Imaging of acute stroke

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Abstract | Brain imaging provides an objective basis for the clinical inferences that direct individual patient management in the acute stroke setting. A brain CT or MRI scan is required for all patients with suspected stroke or transient ischemic attack. Thrombolytic therapy is arguably the most important aspect of acute stroke management; however, most decisions in acute stroke do not relate to this treatment. Stroke imaging must, therefore, provide information beyond the presence or absence of intracranial hemorrhage (ICH) and early evidence of a large infarct. Noncontrast CT and gradient-recalled echo MRI show comparable accuracy in the diagnosis of acute ICH. Diffusion-weighted MRI is more sensitive than noncontrast CT for differentiation of acute ischemic stroke from nonstroke conditions. Combined multimodal parenchymal, perfusion and vascular imaging with CT or MRI has the potential to identify patients with an ischemic penumbra that might be appropriate for acute reperfusion therapies. MRI identifies a broader range of acute and chronic cerebrovascular pathologies than does CT and, hence, could aid decisions about acute intervention, in-hospital management, and secondary prevention. Here, we present an overview of the diagnostic information that clinicians might gain from CT and MRI in the setting of acute stroke, along with the advantages and disadvantages of these techniques.

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Introduction

When evaluating a patient with symptoms suggestive of stroke, the clinician must address several issues, notably whether the case represents an instance of acute cerebrovascular disease and, if so, whether the primary lesion is ischemic or hemorrhagic. The cause of the stroke must be ascertained, along with the nature of the vessel pathology, the pattern and extent of the damage, and the acute intervention that is indicated. In addition, the clinician must decide which secondary prevention therapy is appropriate, and evaluate the patient's prognosis. Brain imaging provides an objective basis for the clinical inferences that direct individual patient management. An accurate diagnosis will determine whether a patient is treated with thrombolytics or other acute interventions, is admitted to a stroke unit, and/or is started on secondary prevention therapies. An error in diagnosis could deprive the patient of effective interventions or unnecessarily expose the individual to potentially harmful treatments.

Current guidelines on the use of intravenous alteplase for the treatment of acute stroke require the use of CT or MRI to exclude intracranial hemorrhage (ICH) or other pathology.[1,2] Noncontrast CT is most commonly used for this purpose because this imaging modality is more widely accessible and available than MRI (Box 1). Thrombolytic therapy is arguably the most important aspect of acute stroke management, but most decisions in acute stroke do not relate to thrombolysis. In the acute stroke setting imaging must, therefore, provide information beyond the presence or absence of ICH.

Multimodal CT, including CT angiography (CTA) and CT perfusion (CTP), and multimodal MRI provide information about the hemodynamic and vascular pathophysiological changes caused by cerebrovascular disease.[3,4] In addition, MRI can provide a link between experimental advances and clinical applications by identifying markers of tissue pathophysiology (for example, infarct evolution, stroke recurrence, blood–brain barrier integrity, and

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amyloid angiopathy), and is being used to investigate parameters—that is dose, duration and time window—to optimize drug delivery to the ischemic brain regions.[5–7] The use of MRI in clinical trials of stroke might lead to improvements in targeted patient selection.[8–10] Moreover, owing to MRI's ability to assess pathobiological variables, this technique can be used to evaluate drug activity.[11–13] Transcranial Doppler ultrasonography can be used to assess the intracranial vasculature. This latter technique has been reviewed elsewhere[14,15] and, since it does not allow visualization of the brain parenchyma, we will not discuss it further here. The purpose of this Review is to give clinicians an overview of the indications and diagnostic information provided by CT and MRI in the setting of acute stroke, highlighting the advantages and shortcomings of each technique.

Key points

- A brain CT or MRI scan is urgently recommended for all patients with suspected acute stroke or transient ischemic attack
- Noncontrast CT and gradient-recalled echo MRI show similar accuracy in the diagnosis of acute intracerebral hemorrhage
- Diffusion-weighted MRI is markedly more sensitive than noncontrast CT for distinguishing acute ischemic stroke from nonstroke conditions
- Combined multimodal parenchymal, perfusion and vascular imaging with CT or MRI could potentially identify patients with an ischemic penumbra that might be amenable to acute reperfusion therapies
- MRI identifies a broad range of acute and chronic cerebrovascular pathologies that could aid decisions about acute intervention, in-hospital management and secondary prevention
- Overall, MRI is diagnostically superior to CT for cerebrovascular indications, but is contraindicated in ≈10% of patients, has limited availability at many hospitals, and can be costly and time-consuming

Box 1 | Practical considerations in CT and MRI

- CT is more readily available than MRI for emergency use
- Equipment costs and patient charges are lower for CT than for MRI
- CT involves exposure to ionizing radiation; no known biological risk exists for MRI
- MRI is markedly more sensitive and accurate than CT in early imaging-based diagnosis of ischemic stroke
- MRI is contraindicated in a subset of patients
- Patients, personnel and equipment must be screened to exclude unacceptable metal or electronics from the MRI scanning environment
- In cases of severe renal failure, intravenous contrast agent is contraindicated for both CT and MRI, but noncontrast alternatives for vascular and perfusion imaging are available for MRI

