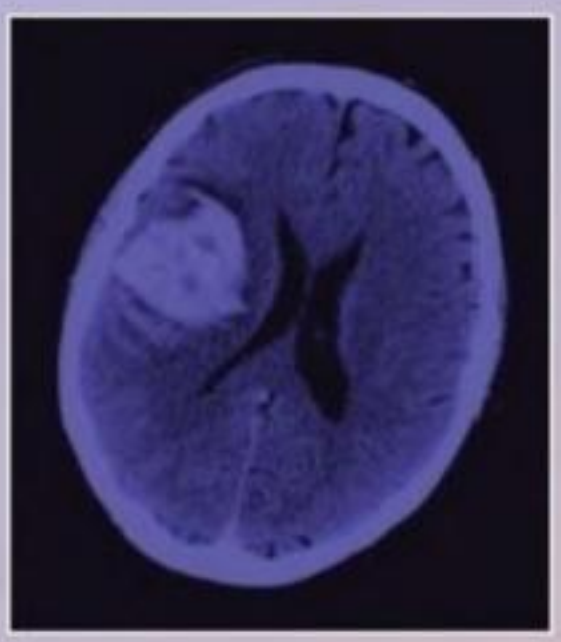
NEUROLOGY IN PRACTICE

Series editors **Robert A. Gross & Jonathan W. Mink**

Stroke



Edited by

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Series Foreword

The genesis for this book series started with the proposition that, increasingly, physicians want direct, useful information to help them in clinical care. Textbooks, while comprehensive, are useful primarily as detailed reference works but pose challenges for uses at the point of care. By contrast, more outline-type references often leave out the "hows and whys" – pathophysiology, pharmacology – that form the basis of management decisions. Our goal for this series is to present books, covering most areas of neurology, that provide enough background information to allow the reader to feel comfortable, but not so much as to be overwhelming; and to associate that with practical advice from experts about care, combining the growing evidence base with best practices.

Our series will encompass various aspects of neurology, with topics and the specific content chosen to be accessible and useful.

Chapters cover critical information that will inform the reader of the disease processes and mechanisms as a prelude to treatment planning. Algorithms and guidelines are presented, when appropriate. "Tips and Tricks" boxes provide expert suggestions, while other boxes present cautions and warnings to avoid pitfalls. Finally, we provide "Science Revisited" sections that review the most important and relevant science background material, and "Bibliography" sections that guide the reader to additional material.

We welcome feedback. As additional volumes are added to the series, we hope to refine the content and format so that our readers will be best served.

Our thanks, appreciation, and respect go out to our editors and their contributors, who conceived and refined the content for each volume, assuring a high-quality, practical approach to neurological conditions and their treatment.

Our thanks also go to our mentors and students (past, present, and future), who have challenged and delighted us; to our book editors and their contributors, who were willing to take on additional work for an educational goal; and to our publisher, Martin Sugden, for his ideas and support for wonderful discussions and commiseration over baseball and soccer teams that might not quite have lived up to expectations. We would like to dedicate the series to Marsha, Jake, and Dan; and to Janet, Laura, and David. And also to Steven R. Schwid, MD, our friend and colleague, whose ideas helped to shape this project and whose humor brightened our lives, but he could not complete this goal with us.

Robert A. Gross
Jonathan W. Mink
Rochester, July 2011

Preface

Stroke is a medical emergency. Rapid bedside diagnosis and interpretation of neuroimaging studies is necessary to identify patients eligible for acute stroke therapies. Identification of the stroke mechanism in conjunction with prompt initiation of appropriate preventative strategies reduces the risk of recurrence. The acute stroke care continuum typically concludes with early establishment of rehabilitation and recovery programs. The purpose of this book is to give providers an evidence-based roadmap that they can use at the bedside for the care of patients with acute stroke.

Each chapter is authored by physicians with experience and expertise in the front-line evaluation and treatment of patients affected by stroke. The content of each chapter is comprehensive, but not exhaustive, which facilitates utility as both a reference and point-of-care resource. Key references have been included, but limited in number, so as to not interfere with readability. Content included in "Tips and Tricks" and "Science Revisited" boxes direct the reader to clinical pearls and the scientific basis supporting key recommendations. An appendix is included for easy access to validated prognostic scales and measures of stroke severity and disability.

We wish to thank Drs. Gross and Mink for the opportunity to edit this book and the staff at Wiley-Blackwell publishing for guiding us through the process of crafting the content outline, inviting expert authors, and final editing. Without their vision and encouragement a project of this magnitude would not have been possible.

We dedicate this book to stroke patients, their families, and their care givers – past, present, and future.

Kevin M. Barrett
James F. Meschia

1

Bedside Evaluation of the Acute Stroke Patient

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Introduction

Emanating from the results of the original National Institute of Neurological Disorders and Stroke recombinant tissue plasminogen activator (NINDS rt-PA) trial [1], the management of acute stroke has evolved as a cornerstone of emergency medical care, hospital medicine, and clinical neurology. While the only treatment for acute ischemic stroke approved by the US Food and Drug Administration (FDA) remains intravenous (IV) rt-PA administered within 3 hours of symptom onset, the field continues to expand with a focus on more timely treatment, expanding the pool of patients eligible for treatment, and optimization of methods of reperfusion. These advances include the use of IV rt-PA beyond the 3-hour window, the direct administration of intra-arterial rt-PA, and implementation of a variety of devices aimed at mechanical thrombectomy and other interventional means of cerebrovascular recanalization. However, integrating all of the scientific evidence guiding the acute stroke paradigm is daunting, even for the most seasoned vascular neurologist. According to the National Guideline Clearinghouse, an initiative of the Agency for Healthcare Research and Quality in the Department of Health and Human Services, there are currently 225 published guidelines related to “acute stroke” from various organizations and societies around the world [2]. The current standard of stroke care in the US is guided by the American Heart Association/American Stroke Association’s (AHA/ASA) Get With the Guidelines (GWTG) program [3].

While stroke therapeutics will be discussed in detail elsewhere in this book, the

aim of this chapter is to offer a simple, practical approach to the bedside evaluation of the acute stroke patient. As the opinions and recommendations herein draw on experience treating acute stroke, they also reflect the literature and guiding evidence. The chapter will broadly highlight seminal studies, published AHA/ASA guidelines, FDA regulations, and The Joint Commission (TJC) certification requirements for primary/comprehensive stroke centers – links to further resources can be found in the Appendix, Chapter 9. Explored in detail will be the various issues facing neurologists or other physicians in acute stroke scenarios, including an accurate gathering of history, essentials of the acute stroke physical exam, radiological diagnosis, and potential hurdles precluding a treatment decision. While these necessary steps are very much protocol driven, the reality of the acute stroke setting dictates a somewhat simultaneous process in order to achieve the efficient delivery of treatment. Ultimately, the aim of the chapter is to further promote rapid diagnosis and timely management for all acute stroke patients, as the medical community continues to strive for the best possible outcomes from this disabling and deadly disease.

