Neuroimaging in Acute Stroke

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INTRODUCTION

Stroke is the fourth leading cause of death and the leading cause of serious long-term disability in the United States. An estimated 7 million American adults have suffered a stroke, and an acute stroke occurs every 40 seconds resulting in approximately 795,000 patients with stroke annually. Of all acute strokes, approximately 87% are ischemic and 13% are hemorrhagic; 10% of total strokes are caused by intracerebral hemorrhage and 3% are caused by subarachnoid hemorrhage.1 Given the high incidence and significant morbidity and mortality of acute stroke, it is imperative that patients suffering from an acute stroke be rapidly diagnosed and managed. The diagnosis of acute stroke is made using a combination of patient history, clinical examination, and imaging procedures. Brain imaging, using either computed tomography or magnetic resonance imaging, in patients presenting with a history and clinical examination consistent with an acute stroke syndrome is essential in differentiating ischemic stroke from hemorrhagic stroke and often helps to guide therapy.

This article reviews the various imaging modalities available for the evaluation of patients presenting with a potential stroke syndrome, specifically acute ischemic stroke (AIS), intracerebral hemorrhage (ICH), and subarachnoid hemorrhage (SAH). It reviews...
the various CT modalities, including noncontrast brain CT (NCCT), CT angiography (CTA), and CT perfusion (CTP). It discusses multimodal MRI in the evaluation of patients with acute stroke, including diffusion-weighted imaging (DWI), T2-weighted sequences (T2W)/fluid-attenuated inversion recovery (FLAIR), MR angiography (MRA), perfusion-weighted imaging (PWI), and gradient-recalled echo (GRE). At the end of this article, a brief review on how to read an NCCT geared toward the emergency physician is included.

ACUTE ISCHEMIC STROKE

Intravenous (IV) thrombolysis approved by the Food and Drug Administration with recombinant tissue plasminogen activator (rt-PA) is currently the only treatment for patients who present with AIS. Treatment with IV rt-PA is limited to within the first 3 to 4.5 hours after symptom onset and only after hemorrhage has been ruled out with brain imaging. The primary goal of brain imaging in the management of patients with AIS is to exclude the presence of hemorrhage. However, as new therapies and treatments are developed for patients with suspected AIS, the goals of brain imaging have expanded to include the evaluation for an intravascular thrombosis that can be treated with thrombolysis or thrombectomy, the identification of the size of a core of irreversibly infarcted tissue, and the determination of the amount of hypoperfused tissue at risk for subsequent infarction unless adequate perfusion is restored. The following section reviews both multimodal CT and multimodal MRI in relation to these goals in the evaluation and treatment of emergency patients presenting with suspected AIS.

COMPUTED TOMOGRAPHY

Brain CT is typically the first choice in imaging patients with acute stroke because of its accuracy in excluding hemorrhage, speed in acquisition, and general availability in most US emergency departments (EDs). Multimodal CT imaging includes NCCT, CTA, and CTP (Table 1) and requires a total scanning time of approximately 10 minutes. These 3 imaging sequences fulfill the requirements for hyperacute stroke imaging by allowing for the exclusion of hemorrhage and many stroke mimics, identifying intravascular thrombus or vascular narrowing, and differentiating between the penumbra and irreversibly infarcted core brain tissue. Multimodal CT has the benefits of rapid image and data acquisition and can be performed with conventional CT equipment available in most EDs. Concerns regarding the use of multimodal CT are often related to the medical risks associated with radiation exposure and IV contrast material.

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Noncontrast Brain CT

NCCT is often regarded as the primary brain imaging study for the evaluation of patients presenting with suspected stroke because it accurately diagnoses most cases of intracranial hemorrhage and may identify nonvascular causes of focal neurologic deficits.\(^5\) Although MRI has been shown to be equivalent to CT in the detection of acute hemorrhage,\(^{10,11}\) NCCT has long been considered the criterion standard for the detection of acute ICH. Additional reasons that NCCT remains the traditional initial imaging modality for the evaluation of suspected AIS are its widespread availability, short acquisition times of 1 to 2 minutes, noninvasiveness, and general safety for both stable and unstable patients.\(^6,9\) According to the “American Heart Association 2010 Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care” in acute stroke, patients with potential AIS who are eligible for IV rt-PA should have the NCCT completed within 25 minutes of ED arrival and interpreted within 45 minutes of ED arrival.\(^{12}\)

Although not as sensitive as MRI for the detection of ischemia, improvement in multidetector technology over the past decades has enabled rapid NCCT to be obtained with submillimeter slice thickness enabling superior contrast resolution and tissue differentiation.\(^6\) This improved resolution allows for better visualization on NCCT for evidence of arterial occlusion or early signs of infarction in patients presenting with AIS, which signs can affect treatment decisions.\(^5\)