CT

Noncontrast CT

CT is considered to be the gold standard for excluding ICH in the acute setting, although this role for CT has never been validated with neuropathological studies. Acute extravascular blood appears as hyperdense regions on the CT scan because of the high protein content of the hematoma.[16] The accuracy with which a clinician can detect parenchymal hematoma on CT varies with experience, and ranges from 73% to 87%.[17] CT is also a useful tool in the diagnosis of subarachnoid hemorrhage (SAH). The sensitivity of CT for detection of blood in the subarachnoid space is ≈90% in the first 24 h following SAH onset, but decreases with time.[18] For this reason, a negative CT scan requires follow-up with a lumbar puncture if SAH is strongly suspected.[19] In addition, suspicion of SAH is a contraindication for thrombolysis, even if the CT scan is negative.[20]

CT can detect the effects of ischemia on brain tissue (Figure 1). Ischemia is a functional state of abnormal blood flow that initially leads to neuronal and endothelial cytotoxic edema and, subsequently, to ionic edema.[21] This increase in the water content of the brain causes X-ray attenuation, and is seen as a hypodensity on CT, most commonly in the arterial watershed territories—namely, the insular cortex, the lentiform nucleus, and the gray–white matter junction (Box 2).[4,22–25] In the NINDS tPA Stroke Trial, investigators found that within 3 h of symptom onset, 31% of patients with stroke had early ischemic signs, including loss of the gray–white matter distinction (27% of patients) and/or focal or diffuse areas of hypoattenuation (9% of patients). Patients with such signs had a high probability of having an infarct on follow-up (positive predictive value [PPV] 87%). CT hypoattenuation was associated with severe strokes and long times from onset of symptoms, but not with functional outcome. The rate of symptomatic hemorrhage was higher in patients with larger areas of hypoattenuation than in those with smaller areas of hypoattentuation, although the difference was not statistically significant.[26] In the Second European–Australasian Cooperative Stroke Study (ECASS-II), which enrolled patients with ischemic stroke up to 6 h after onset, the incidence of CT hypoattenuation (47%) was higher than in the NINDS tPA trial, and the PPV for brain infarction was 96%. The sensitivity and negative predictive values were, however, low (67% and 27%, respectively).[27] In this study, patients without early CT changes were less severely affected, developed smaller infarcts, had fewer intracranial hemorrhagic events, and had a better clinical outcome at 30 days than did patients with early changes.[27] The extent of hypoattenuation on CT was a predictor of parenchymal hemorrhage and symptomatic intracranial hemorrhage in ECASS-II.[28] The use of a quantitative tool, such as the Alberta Stroke Program CT Scale (ASPECTS), might improve a clinician's ability to identify hypoattenuation. In one study, the sensitivity and specificity of the ASPECTS score for functional outcome were 78% and 96%, respectively.[29] The corresponding values for the detection of symptomatic ICH after intravenous thrombolysis were 90% and 62%. In the first few hours after onset of ischemia, CT hypoattenuation is most difficult to detect when it occurs in the posterior fossa, or when the patient has chronic ischemic changes or areas of leukomalacia.[29,30]

Focal and diffuse brain swelling can be seen as sulcal effacement and compression of the cerebrospinal fluid