Is it a stroke?

Despite rapid advances in neuroimaging over the past 20 years, the bedrock of the evaluation of the acute stroke patient remains sound clinical diagnosis. The physician is frequently asked to see a patient in urgent consultation for treatment of acute stroke in the absence of a firmly established diagnosis. Even with the advent of highly advanced neuroimaging techniques, *stroke* remains a clinical diagnosis; as opposed to an *infarct*, which is an imaging or tissue-based diagnosis. Stroke is, by definition, the acute onset of a persistent focal neurological deficit or constellation of deficits referable to a specific cerebrovascular territory. The absence of abrupt onset of symptoms all but precludes acute stroke as the diagnosis. Symptoms that do not all fit into a specific vascular territory suggest either a diagnosis other than stroke or the - possibility of multifocal ischemia as may be seen in cardioembolism. Additionally, stroke typically produces *negative* symptoms –that is to say, loss of strength, sensation, vision, or other neurological function. Presence of *positive* symptoms (paresthesias, involuntary movements, visual phenomena) is uncommon in stroke, unless the patient with a cortical stroke is having a concurrent seizure or occasionally a triggered migraine – as in cervical artery dissection.

Ischemic stroke subtypes in specific vascular territories tend to produce fairly predictable constellations of signs and symptoms, or “syndromes” [4]. Rapid recognition of these syndromes is crucial in early diagnosis and timely treatment of acute stroke or, often of equal importance, the elimination of stroke as a potential diagnosis. In terms of broadly defined clinical stroke syndromes, one can consider large vessel versus small vessel presentations. Generally speaking, large vessel strokes tend to occur in the setting of atherosclerotic and/or embolic

disease, whereas small vessel (lacunar) strokes tend to present in the setting of chronic small vessel occlusive disease related primarily to chronic hypertension and diabetes. The clinical manifestations of commonly encountered large vessel syndromes are described in Table 1.1.

Table 1.1 Large vessel stroke syndromes (laterality assumes left hemispheric dominance)

Vascular territory	Signs and symptoms
Internal carotid artery (ICA)	Combined ACA/MCA syndromes; ipsilateral monocular visual loss secondary to central retinal artery occlusion (amaurosis); branch retinal artery occlusions may present as ipsilesional altitudinal field cuts
Left anterior cerebral artery (ACA)	Right leg numbness and weakness, transcortical motor aphasia, and possibly ipsilesional or contralesional ideomotor apraxia
Right ACA	Left leg numbness and weakness, motor neglect, and possibly ipsilesional or contralesional ideomotor apraxia
Left middle cerebral artery (MCA)	Right face/arm > leg numbness and weakness, aphasia, left gaze preference
Right MCA	Left face/arm > leg numbness and weakness, left hemispatial neglect, right gaze preference, agraphesthesia, stereoagnosia
Left posterior cerebral artery (PCA)	Complete or partial right homonymous hemianopsia, alexia without agraphia; if midbrain involvement, ipsilateral 3rd nerve palsy with mydriasis and contralateral hemiparesis (Weber syndrome)
Right PCA	Complete or partial left homonymous hemianopsia (same as above if midbrain involvement)
Superior cerebellar artery (SCA)	Ipsilesional limb and gait ataxia
Anterior inferior cerebellar artery (AICA)	Vertigo and ipsilesional deafness, possibly also ipsilesional facial weakness and ataxia
Vertebral/posterior inferior cerebellar artery (PICA)	Ipsilesional limb and gait ataxia; if lateral medullary involvement can have Wallenberg syndrome (see Table 1.4)
Basilar artery (BA)	Pontine localization with impaired lateral gaze, horizontal diplopia and dysconjugate gaze, nonlocalized hemiparesis, dysarthria

The syndromes above reflect classical neuroanatomy and may vary depending on individual variations in the circle of Willis or collateral vascular supply.

Cortical syndromes

Between large vessel and cardioembolic disease, there are several classic cortical syndromes that when presenting acutely are most often the result of an ischemic stroke. The classic hallmark of a left hemispheric cortical syndrome involves aphasia. Aphasia is defined as an acquired abnormality of *language* in any form. By and large, aphasia presents as a deficit of verbal language, but truly involves any medium of communication (e.g. reading and writing, or sign

language in the hearing impaired). Specific linguistic properties that may be affected by aphasia include volume of speech, vocabulary, cadence, syntax, and phonics. Often, subtle aphasia is difficult to distinguish from encephalopathy and it is important for the bedside clinician to test specific domains of language – fluency, repetition, comprehension, naming, reading, and writing – in order to make the correct diagnosis.

Specific types of aphasia most often encountered in stroke patients (Table 1.2) classically include expressive/motor/nonfluent (Broca's) and receptive/sensory/fluent (Wernicke's) types. Strokes causing expressive aphasia localize to the posterior inferior frontal lobe, or frontal operculum, whereas receptive aphasias commonly originate from lesions in the posterior superior temporal/inferior parietal lobe. Both of these types commonly affect naming and repetition. Broca's patients are best identified by difficulties with word finding, speech initiation, volume of speech, and in making paraphasic errors (e.g. "hassock" instead of "hammock"). Wernicke's patients have clearly impaired comprehension with nonsensical speech, but preserved speech volume and cadence. The transcortical aphasias mirror motor and sensory types except in preservation of repetition, due to lack of injury to the arcuate fasciculus linking Broca's and Wernicke's areas. Figure 1.1 displays the "aphasia box" showing the overlap between the commonly encountered aphasias.

TIPS AND TRICKS

A common false localizer for aphasia is left thalamic stroke, which may present with a mixed aphasia of nonspecific character.

In the bedside evaluation of the stroke patient, differentiating between aphasia subtypes is less relevant than differentiating aphasia from encephalopathy. As most all aphasia emanates from dominant hemispheric injury, commonly middle cerebral artery (MCA) occlusion, one should consider the abrupt onset of aphasia indicative of stroke until proven otherwise.

TIPS AND TRICKS

Aphasia differs from delirium (acute confusional state) in that attention is usually preserved in isolated aphasia. Moreover, the aphasic patient is often visibly aware of and frustrated by their deficits, as opposed to the poorly attentive patient with encephalopathy.