Evidence of arterial occlusion on NCCT, known as the hyperdense artery sign, can be seen because of increased density within the occluded vessel representing visualization of thrombus.\(^9,13\) It usually spontaneously disappears within a few days, likely because of recanalization with resolution of the thrombus.\(^{13,14}\) The most commonly identified hyperdense artery sign is the hyperdense middle cerebral artery (MCA) sign,\(^{15}\) which corresponds specifically to clots in the MCA and is useful in the diagnosis of MCA occlusion (Fig. 1). It has been found to have a prevalence of 31% to 67% in patients with MCA infarct\(^{13,14,16}\) and is highly specific for MCA occlusion but

Fig. 1. Right hyperdense MCA sign on noncontrast brain CT.
with variable sensitivity from 31% to 79%.\textsuperscript{14,17} False-positive hyperdense MCA signs can occur in patients with higher hematocrits as well as patients with higher levels of calcification within blood vessel walls.\textsuperscript{18}

Early ischemic changes that may be found on NCCT include loss of the gray-white interface in the basal ganglia and lentiform nucleus (obscuration of the lentiform nucleus) or the insular cortex (loss of the insular ribbon), hypodensity/hypoattenuation of the brain parenchyma, and focal and diffuse swelling of the cerebral parenchyma (\textbf{Fig. 2}).\textsuperscript{16,19–23} Early ischemic changes are more likely to be seen in more severe stroke and in longer times from symptoms onset.\textsuperscript{19} Obscuration of the lentiform nucleus and loss of the insular ribbon are the two most common early parenchymal findings on NCCT; these two regions of the brain are particularly vulnerable to early infarction because of tenuous blood supplies via end-arteries to the basal ganglia and a watershed arterial zone to the insular cortex.\textsuperscript{9,21–23}

The significance of early ischemic changes on NCCT is highly debated.\textsuperscript{6} Von Kummer and colleagues\textsuperscript{16} initially showed that extensive parenchymal hypodensity or local brain swelling is highly predictive for fatal outcomes. In the European Cooperative Acute Stroke Study trials I and II, involvement of more than one-third of the MCA territory on NCCT was used as a criteria for exclusion from treatment with IV rt-PA because of the potential increased risk for hemorrhage and poor outcomes.\textsuperscript{24,25} In contrast, Patel and colleagues\textsuperscript{19} demonstrated that in the National Institute of Neurological Disorders and Stroke rt-PA stroke trial in 1995, signs of early ischemic changes on NCCT performed within 3 hours of time of symptom onset were not associated with an increased risk of adverse outcomes after treatment. Given this controversy, current prescribing information for IV rt-PA by the manufacturer Genetech does not list major early infarct signs on NCCT as a contradiction for treatment with IV rt-PA but does state that the risks associated with treatment may be increased in these patients and should be weighed against the anticipated benefits.\textsuperscript{26}

\textbf{Fig. 2.} Left MCA territory ischemic stroke on noncontrast brain CT depicting loss of the gray-white matter differentiation, hypoattenuation within the brain parenchyma, and focal swelling of the cerebral parenchyma with sulcal effacement.
CT Angiography

CTA is performed by administering an appropriately timed bolus of iodinated contrast through a peripheral large bore IV to maximize vascular opacification of the arterial circulation and acquire a volumetric dataset that can be processed to display 2-dimensional (2D) projectional or 3-dimensional (3D) volume-rendered images.\textsuperscript{27,28} It is a minimally invasive tool for the imaging of vessels of the head and neck in patients presenting with suspected AIS, and advances in multidetector CT technology have made CTA the preferred noninvasive alternative to conventional catheter-based cerebral arteriography. Current CT scanners can provide a detailed evaluation of the extracranial and intracranial vasculature in less than 5 seconds by obtaining CTA from the aortic arch up to the circle of Willis with a single data acquisition and excellent isotropic spatial resolution.\textsuperscript{9,29} CTA of the carotids can be performed from the aortic arch to the intracranial circulation to detect carotid artery disease with ulcerations or plaques that may account for an embolus or a stenosis limiting blood flow. CTA can evaluate the intracranial vessels for a site of occlusion or stenosis (Fig. 3)\textsuperscript{29} and may guide diagnosis and therapy by aiding in the decision to administer an IV thrombolytic agent or have patients undergo intra-arterial thrombolysis with or without mechanical thrombolysis.\textsuperscript{6}

With a single bolus of iodinated contrast material, CTA source images (CTA-SI) can provide a qualitative cerebral blood volume map that allows for the evaluation of tissue perfusion with resulting detection of the core of infarction and improved demonstration of tissue at risk for infarction compared with NCCT.\textsuperscript{6} The benefit of CTA-SI is that, unlike other types of perfusion imaging, CTA-SI map the brain, do not rely on the interpretation of nonenhanced images, and are available immediately at the completion of the CTA because they do not require postprocessing. CTA-SI have been shown to be more sensitive that NCCT for the detection of early irreversible ischemia,\textsuperscript{30} and lesion volumes seen on CTA-SI correlate with DWI abnormalities MRI.\textsuperscript{31} CTA-SI seem to be as good as DWI at detecting acute ischemia with the exception of small strokes and strokes in the posterior fossa.\textsuperscript{6}

CT Perfusion

CTP tracks a bolus of infused iodinated contrast material through brain tissue serially through time and, thus, allows a rapid, noninvasive, quantitative evaluation of dynamic brain perfusion. Because of a linear relationship between iodinated CT contrast