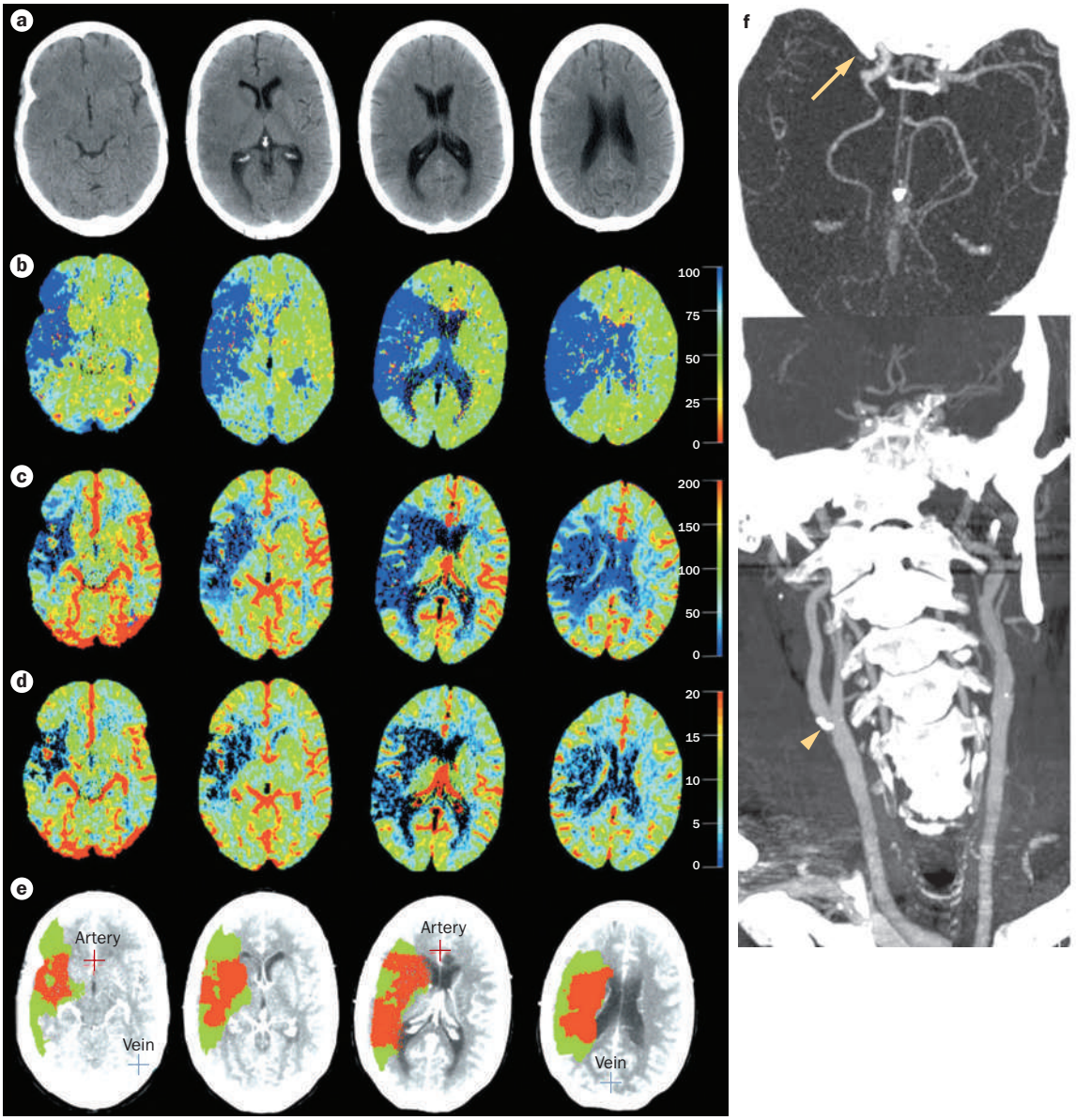

Figure 1 | Multimodal CT survey. A 57 year-old male with a right MCA syndrome underwent CT. **a** | The unenhanced CT scan ruled out a cerebral hemorrhage, and showed effacement of the sulci, and subtle loss of gray–white matter differentiation in the inferior right MCA territory. From the CTP raw data, three parametric maps were extracted, relating to **b** | mean transit time, **c** | cerebral blood flow, and **d** | cerebral blood volume. **e** | Application of the concept of ischemic penumbra led to a prognostic map, which depicted the infarct in red and the penumbra in green, the latter being a potential target for acute reperfusion therapies. **f** | CTA identified an occlusion at the distal right ICA just proximal to the MCA origin (arrow) as the origin of the hemodynamic disturbance demonstrated by CTP. CTA also revealed a calcified atheromatous plaque at the right carotid bifurcation (arrowhead). Abbreviations: CTA, CT angiography; CTP, CT perfusion; ICA, internal carotid artery; MCA, middle cerebral artery. Reprinted from *Radiol. Clin. North Am.* **47**, Ledezma, C. J. & Wintermark, M. Multimodal CT in stroke imaging: New concepts, 109–116, © 2009, with permission from Elsevier.

(CSF) spaces. In the NINDS tPA study, 14% of patients displayed this effect.[26] When identified on CT in the absence of hypoattenuation, brain swelling in cases of acute stroke might not represent severe ischemic damage and, if blood flow is restored, swollen areas do not necessarily progress to infarction.[31]

On noncontrast CT, a hyperdensity within the proximal intracranial arteries—the hyperdense artery sign—represents acute thromboembolism.[32] This sign can be detected in the middle cerebral artery (MCA), as well as in the posterior cerebral and basilar arteries.[33–35] A thrombus in the Sylvian branches of the MCA can appear as a bright dot.[36] The absence of hyperdense artery signs, however, does not imply that a thrombus is not present. False positives can result from atherosclerotic calcifications, although in such instances the hyperdense vessels are usually bilateral. A hyperdense MCA sign (HMCAS) is found in 40–50% of patients with an MCA infarction.[33,37] 36 h after treatment with intravenous alteplase for such strokes, the HMCAS disappears in almost 50% of

Box 2 | Early CT findings in patients with acute stroke

Noncontrast CT

- Sulcal effacement
- Loss of the insular ribbon
- Blurring of the gray–white matter junction
- Obscuration of the lentiform nucleus
- Hyperdense artery sign, indicative of intravascular thrombus

Multimodal CT

- Arterial occlusion on CTA
- Reduction or absence of contrast on CTA source images
- Reduction or absence of perfusion on CT perfusion parameter maps

Abbreviation: CTA, CT angiography.