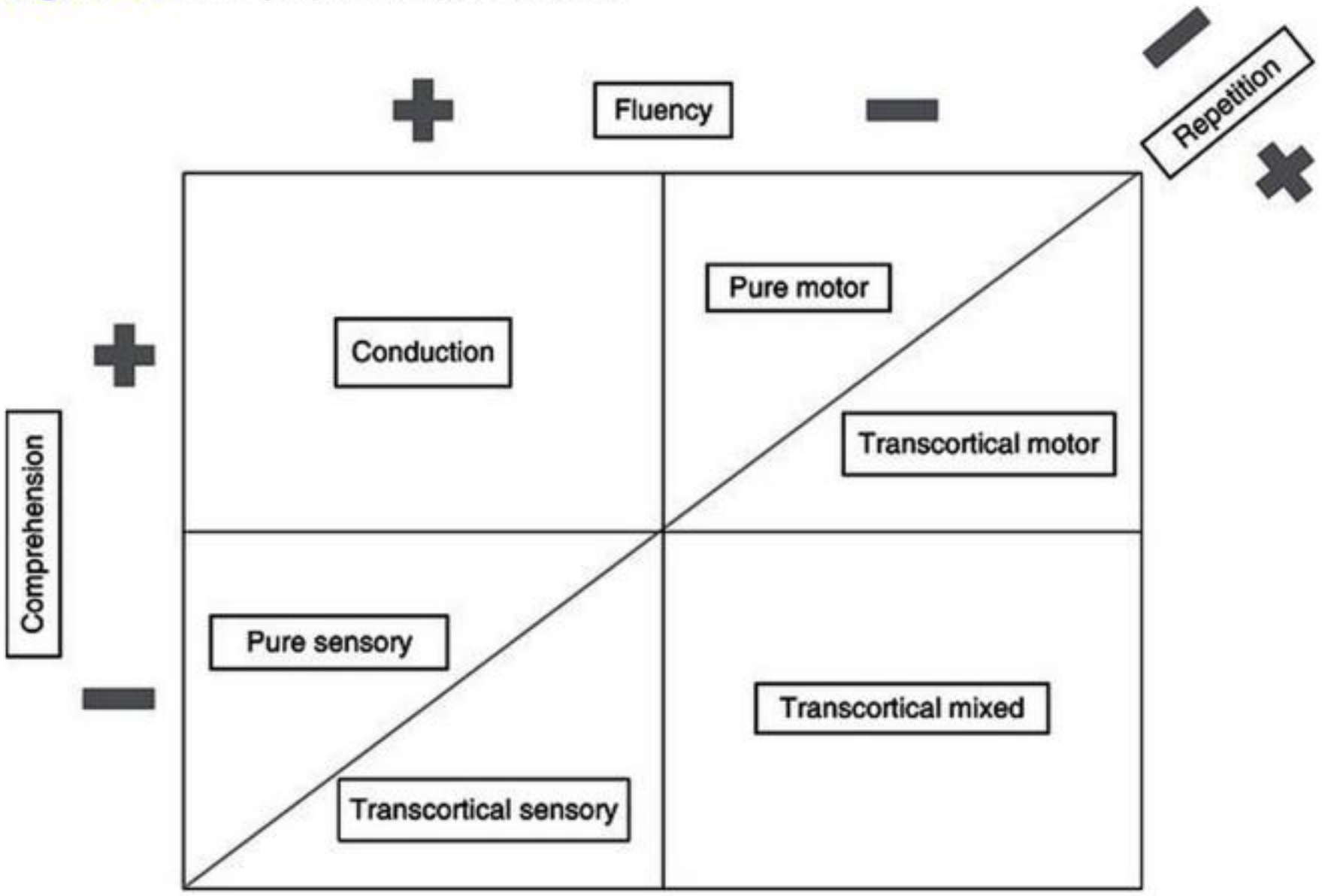
If aphasia is the hallmark of dominant (*left*) hemisphere cortical injury, then hemispatial neglect is the hallmark of injury in the nondominant (*right*) hemisphere. Accordingly, abrupt onset of hemineglect should raise concern for acute stroke by occlusion of the right MCA. Examining the patient with neglect at

the bedside is challenging, primarily due to difficulties in teasing out primary contralateral motor weakness and numbness. The most sensitive bedside test for subtle neglect is double simultaneous stimulation to look for *extinction* of - contralateral sensory modalities. In other words, when presented with bilateral stimuli, the neglectful patient will preferentially identify the ipsilateral stimulus, often in the absence of a primary sensory deficit (see National Institutes of Health Stroke Scale (NIHSS) item 11, in the Appendix, Chapter 9). Extinction may include not only tactile sensation but also other sensory modalities, such as vision or hearing. Motor neglect is typified by preferential use of the ipsilateral limbs when formal confrontational testing reveals no actual hemiparesis. The tactful bedside clinician, when asking the patient to raise both limbs, may observe a delay in or absence of activation of the contralateral side.

Table 1.2 The aphasias

	Fluency	Comprehension	Repetition
Motor/expressive (Broca)	Impaired	Normal	Impaired
Sensory/receptive (Wernicke)	Normal	Impaired	Impaired
Conduction	Normal	Normal	Impaired
Transcortical motor	Impaired	Normal	Normal
Transcortical sensory	Normal	Impaired	Normal
Mixed	Variable	Variable	Variable
Global	Impaired	Impaired	Impaired

Figure 1.1 The graphical aphasia box.