Fig. 3. CTA showing acute thrombus in the right MCA.
concentration and resulting imaging density, CTP is able to quantify cerebral blood volume, cerebral blood flow, and mean transit time required for blood to flow through brain tissue. It allows for the investigation of alteration in cerebral perfusion in patients with suspected stroke and can delineate the ischemic core and ischemic penumbra. However, CTP requires repeatedly scanning the same portion of the brain over the time required for the contrast to pass through the tissue. As such, a large drawback to CTP is that scanners can only cover a limited number of slices of the brain, which does not allow for evaluating exact perfusion deficit volumes if they exceed the volume studied or for investigating areas of small perfusion deficit outside of the area chosen. The 64-slice scanners allow for 8 or more perfusion brain slices thereby increasing the detection rate for AIS, and CTP has an overall sensitivity of about 75% for ischemic strokes with high specificity. Newer, 256-slice and 360-slice CT scanners may offer whole-brain coverage. However, CTP remains investigational because specific CTP and CTA criteria to identify patients who may benefit from thrombolysis has not been determined and the clinical value of the penumbral information that CTP provides has yet to be fully established.

MAGNETIC RESONANCE IMAGING

Both CT and MRI are highly sensitive for the detection of intracranial hemorrhage, but MRI is much more sensitive than CT in detecting acute ischemic changes and, as such, is more accurate in diagnosing patients presenting with acute focal neurologic deficits. Multimodal MRI can be used in the acute setting to evaluate and accurately diagnose patients with suspected acute stroke. It includes the following sequences: DWI, T2W/FLAIR, MRA, PWI, and GRE (Table 2). Using these different imaging sequences, multimodal MRI is able to provide excellent anatomic detail of the brain; differentiate between ischemic and infarcted brain tissue; exclude ICH; and provide angiographic, spectroscopic, and perfusion information of the cerebral vasculature and tissue bed. Additionally, MRI has a higher sensitivity and specificity than CT for the detection of other neurologic diseases that mimic acute stroke clinically, such as cerebral edema, vascular malformations, neoplasms, infection, inflammatory diseases, and toxic-metabolic disorders. Multimodal MRI can be performed in 10 to 20 minutes, thus making it feasible within a 3-hour thrombolysis time window and competitive with multimodal CT regarding study acquisition time.

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In addition to the increased accuracy in diagnosing patients presenting with suspected acute stroke, MRI has the added advantage over CT of the lack of exposure to ionizing radiation. Disadvantages to MRI compared with CT include higher cost and lack of 24-hour availability of MRI at many hospitals. Additionally, there are a few absolute contraindications to undergoing MRI, including the presence of cardiac pacemakers or certain ferromagnetic metallic implanted substances that may be displaced by the magnetic field. Additionally, approximately 5% of patients undergoing MRI experience claustrophobia, which can increase difficulty in obtaining an MRI.

**Diffusion Weighted Imaging and Apparent Diffusion Coefficient**

DWI is able to depict areas of acute brain ischemia using the random motion of water molecules within living tissues (Brownian motion). In the first few minutes of vascular occlusion during an ischemic stroke, cerebral ischemia leads to the disruption in energy metabolism causing a failure of the sodium-potassium adenosine triphosphatase pump and other ion pumps. This membrane channel failure leads to a loss of ionic gradients and a net shift of water molecules into the intracellular compartment with resultant swelling of the cells (ie, cytotoxic edema). This edema leads to a reduction of the extracellular space thereby reducing the Brownian molecular motion of water molecules in this space. The reduction of Brownian molecular motion in infarcted tissue caused by reduced water diffusion can be rapidly detected as a hyperintense lesion on DWI (Fig. 4) within minutes of vessel occlusion and the onset of ischemia. This decrease in water diffusion in ischemic brain tissue can be measured quantitatively with the apparent diffusion coefficient (ADC). Additionally, because DWI is T2 based, shine through of high T2W abnormalities, such as chronic stroke or vasogenic edema, may be misinterpreted as acute ischemia on DWI. The correlation of DWI with the ADC map, which demonstrates restricted diffusion of water molecules as low intensity, greatly increases the specificity of DWI in AIS. Hyperacute ischemic brain lesions have increased signal intensity on DWI and decreased signal intensity on ADC (Fig. 5).

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**Fig. 4.** Diffusion-weighted MRI showing left thalamic infarct.
DWI is the imaging modality of choice for the timely and accurate diagnosis of AIS. It has been shown to detect physiologic changes within 15 minutes of ischemic injury in both experimental animal models and in patients presenting with AIS. Moseley and colleagues first demonstrated that acute occlusion of the MCA in animal models produced DWI hyperintensity in ischemic regions within 45 minutes after the onset of ischemia and much sooner than conventional T2W images. In the mid-1990s, research on DWI in AIS progressed to human patients when DWI showed improved stroke diagnostics with infarcts appearing sooner on DWI than on conventional MRI.