Box 3 | Early MRI findings in patients with acute stroke

- Hyperintensity on diffusion-weighted imaging, with minimal or no changes on T2-weighted or FLAIR sequences
- Hypointensity on apparent diffusion coefficient
- Hypointense ('blooming') artery sign of acute intravascular thrombus on gradient-recalled echo sequences
- Arterial occlusion on magnetic resonance angiography
- Absence of arterial flow void, which is indicative of occlusion, on T2-weighted or FLAIR sequences
- Hyperintense vessel sign, which is indicative of slow or collateral flow, on FLAIR sequences
- Reduction or absence of contrast on dynamic PWI source images
- Reduction or absence of perfusion on PWI perfusion parameter maps

Abbreviations: FLAIR, fluid-attenuated inversion recovery; PWI, perfusion-weighted imaging.

patients, and these individuals have the best outcomes.[38] After 2 weeks, the HMCAS is no longer seen in 95% of patients, even when thrombolytics are not used.[33]

CT angiography

Modern multidetector spiral CT scanners can image the vascular tree from the aortic arch to the distal branches of the large intracranial arteries by tracking the passage of a bolus of iodinated contrast through the vasculature (Figure 1). CTA can pinpoint the site of pathology in the neck and brain vessels through its capacity to detect arterial dissection, grade collateral blood flow, and identify intracranial aneurysms.[4]

CTA is important in the evaluation of acute stroke. This imaging technique has high sensitivity (80–90%) and specificity (90–91%) for identification of high-grade carotid artery stenosis, and can differentiate near occlusion (string sign) from occlusion almost as well as conventional angiography, and more effectively than does ultrasound.[39,40] CTA also has high sensitivity (92–100%) and specificity (82–100%) for the detection of intracranial occlusion and thrombus in the acute setting; however, the sensitivity of this technique is lower for the detection of less-severe stenosis.[1,41–45] Source images from CTA can be used as an alternative to CTP to provide hemodynamic information. The CTA source images give a qualitative picture of cerebral blood volume, which, when low, is predictive of infarction.[46–48]

CTA is a valuable tool in the evaluation of patients with SAH; in the acute setting, its sensitivity and specificity for the detection of intracranial aneurysms are 98% and 100%, respectively, when compared with conventional angiography.[49–51] CTA can also detect vasospasm of large vessels following SAH.[52]

CT perfusion

CTP allows rapid, noninvasive quantitative evaluation of cerebral perfusion, and can delineate the ischemic core and ischemic penumbra (Figure 1).[53,54] CTP images are acquired during rapid intravenous administration of nonionic iodinated contrast medium. The change in CT enhancement is proportional to the concentration of contrast agent in the vessels. Through deconvolution methods, and identification of the arterial input and venous outflow, perfusion parameters can be calculated.[4] The use of brain maps in combination with these parameters enables the calculation of the penumbra–infarct area.[55,56] Specific CTP and CTA criteria that identify patients who might benefit from thrombolysis have not been determined, and different scanner manufacturers use different algorithms to calculate perfusion parameters.[55] CTP is currently limited to several axial slices over an area of the brain 2–4 cm wide, and is, therefore, less likely than MRI to identify small perfusion deficits or fully evaluate large perfusion deficits. Newer 256-slice and 360-slice CT scanners could, however, offer whole-brain coverage.

MRI

The interest in MRI as a tool for acute stroke management lies not only in the capability of this technique to detect early ischemic lesions with high sensitivity, but also in the breadth of the cerebrovascular pathology revealed by such imaging (Box 3). Multimodal MRI can delineate the presence, size, location, extent and effects of acute brain ischemia, identify the hypoperfused tissue that is at risk of infarction, and show additional features of the cerebrovascular pathology (Figure 2). MRI can also detect or exclude ICH with an accuracy comparable to CT.[3] A full clinical multimodal stroke MRI study for acute stroke takes 15–20 min and is feasible even within a 3 h thrombolysis time window. The additional diagnostic information obtained with MRI could result in improvements in patient outcomes and cost-effectiveness.[57–61] Several large stroke centers rely on MRI to screen patients for thrombolytic and other interventional treatments.[62] A typical acute stroke MRI protocol includes the following sequences (Figure 2): diffusion-weighted imaging (DWI), gradient-recalled echo (GRE), T2-weighted