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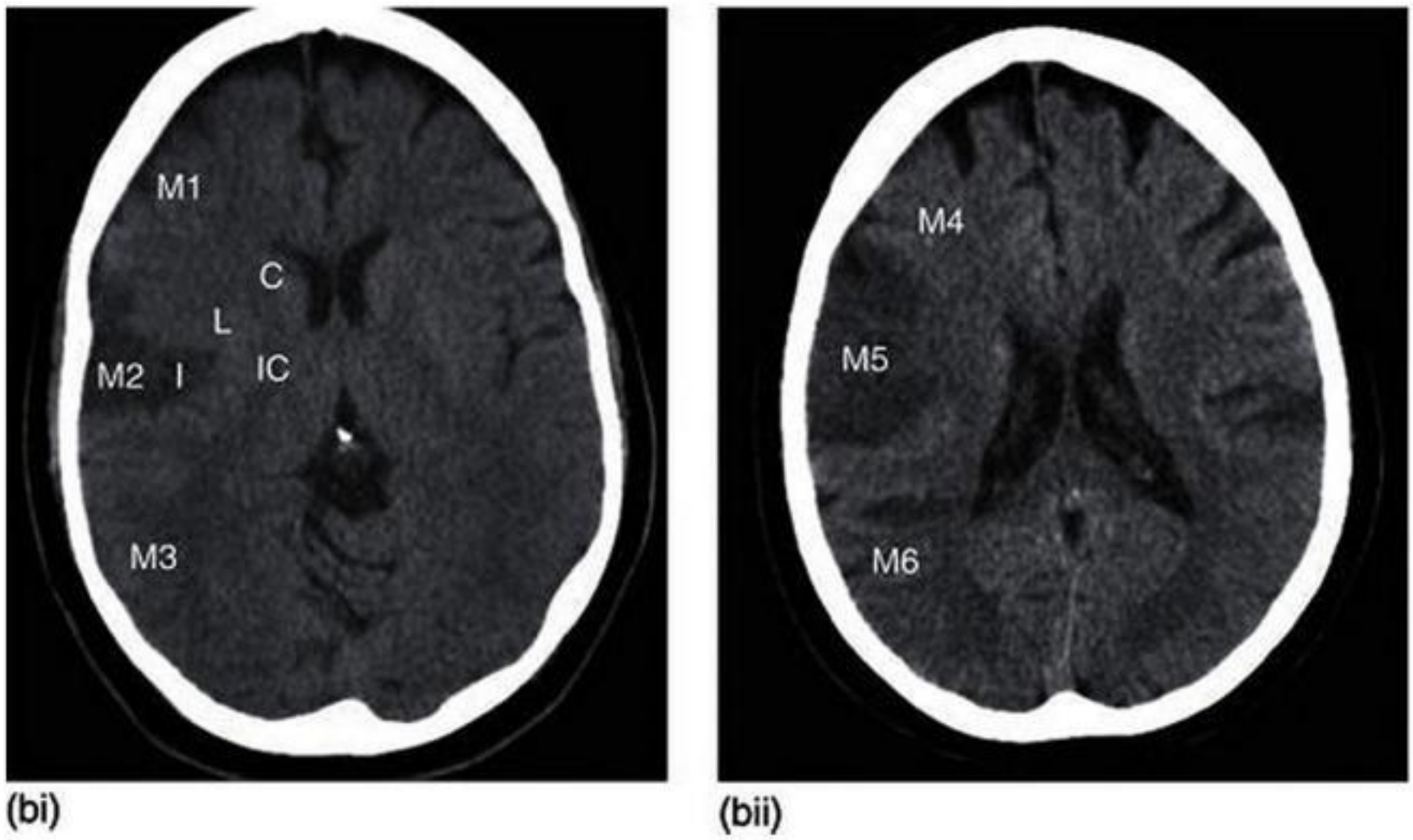

(bi) (bii)

Figure 2.2 (a) Unenhanced CT signs of early stroke – the "insular ribbon" sign and "sulcal effacement." The solid ellipses show portions of the insular cortices with subtle right (versus left) sided low attenuation and loss of gray–white differentiation, secondary to early cytotoxic/vasogenic edema. The dashed ellipses show portions of the frontal cortices with right sulcal effacement. (b) Unenhanced CT detection of stroke: the "insular ribbon sign," displayed using standard "window width" and "center level" gray scale settings. Unenhanced CT at the level of the Sylvian fissure shows left insular hypodensity (white arrow), an additional sign of infarction, the "insular ribbon sign," with loss of cortical/subcortical "gray–white" differentiation and mild effacement of the Sylvian fissure and adjacent sulci by mass effect. (c) Unenhanced CT detection of stroke: the "insular ribbon sign," shown with optimized "stroke window" display parameters. Same image as Figure 2.2a, however now with optimized display parameters for the detection of small changes in gray–white matter attenuation. Display parameters – with narrow window width and center level settings (i.e. "stroke windows") – are optimized to exaggerate the subtle reduction in attenuation accompanying acute cytotoxic and vasogenic edema.

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the above processing algorithms to convert the raw images into visual perfusion maps. Modern multidetector CT scanners have allowed for greater z-axis (superior–inferior) coverage, with whole-brain perfusion imaging now possible with the newest-generation scanners.

Until recently, the core infarct has been defined as the region of low cerebral blood volume on CTP maps with varying thresholds reported in the literature. However, more recent data support the use of thresholded CBF for delineation of irreversible injury [6]. The penumbral region (at risk for infarction without reperfusion) has been variably defined using abnormally low CBF or prolonged MTT. Clearly, CT perfusion requires better validation before it can be used for treatment decision making. The primary challenge is the lack of standardization of postprocessing algorithms and thresholds for defining infarcted versus threatened tissue [7]. These thresholds vary depending on the specific CTP software used. Another challenge is whether perfusion imaging is truly quantifiable. Numerous studies have demonstrated significant errors in perfusion measurement, which would make threshold approaches invalid. Table 2.3 summarizes the advantages and disadvantages of CTP.

TIPS AND TRICKS

Pending further evidence, perfusion imaging should be reserved only for assessing whether or not an ischemic syndrome is present given its high sensitivity to alterations in brain hemodynamics. A stroke is ruled out if the hemodynamic parameters are entirely normal. To date, perfusion imaging has no demonstrated utility for deciding whether a patient should receive reperfusion therapy.

Diffusion-weighted imaging (DWI)

The advent of MRI ushered in a new era in neuroimaging. Its major advantage over CT for acute ischemic stroke evaluation is diffusion-weighted imaging. DWI became clinically available in the 1990s and remains the most accurate method for detecting hyperacute infarction.

SCIENCE REVISITED

While the technical aspects of this imaging technique are beyond the scope of this chapter, DWI is designed to measure the diffusion of water molecules within the brain tissue, and is particularly useful in an acute ischemic stroke where the diffusion of water molecules is restricted.

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Magnetic resonance angiography (MRA)

MR angiography is a common vascular imaging test, and may be performed either with noncontrast or contrast-enhanced techniques. The imaging resolution is inferior to CTA, and the images are susceptible to flow-related artifact (particularly without contrast). Noncontrast MRA utilizes time-of-flight (TOF) techniques, and relies on signals generated by flowing blood. However, such techniques may result in overestimation of stenosis severity and length due to turbulent flow. This is minimized with gadolinium-enhanced imaging. Three-dimensional TOF technique is typically performed for the intracranial circulation, while gadolinium is used for imaging the aortic arch and neck vessels. For the question of proximal intracranial artery occlusion, three-dimensional TOF MRA performs reasonably well with approximately 85% sensitivity and 90% specificity. Table 2.5 summarizes the advantages and disadvantages of MRA.