Multiple studies have confirmed the increased sensitivity and accuracy of DWI over CT and conventional MRI in identifying areas of ischemia in patients presenting with early AIS (within 6–12 hours from the onset of symptoms), and the overall accuracy of DWI diagnosing acute ischemia improves as time of symptom onset decreases. A study by González and colleagues showed that in patients in whom imaging was performed within 6 hours of symptom onset, DWI was 100% sensitive and 100% specific in the diagnosis of AIS. In a subset of patients who underwent imaging within 3 hours of symptom onset in a prospective study by Chalela and colleagues, MRI was found to be superior to CT in the blinded imaging diagnosis of AIS, with 73% sensitivity and 92% specificity versus 12% sensitivity and 100% specificity for CT. The overall false-negative rate for DWI in this study was 17%, and factors associated with false-negative DWI were brainstem location of stroke, time of symptom onset to imaging less than 3 hours, and mild stroke with a low National Institutes of Health Stroke Scale score (less than 4). None of the false-negative DWI cases were positive on CT.

Although DWI hyperintensity appears within minutes of ischemic injury, DWI lesions may be at least partially reversible in the early phase of brain ischemia, and the size of the DWI abnormality does not necessarily reflect irreversibly damaged tissue. A study by Fiehler and colleagues evaluating 68 patients with AIS presenting within 6 hours of symptom onset who underwent serial MRI examinations found that 20% of these patients had ADC normalization in greater than 5 mL of brain tissue on MRI performed between days 5 to 8. All patients with partial ADC normalization demonstrated at least partial tissue reperfusion, and tissue with a more severe initial decrease in ADC was less likely to demonstrate normalization. This study suggests brain tissue with initially decreased ADC, especially within 3 hours of symptom onset, may still represent salvageable tissue at risk that could benefit from thrombolytics. As such,
DWI is no longer thought to be a simple indicator of tissue irreversible infarction but a more complex variable that requires additional careful study. Additionally, other cerebral pathologic conditions can cause false-positive DWI through restricted diffusion, such as infection, inflammatory conditions, and certain tumors.6

**T2-Weighted and Fluid-Attenuated Inversion Recovery**

On T2W and FLAIR images, ischemic infarction appears as a hyperintense lesion usually within the first 3 to 8 hours after stroke onset.9 FLAIR imaging provides an advantage over the more conventional T2W imaging in that it nulls the signal from the cerebrospinal fluid (CSF) while providing a heavily T2W image of the brain parenchyma. The suppression of the CSF signal allows for better detection of acute infarcts, especially the cortical gray matter infarcts.51–53 Although superior to T2W imaging, the sensitivity of FLAIR is lower than DWI for the diagnosis of AIS and increases with increased time from symptom onset. A recent study of patients with AIS presenting within 6 hours of symptom onset by Thomalla and colleagues53 found that patients with a mismatch with a positive DWI and negative FLAIR were likely to have been imaged within 3 hours of symptom onset with a 93% specificity and 94% positive predictive value. As such, a DWI positive–FLAIR negative mismatch may be useful in identifying patients with an unknown time of stroke onset who may benefit from thrombolysis,53 which is described in more detail later in this article.

Unique signs of AIS may be identified on FLAIR imaging within the first 24 hours after the onset of symptoms. Acute infarcts may appear on FLAIR imaging as swollen cortical gyri with increased signal intensity. These hyperintense, swollen gyri represent cytotoxic edema and correspond to areas of ischemia seen on DWI.52,54 Increased signal intensity in the lumen of vessels may be observed on FLAIR imaging in patients with AIS.52,54,55 This finding is known as the hyperintense vessel sign (HVS) or arterial hyperintensity and has been found to be associated with large vessel occlusion or severe stenosis.55 The exact pathophysiology of the HVS remains unclear; it may represent slow moving or stationary blood, intraluminal thrombus, or retrograde collateral circulation. The sensitivity of HVS is highest during the first 6 hours of onset, and the presence of HVS accompanied by ischemic changes on DWI indicates impending infarction and should prompt consideration of revascularization and flow augmentation strategies. Occasionally, the HVS on FLAIR imaging may be the earliest ischemic change noted on MRI and may precede diffusion abnormalities.54–57 In patients presenting with stroke symptoms who are not suffering an ischemic event, FLAIR imaging may also depict hyperintense intracranial hemorrhagic lesions as well as cerebral venous thrombosis.54 Additionally, both T2W and FLAIR imaging can be used to assess for older ischemic strokes and the extent of small vessel disease.39