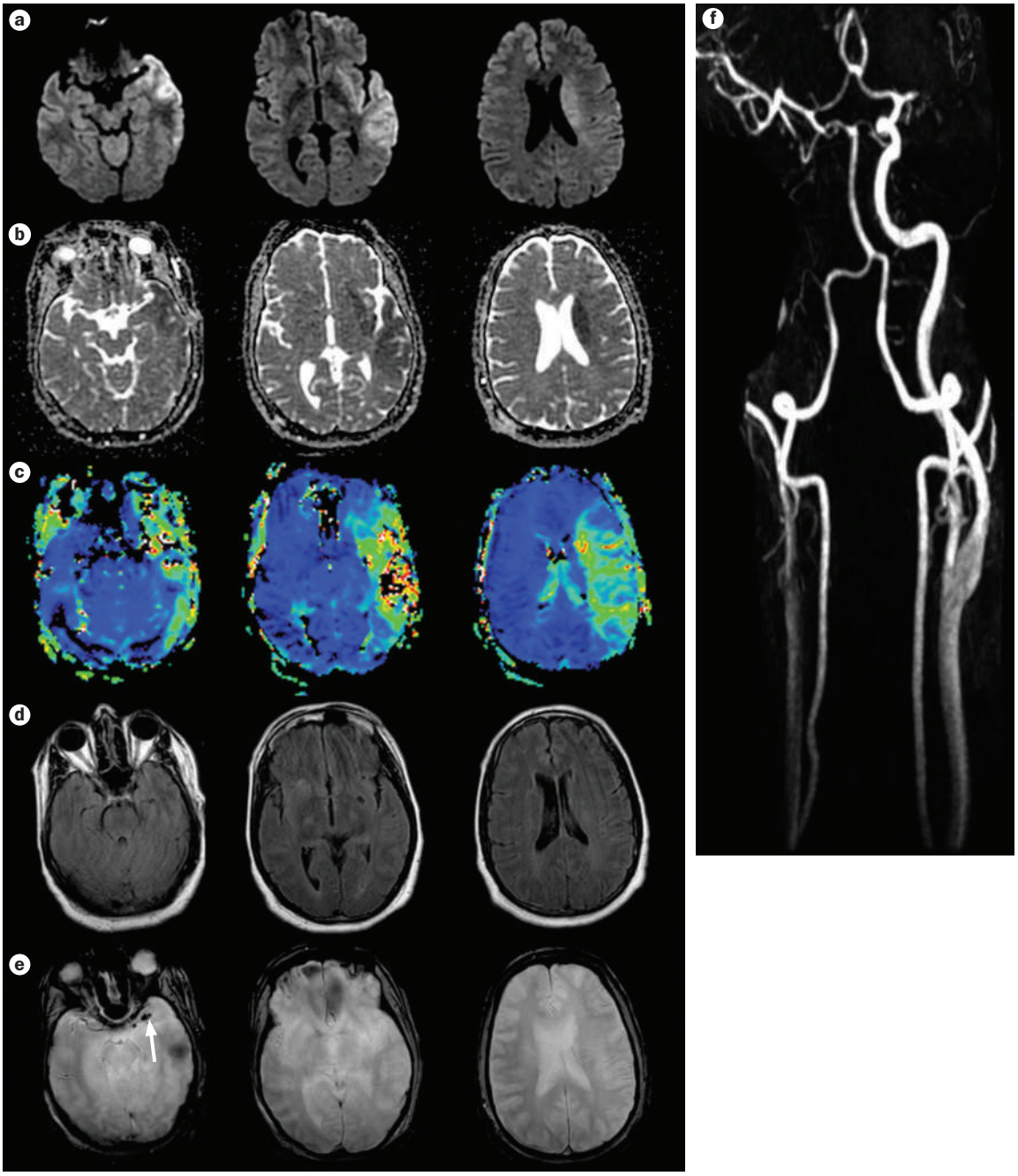

Figure 2 | Multimodal MRI. The patient arrived at the emergency room 45 min after symptom onset. MRI was started 20 min later, and the patient was treated with intravenous tissue plasminogen activator 55 min after arrival. **a** | DWI sequence showed an area of hyperintensity in the right temporal, insular and frontal lobes. **b** | Apparent diffusion coefficient map showed a matching area of hypointensity, confirming that the DWI lesion was due to acute ischemia. **c** | Mean transit time maps showed an area of hypoperfused tissue larger than the DWI abnormality; the difference represented the penumbra. **d** | Fluid-attenuated inversion recovery showed no matching hyperintensity, indicating that the DWI lesion was <6 h old. **e** | The gradient-recalled echo sequence showed no evidence of acute or chronic hemorrhage, but a clot was seen in the right MCA (arrow). **f** | Contrast-enhanced MRA of the neck and brain revealed a chronic asymptomatic right carotid occlusion, although the patient had good collateral flow through the anterior communicating artery, and his right carotid artery was normal. The proximal right MCA abruptly terminated in the proximal portion, as confirmed by axial MRA. Abbreviations: DWI, diffusion-weighted imaging; MCA, middle cerebral artery; MRA, magnetic resonance angiography.

fluid-attenuated inversion recovery (FLAIR), magnetic resonance angiography (MRA), and perfusion-weighted imaging (PWI). These sequences show pathology specific to stroke, and the sequences are complementary and confirmatory, as we will discuss below.

Diffusion-weighted imaging

DWI has transformed the diagnosis of ischemic stroke in its earliest stages, from reliance on a mostly clinical inference about the presence, localization and size of an ischemic lesion to imaging confirmation of the infarct.

This technique is the only brain imaging method to reliably demonstrate ischemic parenchymal injury within the first minutes to hours after onset.