Magnetic resonance perfusion weighted imaging (MRP)

The principles of MRI perfusion imaging are similar to CTP. Dynamic brain imaging is performed after the injection of gadolinium to measure the first-pass transit of contrast through the cerebral vasculature. Postprocessing techniques yield similar perfusion parameters to CTP, which have been previously described. Renal function should be tested prior to gadolinium administration, as gadolinium carries the risk of nephrogenic systemic fibrosis (NSF) in patients with severe renal impairment. NSF results in fibrosis of the skin and internal organs and may be fatal. Physicians should refer to their local institutional policy on gadolinium administration for further guidance. More recently, perfusion imaging using arterial spin labeling has been introduced into clinical practice, and does not require the administration of a contrast agent. Instead, endogenous contrast is created by tagging arterial water spins prior to entry into the brain. Similar to CTP, MRI perfusion imaging demonstrates significant errors in cerebral perfusion quantification, for both dynamic contrast methods and arterial spin labeling. Therefore, MRP cannot be used to characterize at-risk tissue and is not validated for decision making regarding thrombolysis. It should be used only to assess if the patient's symptoms are ischemic in origin. Table 2.6 summarizes the advantages and disadvantages of MRP.

Table 2.6 Advantages/disadvantages of MRI perfusion weighted imaging (MRP)

Advantages/pearls	**Disadvantages/pitfalls**
Does not use ionizing radiation	Contraindicated in people with pacemakers or other ferromagnetic implants
Provides a sensitive evaluation for altered cerebral hemodynamics	Gadolinium carries the risk of nephrogenic systemic fibrosis in patients with severe renal impairment

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outcomes after IAT [13]. This has been shown using various modalities, including Xenon CT, MRI DWI, CT perfusion, and NCCT. Of these techniques, the most accurate and reliable is MRI diffusion imaging. It has the added advantage of allowing straightforward infarct volume quantification. Based on available data, acute DWI lesion volumes greater than 70–100 mL are highly predictive of poor outcomes despite successful IAT. In the clinical setting, infarct volume is typically calculated manually using the ABC/2 method (i.e. ellipsoid approximation) but future automated algorithms may provide a more precise measure.

While some point to the reduced availability of MRI in the treatment setting, this is unlikely to be true at comprehensive stroke centers that offer IAT. Importantly, the clinical utility of perfusion imaging to assess the size of viable but hypoperfused tissue appears limited given that patients with proximal occlusions who have a small core infarct are almost assured to have a significant volume of penumbral tissue. Instead, utilizing the NIH Stroke Scale (NIHSS) to document a significant neurologic deficit is more informative for suggesting the presence of a clinically significant penumbra, which can then be defined as the combination of a proximal occlusion, small core infarct (e.g. <70–100 mL) and significant deficit (e.g. NIHSS score >8–10) [14].

If MRI is unavailable or contraindicated (e.g. ferromagnetic implants), evidence supports using NCCT parenchymal evaluation based on ASPECTS (Figure 2.1b). This semiquantitative method for infarct size determination partitions the MCA territory into ten distinct regions. When hypoattenuation is identified in a region, a point is subtracted such that lower scores indicate larger infarcts. Using ASPECTS, a post hoc analysis of PROACT II demonstrated that patients with NCCT ASPECTS >7 demonstrated a treatment benefit while those with ASPECTS 0–7 had no better outcomes with IAT [15]. However, more recent data from studies of the Penumbra Stroke System suggest that patients with ASPECTS 5–7 may benefit from early revascularization, and that only scores between 0 and 4 should be excluded. Clearly, prospective validation of these thresholds is needed. While some centers utilize CT perfusion to delineate the core infarct size, this remains poorly validated as discussed above. Challenges to CTP include poor standardization of acquisition and analysis and questionable reliability of perfusion quantification. The imaging approach to acute ischemic stroke at Massachusetts General Hospital is provided in Figure 2.7.

CLINICAL PEARLS

- Vessel imaging with CTA or MRA can rapidly and accurately identify proximal intracranial artery occlusions amenable to IAT.
- Pretreatment core infarct volume predicts the clinical response to IAT.
- A clinically significant penumbra for IAT decision making may be defined as a proximal occlusion, small core infarct, and significant neurologic deficit.

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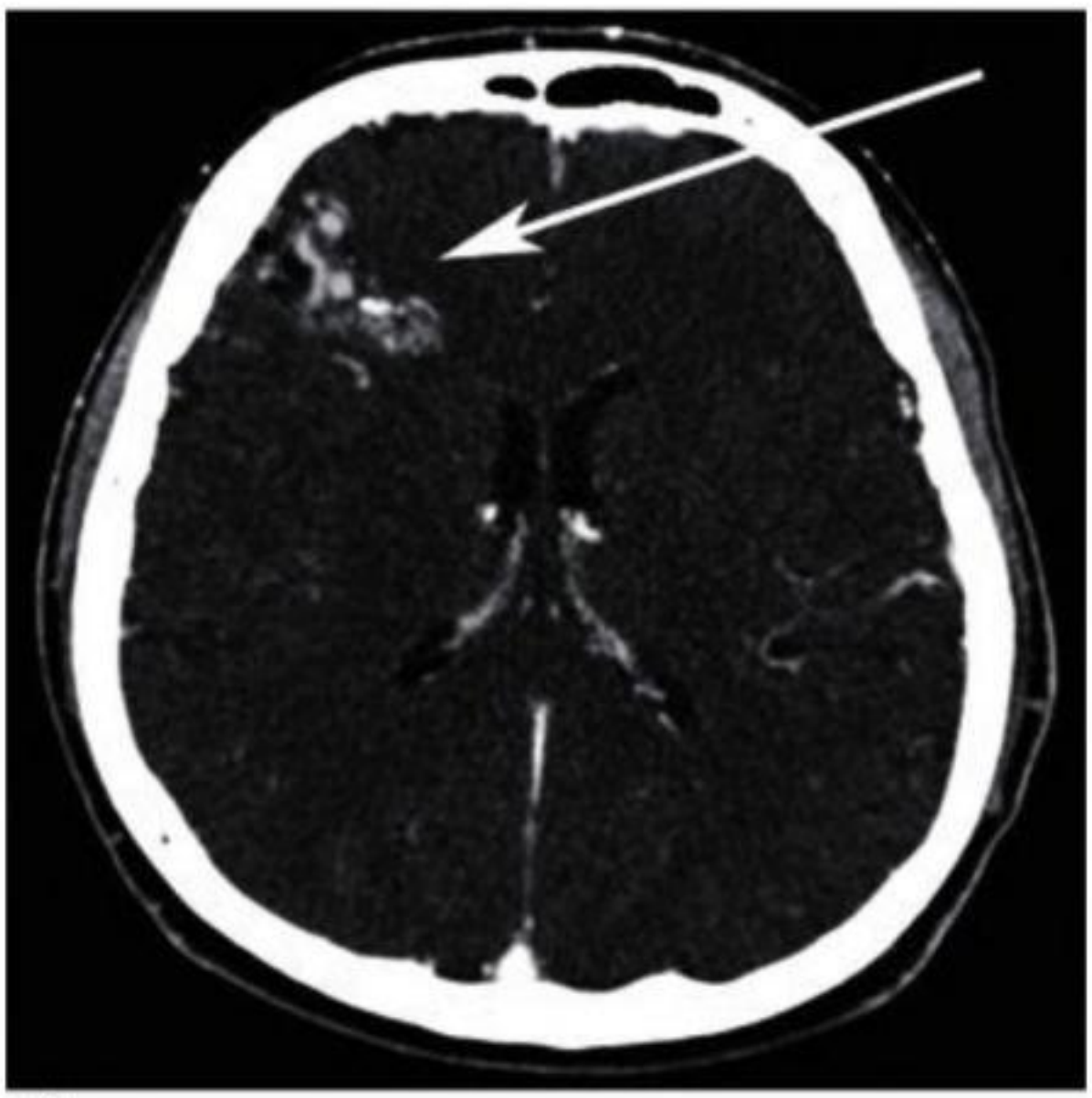