**MR Angiography**

Noncontrast 3D time-of-flight (TOF) MRA is the mainstay of intracranial arterial evaluation by MRI allowing for high-spatial-resolution isotropic imaging of the cranial vascular system. TOF MRA is based on the differences between protons in stationary tissue, which are saturated by repeated radiofrequency excitations and produce low signal intensity, and the high signal from fresh unsaturated protons that move into the imaging slab via the cranial arteries between each excitation pulse. It produces flow-dependent luminal imaging, and visualization of the vessel wall is limited.58 TOF MRA can be both 2D and 3D and has the benefits of not requiring a carefully timed contrast agent to produce, being easily repeatable,59 and not exposing patients to radiation. However, compared with CTA, TOF MRA has limitations because of its sensitivity to patient motion artifact and flow artifact, which may result in the
overestimation of vessel stenosis. A study by Bash and colleagues evaluating CTA and TOF MRA in the detection and quantification of intracranial stenoses and occlusions compared with reference standard digital subtraction angiography (DSA) showed that TOF MRA has a lower sensitivity than CTA for intracranial stenosis (70% vs 98%) and occlusion (87% vs 100%) as well as a lower positive predictive value than CTA for intracranial stenosis (65% vs 93%) and occlusion (59% vs 100%). A study by Tomanek and colleagues evaluating the accuracy of MRA compared with DSA in the evaluation of intracranial vessels in patients with AIS and transient ischemic attack showed that the 3D TOF MRA had a sensitivity of 84.2% and specificity of 84.6%. Although not as accurate as CTA or DSA in the evaluation of the intracranial vasculature in patients presenting with AIS, TOF MRA is a good noninvasive screening tool and a useful sequence in the multimodal MRI evaluation of patients with suspected stroke.

Contrast-enhanced MRA (CE-MRA) with gadolinium is the MRI technique of choice for extracranial artery imaging. CE-MRA provides more accurate imaging of the extracranial vessel morphology and the degree of stenosis and has improved the detection of arterial dissection over noncontrast TOF MRA. However, high doses of gadolinium-based contrast material for CE-MRA can be associated with the debilitating and occasionally life-threatening nephrogenic systemic fibrosis, and as such, it is necessary that patients with moderate to severe renal insufficiency have a nonenhanced alternative for angiography.

**Perfusion Weighted Imaging**

PWI allows for the visualization of capillary blood flow via an IV bolus of a gadolinium-based contrast agent. Gadolinium is a paramagnetic agent that allows it to transiently alter the magnetic susceptibility of tissues during passage through the microvascular bed with resultant nonlinear signal loss on T2W or T2*W imaging. Repeated images are acquired before and after the injection of the gadolinium bolus to track the signal change and provide relative measures of cerebral hemodynamic status, including mean transit time, time to bolus peak, cerebral blood volume, and cerebral blood flow.

PWI depicts areas of brain tissue with reduced cerebral blood flow that occur with the onset of an acute occlusion, whereas lesions on DWI have long been thought to represent severely injured tissue. DWI in combination with PWI has shown great promise for the identification of brain tissue in patients with AIS that is dysfunctional because of low blood flow but potentially salvageable on restoration of blood flow. This DWI-PWI mismatch may estimate the extent of an ischemic penumbra, which has the potential to progress to tissue infarction if blood flow is not restored and may be saved with proper therapeutic intervention.

Multiple clinical trials have been performed using DWI-PWI mismatch to identify patients with ischemic penumbra that may benefit from thrombolytic therapy. Desmoteplase in Acute Ischemic Stroke (DIAS) and Dose Escalation of Desmoteplase for Acute Ischemic Stroke (DEDAS) were the first two clinical trials using DWI-PWI mismatch as an eligibility criteria for treatment with IV desmoteplase in patients with AIS from 3 to 9 hours of symptom onset. Although DIAS and DEDAS were both small randomized phase II dose-escalation trials, treatment with IV desmoteplase in this specific group of patients selected by DWI-PWI mismatch was associated with a higher rate of reperfusion and better clinical outcome than placebo. The follow-up phase III DIAS-2 trial did not show a clinical benefit of IV desmoteplase given 3 to 9 hours after onset of AIS for reasons that are not well understood, and additional phase III studies of IV desmoteplase in AIS (DIAS-3 and DIAS-4) are currently
enrolling. Two clinical trials evaluating whether DWI-PWI mismatch could be used to extend treatment with IV rt-PA from 3 to 6 hours were the Diffusion and Perfusion Imaging Evaluation for Understanding Stroke (DEFUSE) study and the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET). In DEFUSE, early reperfusion was associated with a favorable clinical response in patients with DWI-PWI mismatch, whereas patients without mismatch did not benefit from early reperfusion. In EPITHET, patients with DWI-PWI mismatch who were treated with IV rt-PA had increased reperfusion. Although these past trials using DWI-PWI mismatch is encouraging, further research is required to further define and validate the role of mismatch in the treatment of patients with AIS.

**Gradient-Recalled Echo**

A necessary component of the workup of patients with suspected AIS is the exclusion of ICH. GRE is the preferred MRI sequence for detecting acute or chronic ICH, including hemorrhagic transformation. It is a T2*-weighted sequence that is sensitive to local magnetic field inhomogeneities produced by iron in the blood and hemoglobin degradation products. As blood extravasates into the parenchyma in ICH, hemoglobin in the blood becomes deoxygenated and the presence of unpaired electrons makes it a paramagnetic substance. The deoxyhemoglobin produces a nonuniform magnetic field that results in rapid dephasing of proton spins and subsequent signal loss, known as the susceptibility effect, best seen as hypointense (dark) lesions on GRE (Fig. 6).