Ischemia-induced membrane dysfunction and cytotoxic edema restrict the diffusion of water and lead to a decrease in the apparent diffusion coefficient (ADC), a physiological measure of the rate of water movement through brain parenchyma. As a result, acute focal ischemia is hyperintense on DWI scans and hypointense on ADC maps (Box 3).[63,64] Typically, the ADC remains low for the first 4 days after an ischemic event, but later increases, so that in the subacute and chronic stages of the infarction this coefficient seems normal (pseudonormalization) or high.[65] Lesions resulting from chronic stroke and peritumoral edema that are hyperintense on FLAIR and T2 sequences can also appear bright on DWI (the 'T2 shine-through' effect). Such lesions can be differentiated from acute ischemia, as the former are also bright on ADC maps.

DWI is an ideal sequence for imaging patients with acute stroke. In a prospective, blinded comparison of noncontrast CT and MRI in a consecutive series of patients referred for emergency assessment of suspected acute stroke, the sensitivity of DWI for ischemic acute stroke ranged from 73% (3 h after the event) to 92% (>12 h after the event). By contrast, the sensitivity of CT at these times was 12% and 16%, respectively. The specificity of MRI for stroke detection was 92% (at 3 h) and 97% (>12 h).[66] Despite the high sensitivity of DWI, clinicians must recognize that false negatives might occur with this technique: the reported rate of false negatives with DWI in this study was 17% (versus 84% for CT) for the entire sample and 27% (versus 88% for CT) within the first 3 h.[66] Mild or small infarcts, early imaging, and brainstem location are factors associated with false-negative scans, and the false-negative rate is higher when patients have two or more of these factors than when they have one or none.[66,67] The sensitivity of DWI for the diagnosis of acute ischemic stroke is higher than that of CT (39–75%) or FLAIR (46%).[68,69]

Acute ischemic lesions on DWI are dynamic: information from clinical trials and case series shows that DWI lesions grow with time.[70–73] DWI reveals the ischemic core that evolves to irreversible infarction in the absence of effective reperfusion or cytoprotection; however, some of the DWI lesion could be reversible if blood flow is restored promptly.[74–80] Several studies show that the initial diffusion lesion volume correlates well with final infarct volume and neurological and functional outcomes, suggesting that DWI can provide important early prognostic information.[81–84] Patients with multiple DWI lesions of different ages have a high risk of recurrent stroke.[85] DWI can detect early recurrent strokes: in a study of patients with stroke imaged within 6 h of onset, 34% of individuals had additional lesions when re-imaged 1 week later, and in almost 50% of cases the new lesions were outside the area of perfusion abnormality at baseline.[5] Patients with multiple DWI lesions or large-artery disease are more likely to have recurrent lesions than stroke patients with single lesions on DWI.[5] This 'stroke-prone' state persists for up to 90 days, but the greatest risk occurs during the first month after the initial stroke.[6]

DWI lesions can help identify stroke etiology, as certain lesion patterns are associated with specific stroke subtypes.[86] Single cortico-subcortical lesions, multiple lesions in the anterior and posterior circulation, and multiple lesions in multiple cerebral territories are associated with cardioembolism.[86,87] Multiple lesions in the unilateral anterior circulation, and small scattered lesions in one vascular territory, particularly in a watershed distribution, are related to large-artery atherosclerosis.[86,88] These imaging patterns, together with information obtained from other MRI sequences, such as MRA, might help in the selection of the most appropriate measures for secondary prevention of stroke.

DWI is important in the evaluation and management of patients with transient ischemic attack (TIA).[89,90] Up to 30% of individuals who experience a classic TIA—a sudden focal neurological deficit of presumed vascular origin lasting <24 h—have lesions on DWI. Among patients with transient symptoms, individuals who have a DWI lesion or a vessel occlusion on MRI have a higher risk of stroke and functional dependence than do individuals without acute abnormalities on MRI, particularly when symptoms last >1 h.[91–93] MRI has led to a redefinition of the TIA concept: TIA now refers to a brief episode of neurological dysfunction caused by focal brain or retinal ischemia, with clinical symptoms typically lasting <1 h, and without evidence of acute infarction.[94]

Gradient-recalled echo

GRE MRI can detect acute or chronic ICH. As GRE is T2*-weighted, this sequence is very sensitive to local magnetic field inhomogeneities induced by iron in the blood and blood-breakdown products. GRE is the preferred MRI sequence for detecting acute or chronic hemorrhage, including hemorrhagic transformation. Newer susceptibility-weighted imaging sequences (SWI; Figure 3) have an even greater sensitivity to intravascular and extravascular blood.[95] The pattern of ICH on T1-weighted and T2-weighted sequences evolves over time (from acute to chronic stages); however, the characteristic hypointense (dark) appearance of such hemorrhages on GRE is present at all stages.[96] MRI scans incorporating a GRE sequence are suitable for examining patients with suspected acute stroke,[66,96–101] including candidates for thrombolytics and individuals in whom ICH is suspected.[96,97,99] In a prospective multicenter study evaluating patients who had experienced stroke symptoms ≤6 h after onset, GRE MRI was as accurate as CT for the detection of acute hemorrhage, and more sensitive than the latter for the detection of chronic hemorrhage.[97] Among 200 patients, the concordance between CT and MRI in the diagnosis of ICH was 96%. In another series of 124 patients imaged ≤6 h after stroke onset, half of whom had ICH, experienced readers could identify ICH with 100% sensitivity and overall accuracy.[101] Punctate acute hemorrhages on GRE MRI might not be indicative of edema, and might, thus, be difficult to differentiate from chronic microbleeds. CT might, therefore, be required to