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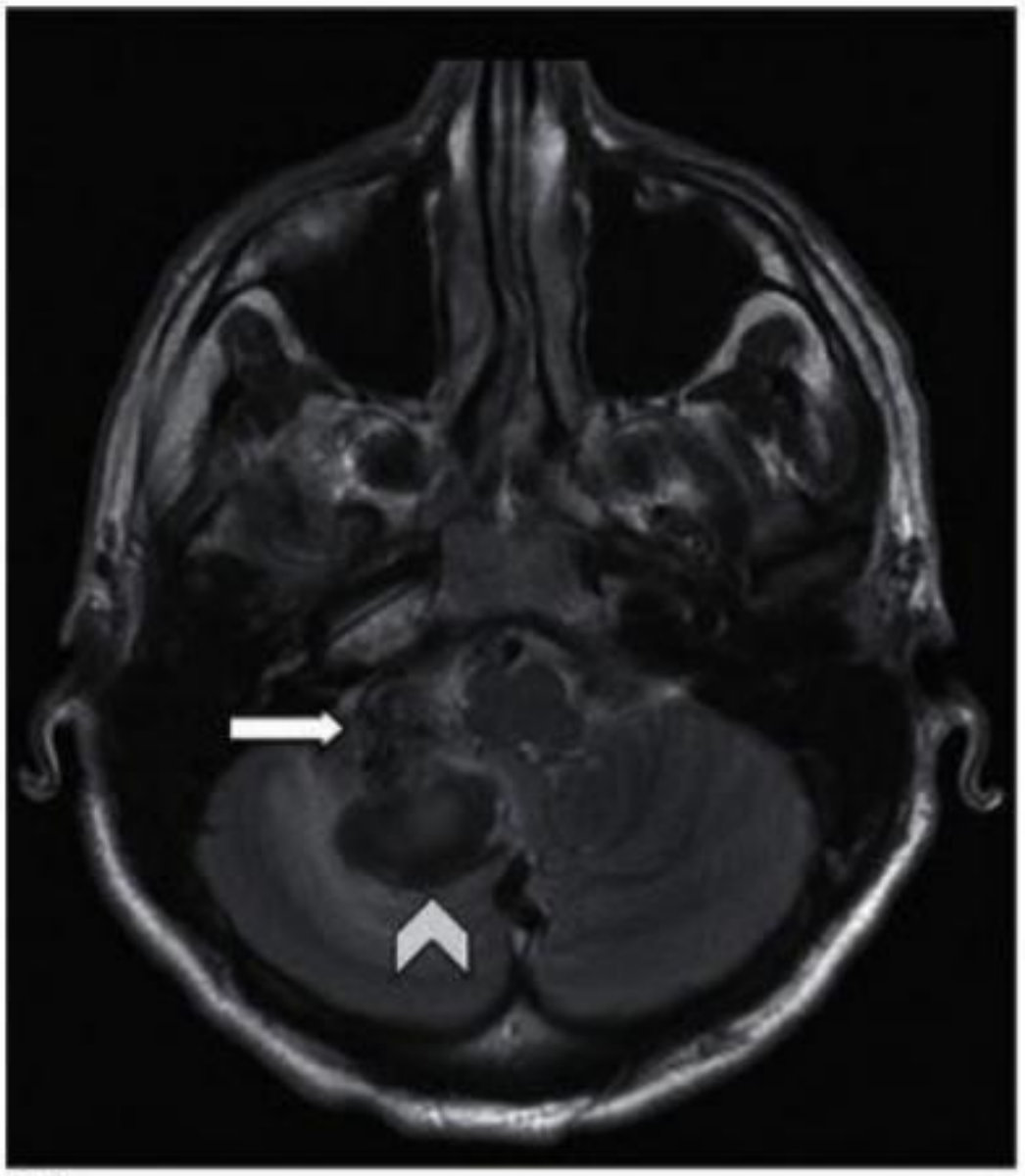

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Approximately 5% of thoracic aortic dissections are associated with cerebral embolism. The mechanism for cerebral embolism is likely related to aortogenic emboli or emboli originating in cervical arteries propagating distally. Clinicians should consider the presence of aortic dissection when chest and/or upper back pain occurs as part of an acute stroke syndrome. Chest pain may not be reported by patients with acute aphasia related to cerebral infarction, which makes the diagnosis of aortic dissection difficult in patients with large dominant hemisphere infarctions. The chest X-ray usually shows mediastinal widening; however, it may be negative in 20% of cases. The diagnosis can be confirmed by computed tomography of the chest. Although, aortic dissection was not included as an exclusion criterion in the NINDS or ECASS III trials, it is generally considered a contraindication for IV thrombolysis in acute ischemic stroke. Thrombolysis of patients with aortic dissection carries possible risks such as aortic rupture, hemothorax, and hemopericardium. In addition, administration of rt-PA is also likely to delay emergent cardiothoracic surgical procedures. There are no adequate studies that delineate the absolute frequency and magnitude of complications following intravenous thrombolysis in the presence of aortic dissection.

CAUTION

Intravenous thrombolysis should be avoided in acute ischemic stroke associated with aortic dissection due to the high potential to cause serious harm to the patient.

