with warfarin or a heparinoid may be required.

Less Established Treatment Options

Thrombolytic therapy via infusion of the thrombolytic agent into the dural venous sinus utilizing a microcatheter may be performed in specialized centers. This method is indicated in patients with significant neurologic deficits. However, in a 2003 Cochrane review [3], it was noted that there is currently no available evidence from randomized controlled trials regarding the efficacy or safety of thrombolytic therapy in dural sinus thrombosis. Surgical care with

open thrombectomy and local thrombolytic therapy may also be performed in patients who deteriorate despite anticoagulant therapy.

A special rheolytic catheter to mechanically disrupt the clot combined with thrombolytic therapy has been described as beneficial in a patient who failed microcatheter instillation of thrombolytic. However, procedures such as this have not been widely studied and are not available in most institutions.

General Care

The general care of the patient with CVT is similar to the management of arterial stroke. Patients should be given nothing by mouth if they are hemiplegic or have depressed awareness until evaluated for swallowing deficit. This may require a video swallowing study. Intravenous solutions should be normal saline with avoidance of dextrose containing or hypotonic solutions. As many of these patients may have increased intracranial pressure, methods to decrease the pressure such as elevating the head of the bed 30 degrees, hyperventilation, osmotic agents, and 3% hypertonic saline to maintain the serum Na in the 145–155 mmol/L range may be helpful. Corticosteroids have been beneficial in the setting of neoplasm-associated intracranial pressure, but have not shown benefit in cerebral infarction. They are therefore not recommended in CVT.

Seizures should be treated with appropriate anticonvulsants. This may include an initial dose of an intravenous benzodiazepam such as lorazepam or diazepam for the treatment of status epilepticus. A longer acting medication such as phosphenytoin may also be utilized as a parenteral formulation. If the patient is allergic to phenytoin or a second agent is needed to control seizures, parenteral formulations are also available for phenobarbital, valproic acid, and leveteracitam. Oral forms are also available when the patient is able to safely take them.

Prognosis

The mortality of CVT has been variably reported, ranging from 14 to 48%. This variability likely reflects differences in the severity of deficit at the time of diagnosis. Full recovery from neurological deficit occurs on 25–30% of patients. Patients at the extremes of the age group curve, and those presenting with coma or severe focal deficits, are more likely to have a poor outcome. Residual dysfunction may include headache in 30%, pyramidal signs in 11.7%, visual defects in 5.9%, aphasia in 8.8%, and memory deficit/depression in 17.6% of patients. Patients who had visual field defects should be closely monitored to ensure there is no continued increased intracranial pressure leading to visual field deterioration.

Imaging studies such as MR venography may be beneficial in following patients for evidence of recanalization of the venous system. However, the venous sinus often remains occluded.

Summary of Management

1. Diagnosis is based on Clinical Presentation. The symptom onset may be slow. Diagnosis is established by neuroimaging techniques with MRI and MRV being the most useful. Avoid overdiagnosing thrombosis as a significant number of patients will have an anatomical variant with an absent or hypoplastic transverse sinus.
2. Look for medical conditions that may be associated with venous thrombosis such as infection, medications, and hypercoaguable states.
3. General management of CVT shares many of the same principles as arterial stroke such as preventing aspiration and appropriate management of increased intracranial pressure.
4. Heparin is indicated to prevent propagation of the clot in the venous system and to therefore allow improved venous drainage leading to decreased venous congestion. Heparin appears to be safe with no increased risk of intracerebral bleeding.
5. The prognosis is generally good but patients who present with coma or severe focal deficit as well as the very old and very young have a less favorable prognosis.
6. For the long term, anticoagulation may be indicated if a patient is found to be hypercoagulable. Visual fields may need to be monitored frequently because of increased intracranial pressure with lateral sinus thrombosis, and antiepileptic medications may need to be continued if seizures occurred.

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