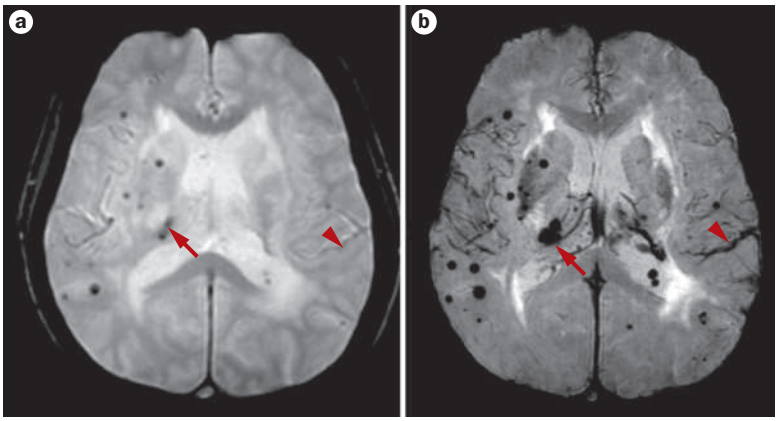

Figure 3 | Suceptibility-weighted imaging. Multiple microbleeds (arrows) and enlarged veins (arrowheads) seen on **a** | gradient-recalled echo and **b** | susceptibility-weighted imaging maps. Susceptibility-weighted imaging is more sensitive than gradient-recalled echo to venous structures.

establish the acuity of these small lesions, because acute but not chronic ICH will be evident on such imaging.[97]

MRI is superior to CT for the detection of chronic hemorrhage, particularly chronic microbleeds (Figure 3)[97]—focal areas of MRI signal loss resulting from hemosiderin deposits from prior small bleeds.[102,103] The differential diagnosis for small black dots on GRE includes areas of calcification and other mineralization. Calcifications are commonly found in the basal ganglia, choroid plexus, pineal gland, and falx cerebri, and must not be mistaken for old microbleeds. Vascular flow voids in blood vessels can also appear as black dots on GRE, but such voids can be differentiated from microbleeds, as the former are found in the sulcal space, and have a linear structure when examined over multiple slices.[103] Microbleeds might help identify possible etiologies and act as markers of accompanying vascular pathology.[103] Patients with long-standing hypertension can have microbleeds in the basal ganglia, thalamus, brainstem and cerebellum.[102] The microbleeds in patients with amyloid angiopathy tend to have a lobar distribution, favoring posterior cortical lesions in the gray–white matter junction.[104] Microbleeds are also common in cortical and subcortical areas in patients with infective endocarditis.[105] Chronic microbleeds can indicate an increase in risk of primary brain hemorrhage and/or hemorrhagic transformation after ischemic stroke.[57,106–109] Such microbleeds also increase the risk of recurrent ICH in patients with ICH, and of ischemic stroke in patients with minor ischemic stroke or TIA.[110,111] In a large multicenter study of 570 patients with acute stroke who were treated with alteplase ≤6 h after stroke onset, however, the risk of symptomatic hemorrhagic transformation was not markedly higher in patients with microbleeds than in patients without such bleeds (5.8% and 2.7%, respectively; $P = 0.17$ on Fisher's exact test).[108]

A thrombus in the intracranial vasculature might appear as an intravascular hypointensity on GRE sequences.[112,113] Such images can also highlight subarachnoid and subdural blood, and MRI that includes GRE and FLAIR sequences can be used as the initial imaging modality for patients with suspected SAH.[114] Readers of such images should be aware, however, that on FLAIR sequences CSF pulsation artifacts can mimic blood in the third and fourth ventricles and around the cisterns.

Fluid-attenuated inversion recovery

FLAIR is a T2-weighted sequence in which the CSF signal is suppressed. On traditional T2-weighted MRI, CSF appears bright, whereas on FLAIR this fluid appears dark. As a result, FLAIR is a very useful sequence to detect blood or gadolinium-based contrast agents in the CSF, and can, therefore, readily identify SAH and subdural hemorrhage. Early blood–brain barrier disruption in stroke appears as delayed gadolinium enhancement of hemispheric sulci on FLAIR sequences.[7] Such enhancement—termed hyperintense acute reperfusion marker, or HARM—is associated with reperfusion, a higher risk of hemorrhagic transformation after thrombolytic therapy, and an increase in plasma levels of matrix metalloproteinase-9.[7,115–117]