Infectious endocarditis

Endocarditis is a microbial infection of the intracardiac structures. The most common etiology of infectious endocarditis is bacterial. Fungal infections account for a small minority of cases. Stroke is the most frequent neurologic complication of infectious endocarditis, with stroke occurring in nearly one-third of cases. Ischemic stroke in the setting of infectious endocarditis is presumed to be due to septic cardiogenic embolism. Embolic stroke is one of the most frequent presenting medical events associated with infectious endocarditis. Hemorrhagic transformation of acute septic embolic infarctions is not infrequent and relates to septic arteritis with vascular wall erosion.

There are limited safety data regarding the use of thrombolysis in patient with acute ischemic stroke related to bacterial endocarditis. Case reports of intracranial hemorrhages occurring in patients with infective endocarditis treated with thrombolytic agents for acute coronary syndrome have been published.

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	Proact II	MERCI*	Multi-Merci*	Penumbra*
Treatment type	IA pUK + Hep vs. Hep	IA Merci + IAT	IA Merci + IAT + IVT	IA Pen + IAT
Patients	180 (121 vs. 59)	141	164	125
Time window (hours)	0–6	0–8	0–8	0–8
Mean baseline NIHSS	17 vs. 17	20	19	17
Recanalization (%)	66 vs. 18	60.3 (48 device alone)	68 (55 device alone)	81.6 (device alone)
Outcome (%) at 3 months mRS <2	40 vs. 25	36	36	25
SICH rate (%)	10 vs. 2	7.8	9.8	11.2

*Historical controls were used as the comparison arm for these clinical trials – a concurrent control group was not included in the study design.
IA, intra-arterial; IAT, intra-arterial therapy; IVT, intravenous thrombolysis; NIHSS, National Institutes of Health Stroke Scale; mRS, Modified Rankin Scale; SICH, symptomatic intracerebral hemorrhage.

SCIENCE REVISITED

Urokinase is a naturally occurring protease that is manufactured by uroendothelial cells. Urokinase, like rt-PA, converts plasminogen to plasmin. Prourokinase is a proenzyme that remains inactive in the absence of fibrin and is not activated in circulating blood. It is activated by plasmin at the site of thrombosis. Since it is not active in circulating blood, the thrombolytic activity of prourokinase is restricted to the embolus or thrombus obstructing an artery. Prourokinase utilized in the PROACT II Study was manufactured with recombinant technology.

Special clinical scenario: acute basilar artery occlusion

Clinical outcomes documented in series of patients with angiographically demonstrated basilar artery occlusions suggest a high case fatality rate and poor neurological outcome in survivors. Benign outcome, without interventional thrombolysis, is most often associated with short segment basilar occlusions of mostly atherothrombotic origin in patients with good collateral supply. An IAT approach to treating acute basilar artery occlusion has not been the subject of a randomized clinical trial comparing it to a medical therapy or intravenous thrombolysis. It is unlikely that any large-scale randomized clinical trials of intra-arterial therapy will be conducted in patients with basilar occlusion.

Single-center case series suggest that interventional thrombolysis can reduce mortality and improve outcome in selected patients (Table 3.7). In these single-center experiences, treatment windows have been longer than those utilized for intra-arterial recanalization in the anterior circulation. This longer window relates to the lower likelihood of SICH in the posterior circulation and the possibility that

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the intracranial circulation using a suction catheter to aspirate an occlusive thromboembolus while using an internal separator to fragment the clot. A continuous aspiration–debulking process is made possible by advancing and withdrawing the separator through the Penumbra reperfusion catheter into the proximal end of the clot.

The system also contains a thrombus removal ring that can envelop an occlusive clot. If a thrombus remains despite application of the aspiration–-debulking components, direct mechanical retrieval by the thrombus removal ring can be used to augment revascularization. Thrombus extraction using the thrombus removal ring is accomplished by engaging the clot proximally and extracting the clot under flow arrest conditions by inflating a proximal balloon guide catheter. Duration of flow arrest is typically less than 1 minute. Patients who have received IV rt-PA can be treated. A video of device deployment can be watched at http://www.youtube.com/watch?v=ajcgsAr6K2A.

Key clinical trials

The Penumbra trial was a prospective, multicenter, single-arm study designed to assess the safety and utility of this device in acute ischemic stroke [9]. Main inclusion and exclusion criteria are listed in Table 3.9. Key clinical inclusion criteria are presentation within 8 hours of symptom onset and a baseline NIHSS of ≥8. Patients treated with intravenous IV r-tPA were eligible if they had persistent neurologic deficit and angiography demonstrated an occlusion of an appropriate large artery. One hundred twenty-five patients were enrolled at 24 centers. Target arteries were vertebrobasilar (n = 11; 9%), middle cerebral (n = 87; 70 %), internal carotid (n = 23, 18%), and other (n = 4; 3%). Twelve of the enrolled patients received intra-arterial thrombolytics (considered a protocol violation) as adjunctive therapy, of which six were targeting the primary obstruction and the remainder aimed at distal branches. Vessel recanalization in those treated with the device alone occurred in nearly 80% of the cases. This recanalization rate is higher than the values observed in the PROACT II, Merci, and Multi-Merci trials (Table 3.6). Twenty-five percent of patients had good neurological outcome, defined as a modified Rankin scale score ≤2 at 3 months - following treatment.

Table 3.9 Penumbra trial inclusion/exclusion criteria

Inclusion
Presentation within 8 hours of symptom onset
NIHSS ≥8
Angiographically verified occlusion of a large intracranial vessel
Patients who presented within 3 hours must have been either not eligible or refractory to intravenous recombinant tissue plasminogen activator therapy as defined by the persistence of neurological symptoms and the presence of an occlusion in the target vessel despite the lytic therapy
Exclusion
Baseline CT showing infarctions greater than one-third of the territory of the middle cerebral artery (MCA), severe edema, or intracranial hemorrhage
Pregnancy

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intravenous rt-PA provided the treatment can be administered within the 3 or 4.5-hour window. Patients eligible for intravenous rt-PA should generally not be initially considered for an endovascular therapy as this may introduce unnecessary delays in treatment. In addition, there have not been clinical studies examining the effectiveness of intra-arterial reperfusion procedures versus intravenous thrombolysis in very early stroke. Occasionally, the clinician will care for a patient who does not qualify for intravenous thrombolysis based on the presence of an exclusion criterion. This patient, however, may still be a candidate for IAT (Figure 3.5). If IAT is available, the patient should be evaluated for mechanical thrombectomy.