Multimodal MRI that includes a GRE sequence is suitable for the imaging of patients with suspected acute stroke, including those patients who are eligible for treatment with thrombolytics or in whom ICH is suspected. A prospective multicenter trial by Fiebach and colleagues assessing the accuracy of blinded readers in identifying acute ICH (imaged within 6 hours of symptom onset) found that hyperacute ICH was identified by experienced readers with 100% sensitivity and 100% overall accuracy. Kidwell and colleagues compared the accuracy of GRE and CT for the detection of acute ICH in patients presenting with focal stroke symptoms within 6 hours of onset and found that GRE was as accurate as CT for the diagnosis of acute ICH and

![Fig. 6. Acute ICH in the left thalamus and posterior limb of the left internal capsule depicted on noncontrast brain CT (A) and GRE MRI (B).](image-url)
more accurate than CT in the detection of chronic hemorrhage. These results were confirmed in a prospective study by Chalela and colleagues\textsuperscript{11} comparing NCCT with MRI in the evaluations of consecutive ED patients presenting with suspected acute stroke. 217 of the 356 patients in this study had a final diagnosis of acute stroke with MRI being similar to CT for the detection of acute ICH and better than CT for the detection of acute ischemia and chronic hemorrhage.\textsuperscript{11}

GRE is superior to CT for the detection of chronic hemorrhage, particularly cerebral microbleeds (CMBs), which are small collections of hemosiderin deposits that are foci of past hemorrhages. CMBs appear as small, round, black dots on GRE. Recent evidence suggests that CMBs may be a marker of underlying vascular pathologic conditions, particularly hypertensive vasculopathy and cerebral amyloid angiopathy. The presence as well as the number of CMBs may predict future risk of symptomatic ICH in patients who have suffered a primary ICH or AIS.\textsuperscript{71} However, a recent large multicenter study of 570 patients with AIS who were treated with IV rt-PA found no significant absolute increase in the risk of symptomatic ICH in patients with CMBs identified on initial GRE versus those without.\textsuperscript{72} Presently, whether CMBs should affect clinical decision making remains an area of future research.\textsuperscript{71}

Much like the hyperdense artery signs seen on CT (described earlier in this article), a hypointense signal in a cerebral artery on GRE may indicate acute thrombosis in the vessel. The presence of this susceptibility sign on GRE indicating thrombotic occlusion may help to guide treatment. However, it is important to be sure to distinguish between the hypointense signal indicating vessel occlusion and a hypointense region of intraparenchymal hemorrhage.\textsuperscript{73,74}

**MRI in Patients with Unknown Time of Symptom Onset**

AIS occurs unwitnessed or during sleep in as many as 25\% of all patients.\textsuperscript{76} However, treatment with IV rt-PA is time dependent, with late treatment being ineffective or harmful\textsuperscript{76}; clinical guidelines exclude treatment with IV thrombolysis in patients in whom time of onset is unknown and last seen normal is outside of 3 to 4.5 hours.\textsuperscript{5} Many stroke investigators and clinicians advocate the use of imaging criteria to make treatment decisions in patients presenting with AIS whose exact time of onset of symptoms is unknown or is outside of the approved 3- to 4.5-hour treatment window for thrombolytic therapy. These stroke experts argue that treatment should be based on a tissue clock over a ticking clock to select patients who would most likely respond favorably to extended time window therapy.\textsuperscript{41}

Multiparametric MRI has been suggested as a means to identify patients with AIS who are likely to be within a 3- to 4.5-hour time window and benefit from IV thrombolysis. Because DWI lesions can be detected with minutes from onset of ischemia and FLAIR is sensitive for subacute ischemia but cannot usually detect hyperacute ischemic lesions within the first few hours, one MRI combination sequence that may be favorable for detecting AIS within 3 to 4.5 hours from ischemia onset is a DWI-positive with FLAIR-negative mismatch. A recent large multicenter observational study, Predictive Value of FLAIR and DWI for the identification of patients with Acute Ischemic Stroke within 4.5 hours of symptom onset, showed that DWI-FLAIR mismatch can be used to identify patients within 4.5 hours of symptom onset with 78\% specificity and 83\% positive predictive value. The investigators concluded that patients with an acute ischemic lesion detected on DWI but not on FLAIR imaging are likely to be within a time window in which thrombolysis is safe and effective.\textsuperscript{77}

In addition to MRI sequences potentially serving as a surrogate for duration of ischemia, it is hypothesized that imaging may be used as a marker of tissue salvage-ability. As described previously, it has been proposed that the use of DWI-PWI
mismatch identifies tissue that may be saved and can be used in triaging patients that may benefit from thrombolytic therapy, even if their symptom onset is outside of 3 to 4.5 hours. Multiple trials have used DWI and PWI mismatch for inclusion criteria with variable results and the clinical utility remains yet unknown and investigational.