Future directions

Additional research is needed to discover methods that safely magnify the therapeutic effects of thrombolytic therapy and mechanical thrombectomy. Combining intravenous rt-PA with drugs that are neuroprotectants, drugs that promote collateral blood flow to an ischemic zone, or drugs that are antithrombotic are areas of current investigation. Combining rt-PA and transcranial Doppler ultrasound, so-called sonothrombolysis, is another current avenue of investigation. In the future, well-designed clinical trials may demonstrate that new generation thrombolytic drugs with shorter infusion times and longer half-lives, such as tenecteplase, improve clinical outcomes. Development of appropriate bridging strategies, which utilize upfront treatment with intravenous rt-PA followed by an interventional procedure, is also a subject of ongoing research.

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etiology of cerebral infarction can increase or decrease with the following factors: age greater than versus less than 50 years, race, certain historical or examination findings, and tertiary care versus primary care. The overall prevalence of selected cerebral infarction etiologies in a general population of patients is: cardioembolic (27%), large vessel disease (18%), small vessel disease (17%), other (3%), and cryptogenic (35%) [2].

The prevalences, available diagnostic tests, and their sensitivities and specificities for each specific mechanism are in the section below entitled "Diagnostic evaluation and treatment by etiology."

What are the potential treatment options?

For most mechanisms of cerebral infarction or TIA, antiplatelet agents are indicated. Therefore, diagnostic evaluation is aimed at evaluating potential etiologies that would require something other than an antiplatelet agent, such as surgery, endovascular intervention, anticoagulation, antibiotics, or immunosuppressants (Box 4.2). In addition to discerning the appropriate antithrombotic, careful review and treatment of potential risk factors are important. Treatment recommendations for each mechanism as well as controversies in treatment are elaborated in the section below entitled "Diagnostic evaluation and treatment by etiology."

General approach

As previously mentioned, an algorithmic approach to the diagnostic evaluation of ischemic stroke can be complex due to the potential mechanisms of stroke and the controversies in treatment for some mechanisms. Figure 4.1 displays a general algorithm that can be followed. In addition, Table 4.5 displays tips in the history, physical examination, and/or initial studies that might increase the pretest probability of individual etiologies of cerebral ischemia. In the following section, utility of cross-sectional CT versus MRI will be discussed. In the "Diagnostic evaluation and treatment by etiology" section you will learn more in detail about the particular source, diagnostic testing, and treatment recommendations in addition to the current American Heart Association class recommendation and level of evidence (Table 4.6). Also, this section will alert you to the controversies that exist due to lack of definitive evidence on treatment. In the final section, two cases help illustrate the overall approach taking into account the six questions - discussed above.

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pretest probability of extracranial disease is generally higher in both young and older patients.

- Similarly, the pretest probability of a cardioembolic source may be higher and consideration of echocardiogram should be made on an individual basis (see cardioembolic section above). This is important since most forms of extracranial disease and cardioembolic sources have definitive management strategies.
- After more common entities have been eliminated as sources, evaluation of the intracranial circulation may be recommended in the following patients or situations where the prevalence may be higher: (1) young patient (less than 50 years old) with negative *extra*cranial evaluation and cardiac evaluation; (2) patient has failed antiplatelet therapy and may have recurrent - stereotyped TIAs or *cortical* stroke in a single vascular territory; (3) posterior circulation event with negative cardiac evaluation; and (4) preoperative evaluation of collateral circulation prior to carotid endarterectomy.

Small vessel disease

Prevalence

Small vessel (lacunar) infarctions account for up to 20% of all cerebral ischemic events. Since lacunar infarctions are associated microscopically with microatheroma, lipohyalinosis, and fibrinoid necrosis, the pretest probability increases with typical atherosclerotic risk factors, most notably hypertension, smoking, and diabetes.

Sources

A lacunar stroke is a small subcortical infarction generally defined as a stroke less than 1.5 cm resulting from the occlusion of a penetrating end artery. Penetrating end arteries may include: lenticulostriates, thalamoperforates, basilar artery perforates, and others. Thus lacunes predominate in the basal ganglia, thalamus, centrum semiovale, brain stem, and internal capsule. Typical lacunar clinical syndromes and common anatomic locations are noted in Table 4.8. Autopsy studies have shown that the pathology underlying lacunar infarctions is most commonly microatheroma, lipohyalinosis, and fibrinoid necrosis. However, in approximately 5–10% of autopsy cases these findings are not seen, implying the possibility that lacunar infarctions could result from an embolic source. While some believe that carotid imaging is not necessary in classic cases of lacunar disease, the NASCET study evaluating the efficacy of carotid endarterectomy for carotid stenosis as well as the CREST study did consider patients with lacunar infarctions and ipsilateral carotid disease as symptomatic.

Other etiologies of stroke may result in small vessel pathology. These include:

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regarding sleep apnea symptoms, and tobacco and alcohol use. One may also consider screening for medical complications related to cerebral ischemia including: depression, venous thromboembolism risk, aspiration risk, fall risk, and gastrointestinal bleed risk.

Case examples

CASE 1

A 72-year-old Caucasian man with a history of hyperlipidemia and hypertension who presents with a 5-minute spell of right face and arm heaviness. An hour later he had another spell of right face and arm heaviness, this time accompanied by difficulty getting words out. This lasted approximately 5 minutes and resolved. The patient was taken to the emergency room where initial head CT, EKG, and laboratory studies are normal.

Answering the questions

1) Is it an ischemic event?

The patient's symptoms came on acutely and are in a vascular territory. He is of a common age and gender with vascular risk factors for cerebral ischemia. Therefore one would consider this a probable ischemic vascular event.

2) Where does the process localize?

Right face and arm heaviness or weakness should localize to the left hemisphere in the anterior circulation (carotid distribution). Since it is face and arm more than leg, it may be more cortical than subcortical. Furthermore the word-finding difficulty may suggest cortical involvement as well, that is aphasia.

3) What mechanisms and etiologies are possible?

The past medical history of hypertension and hyperlipidemia are risk factors for atherosclerotic disease. The fact that patient has had three stereotyped spells in one vascular territory suggest a possible focal arterial stenosis. In this man, extracranial internal carotid artery stenosis is most likely given the higher prevalence of extracranial carotid disease in Caucasians compared to intracranial atherosclerotic disease. Stenosis of the middle cerebral artery is also a consideration.

4) What is the prevalence (pretest probability) of each etiology in this patient?

The pretest probability of extracranial carotid artery disease in this patient is approximately 15–20%. The prevalence of intracranial stenosis is approximately 5–8%.

5) What treatment is available for this etiology?

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