Currently, several interventional trials in patients with stroke with unknown symptom onset are proposed with varying trial designs and imaging enrollment criteria. It is hoped that the results of these trials in conjunction with future research will provide imaging techniques that allow additional insight into tissue injury and salvageability so as to safely and effectively extend treatment with IV thrombolysis to patients with an unclear onset of symptoms who may benefit from therapy.\textsuperscript{78}

**INTRACEREBRAL HEMORRHAGE**

ICH is defined as spontaneous, nontraumatic bleeding into the brain parenchyma (Fig. 7).\textsuperscript{79} Patients suffering from ICH present similarly to patients with AIS with sudden onset focal neurologic deficits. Certain clinical findings are more likely to be associated with ICH over AIS, including loss of consciousness, coma, neck stiffness, seizure accompanying the neurologic deficit, diastolic blood pressure greater than 110 mm Hg, vomiting, and headache. Although these additional characteristics are more often associated with patients with ICH, many patients with ICH lack any of these distinctive findings. The diagnosis of ICH, and its differentiation from AIS, cannot be made clinically and requires definitive neuroimaging.\textsuperscript{80} Guidelines on the management of ICH from both the AHA Stroke Council and the European Stroke Initiative state that rapid neuroimaging is required to distinguish ICH from AIS.\textsuperscript{81,82}

As discussed previously, both CT and MRI can be used in the initial evaluation of patients presenting with possible ICH. NCCT is thought to be 100% sensitive for detecting clinically relevant acute hemorrhage and is considered the criterion standard for diagnosing ICH.\textsuperscript{81} As discussed previously, GRE is as sensitive as NCCT for the detection of acute intracranial hemorrhage, and MRI is a more accurate imaging

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**Fig. 7.** Acute ICH in the right cerebellum on noncontrast brain CT.
modality for patients presenting with possible acute stroke given its increased sensitivity for AIS and chronic hemorrhage.\textsuperscript{10,11} However, certain patient and hospital factors, such as the availability of MRI, patient contraindications, and patient medical instability, may make obtaining an MRI impossible or impractical in the acute setting.\textsuperscript{83}

Once ICH is diagnosed, additional neuroimaging may be performed to identify patients at risk for hematoma expansion and evaluate for secondary causes of ICH that may be amenable to treatment or intervention. CTA and contrast-enhanced CT may identify patients at risk for hematoma expansion. Contrast extravasation into the hematoma on a CTA or contrast-enhanced CT appears as a small, enhancing focus within the hematoma that is known as a spot sign. Patients found to have a spot sign are at a high risk for hematoma expansion\textsuperscript{84,85} and the clinical use of this radiological marker is an area of active research. MRI, MRA, MR venogram, and CTA may be useful to exclude secondary causes of ICH, such as aneurysms, tumors, cerebral venous thrombosis, arteriovenous malformations, or fistulas.\textsuperscript{81} Non-lobar hemorrhages involving the putamen, globus pallidus, thalamus, internal capsule, periventricular white matter, pons, and cerebellum in patients with known hypertensive vasculopathy are often, although not exclusively, caused by hypertensive vasculopathy. Patients with hemorrhages in other locations, including isolated intraventricular hemorrhage, and younger patients or patients without a history of hypertension are at a higher risk for secondary ICH.\textsuperscript{82,86}

**SUBARACHNOID HEMORRHAGE**

Headache is a common complaint accounting for approximately 2\% of all ED visits.\textsuperscript{87} Although most headaches are caused by primary headache disorders, such as migraines or tension-type headaches, some acute headaches are caused by serious pathologic conditions with significant morbidity and mortality, such as SAH. In fact, of all patients presenting to the ED with headache, approximately 1\% had SAH.\textsuperscript{88} Many patients with SAH present with sudden-onset severe headache with variably associated signs or symptoms, including nausea and vomiting, stiff neck, loss of consciousness, or focal neurologic deficits. Given the variability in types of headaches and inconsistency in associated symptoms, misdiagnosis or delayed diagnosis in SAH is common, with the most common diagnostic error being the failure to obtain proper imaging.\textsuperscript{89}

The first best diagnostic study to obtain in the workup of SAH is the NCCT (Fig. 8).\textsuperscript{88–90} NCCT should be obtained with very thin cuts through the base of the brain so as not to miss small collections of blood.\textsuperscript{88} NCCT is highly accurate in the diagnosis of SAH, but the probability of detecting SAH on NCCT is proportional to the amount of hemorrhage and the time from hemorrhage onset.\textsuperscript{89} The accuracy of the NCCT declines over time because of the circulation of the CSF and the resulting dilution and breakdown of the blood.\textsuperscript{90} In the first 12 hours after hemorrhage, the sensitivity of NCCT for SAH is 98\% to 100\%, declining to 93\% at 24 hours and to 57\% to 85\% 6 days after the onset of SAH.\textsuperscript{89} As technology improves, modern multidetector CT scanners show improving sensitivity for the diagnosis of SAH. A recent study by Perry and colleagues\textsuperscript{91} evaluating the sensitivity of modern third-generation CT for diagnosis of SAH showed an overall sensitivity of NCCT of 93\% and 100\% sensitivity for patients who underwent NCCT within 6 hours of headache onset. However, until further large studies confirm the 100% sensitivity of modern and early NCCT, patients being evaluated for SAH with negative NCCT should undergo lumbar puncture to look for small amounts of xanthochromia or blood in the CSF.\textsuperscript{92}

MRI is constantly advancing and shows promise for the evaluation and diagnosis of SAH.\textsuperscript{90} Both proton-density–weighted images and FLAIR images have shown to
reliably detect hyperacute SAH in patients with NCCT-positive SAH. However, in patients with NCCT-negative SAH that was diagnosed by lumbar puncture, FLAIR MRI was found to be infrequently positive. Additionally, on FLAIR, CSF pulsation artifacts can mimic blood in the third and fourth ventricles and around the cisterns and give a false-positive result. No large prospective studies of MR diagnosis in patients with suspected SAH exist, and CT remains the study of choice because of its speed, availability, and ease of diagnosis.

Once SAH is diagnosed, the intracranial vessels should be imaged as soon as possible after patient stabilization to evaluate for aneurysms or other vascular abnormalities that may be intervened on. In nontraumatic SAH, 80% of cases are caused by ruptured intracranial aneurysms, 10% by nonaneurysmal venous peri-mesencephalic hemorrhages, and the remaining 10% by other vascular lesions, tumors, and other less common causes. Imaging of the intracranial vessels for aneurysms can be accomplished by DSA, CTA, or MRA, with CTA and DSA having a higher accuracy rate than MRA. It has been shown that 3D TOF MRA and CE-MRA have a sensitivity and specificity similar to those of CTA for the detection of intracerebral aneurysms that are 5 mm or larger and have a lower sensitivity for the detection of aneurysms smaller than 5 mm.

READING A NONCONTRAST HEAD CT SCAN

As described previously, the “2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care” for patients with acute stroke recommend that an NCCT should be completed within 25 minutes of the patients’ arrival and interpreted within 45 minutes of ED arrival. Given the time-sensitive nature of acute stroke, emergency physicians should have the ability to interpret an NCCT and identify acute pathologic conditions in patients presenting with acute onset of focal neurologic deficits. The following section briefly reviews a rapid and thorough manner with which to read an NCCT to evaluate for significant pathologic conditions that requires emergent intervention. As with any radiologic interpretation, a knowledge of the basic normal anatomy and function of the brain parenchyma,
its vasculature, and its ventricles and cisterns is necessary in interpreting potential pathologic conditions on a head CT. A full review of cranial neuroanatomy is beyond the scope of this article, and the clinician is encouraged to review basic neuroanatomy as is necessary for his or her understanding.

In reviewing the NCCT, the emergency physician must be systematic in his or her approach. Several different approaches to reading the head CT have been recommended, including a checklist of items to follow when interpreting a NCCT96 or a central to peripheral approach on each image from the first through the last.97 To aid the emergency physician who does not frequently review head CT scans, Dr Perron and his colleagues98,99 developed the mnemonic “blood can be very bad” in which the first letter of each word prompts the clinician to evaluate a certain portion of the head CT for pathologic conditions. This method has been demonstrated to work in the ED, and the clinician may use the mnemonic when examining a cranial CT scan because the presence of one finding does not rule out additional pathologic conditions. The components of the mnemonic “blood can be very bad”, developed by Dr Perron and his colleagues99 are reviewed subsequently.

**Blood**

Review the head CT to evaluate for hemorrhage. Acute hemorrhage appears hyperdense (bright white) on a CT (Fig. 9A). Hemorrhage appears isodense around 1 to 2 weeks and hypodense by 2 to 3 weeks. Evaluate the head CT for epidural hematomas

![Fig. 9. “Blood can be very bad” (as described).99 Acute intracerebral blood in the left front lobe appears as a hyperintense (bright white) lesion (A). Cisterns are CSF collections jacketing the brain; suprasellar and circummesencephalic cisterns on NCCT (B). Appearance of normal brain on NCCT (C). Lateral ventricles on NCCT (D). Left parietal skull fracture on bone windows of NCCT (E).](image-url)
(lens shaped), subdural hematomas (crescent shaped), intraparenchymal hemorrhage, intraventricular hemorrhage, SAH, and extracranial hemorrhage.

**Cisterns**

Cisterns are CSF collections jacketing the brain (see Fig. 9B). Four key cisterns, circummesencephalic, suprasellar, quadrigeminal, and sylvian, must be examined for blood, asymmetry, and effacement (evidence of increased intracranial pressure).

**Brain**

Normal brain parenchyma is inhomogeneous where cortical gray matter is denser than subcortical white matter (see Fig. 9C). When examining the brain parenchyma, the clinician should look for symmetry, gray-white differentiation, evidence of shift, and evidence of hyperdensity or hypodensity. Hyperdensity is caused by blood, calcification, or IV contrast. Hypodensity may be caused by pneumocephalus, ischemia, edema, or tumor.

**Ventricles**

Pathologic processes can cause hydrocephalus or compression/shift of the ventricular system (see Fig. 9D). Hydrocephalus is usually first evident in the dilation of the temporal horns.

**Bone**

Fractures may occur at any portion of the skull, and the presence of a skull fracture should increase suspicion for an intracranial injury (see Fig. 9E). The diagnosis of a linear skull fracture can be confusing because of sutures, and the clinician should compare with the other side of the skull to look for suture symmetry versus fracture.

**REFERENCES**


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