In general, acute ischemic stroke produces no signs on FLAIR in the first 6 h from onset, with areas of hyperintensity evolving thereafter. In patients with unwitnessed onset of stroke, including those whose deficits are present on awakening, a DWI lesion without a matching hyperintensity on FLAIR suggests that the stroke occurred <6 h previously. Studies to evaluate the use of MRI in this setting to select patients for treatment are ongoing.[118–121]

In patients with acute ischemic stroke, portions of the intracranial arterial tree can appear hyperintense on FLAIR. This hyperintense vessel sign is indicative of slow blood flow distal to the site of acute arterial obstruction. This slowdown in blood flow is attributable to anterograde flow through an incomplete occlusion, or flow via leptomeningeal collaterals, and is associated with a large diffusion–perfusion mismatch, but is not predictive of response to thrombolytic therapy.[122–125]

Magnetic resonance angiography

Two MRA techniques are routinely used in clinical practice and research: contrast-enhanced MRA (CE-MRA) and time-of-flight MRA (TOF-MRA). In CE-MRA, a rapid magnetic resonance acquisition is timed to a bolus injection of contrast medium over a large field of view, permitting routine imaging of the vasculature from the aortic arch through to the branches of the circle of Willis (Figure 2). The vascular anatomy is outlined by the contrast-containing blood.

In TOF-MRA, no contrast medium injection is required, and the vascular signal depends on direction and velocity of blood flow into the plane of imaging. The limitations of TOF-MRA comprise a tendency to overestimate the degree of stenosis (particularly when blood flow is slow or turbulent, or calcifications are present) and an insensitivity to collateral sources of blood flow. This MRA technique has greater spatial resolution than CE-MRA for the intracranial circulation, however, and it can be used to image the cerebral venous system (magnetic resonance venography). TOF-MRA is an alternative for patients who are unable to receive contrast—something that is not possible with CTA. Notwithstanding the tendency of

TOF-MRA to overestimate the degree of stensosis, this technique rivals CTA and conventional angiography for the detection of arterial stenoses, occlusions and dissections.[126–129] The sensitivity of MRA to detect aneurysm after SAH is 69–100%, with a specificity of 75–100%.[51] The sensitivity of this technique for the detection of small aneurysms is lower.[130]

Perfusion-weighted imaging

PWI visualizes capillary blood flow and, thus, can demonstrate the presence of cerebral ischemia. The most commonly used MRI method to study cerebral perfusion in clinical practice and research is dynamic susceptibility contrast-enhanced imaging. In this technique, a gadolinium-based contrast agent is injected as an intravenous bolus. Gadolinium is paramagnetic and, therefore, has a local susceptibility effect that can be detected with T2-weighted or T2*-weighted imaging as a drop in signal intensity. Repeated series of susceptibility-weighted, T2*-weighted images are acquired for several seconds before and after the injection of the gadolinium bolus to track the signal change.[131] Relative hemodynamic measures can be derived from the changes in signal intensity, including mean transit time (MTT), time to bolus peak (TTP), cerebral blood volume and cerebral blood flow. The means of quantification and comparison of perfusion parameters to best characterize the ischemic region is a topic of current debate and research, and the optimal parameters to select patients for acute treatments have not been definitively established.[132,133] In routine clinical practice, however, the identification of regions of brain tissue that are abnormally perfused is relatively straightforward when scanner-generated hemodynamic maps related to the first passage of contrast (such as from MTT or TTP) are used (Box 4).

Interpretation of the source PWI images is an alternative option when hemodynamic maps are not available or are affected by patient motion. PWI source images are T2* weighted and can, therefore, be used to confirm (or identify, if a GRE sequence is not available) the presence of ICH or an intravascular thrombus.

The mismatch between DWI and PWI lesions can be used to estimate the extent of the ischemic penumbra (Figure 2).[70,76,134] Some of the DWI lesion is potentially reversible, and some of the peripheral region of the perfusion abnormality does not progress to infarction (Box 4). The EPITHET, DEFUSE, DIAS and DEDAS studies all showed that patients with a DWI–PWI mismatch could benefit from acute thrombolytic therapy.[8–10,135] The DEFUSE study involved patients treated with intravenous alteplase 3–6 h after onset of symptoms. These patients were not selected on the basis of the DWI–PWI mismatch; however, early reperfusion in patients with a mismatch (a PWI lesion of at least 10 ml in size and at least 20% larger than a DWI lesion) was associated with a favorable clinical outcome, and the benefit of treatment was even greater in individuals with a target mismatch profile (those with mismatch who did not have a DWI or PWI lesion greater than 100 ml). Patients without a mismatch did not benefit from reperfusion.[9] In EPITHET, treatment with intravenous alteplase led to attenuation of infarct volume growth in patients with a mismatch.[10] The trials of desmoteplase (DIAS and DEDAS) enrolled patients with a DWI-PWI mismatch 3–9 h from onset of symptoms, and were the only studies to use outcome on MRI as a selection criterion in a randomized controlled manner for late thrombolysis. The DIAS and DEDAS studies showed a positive dose–response effect of desmoteplase on early reperfusion, and clinical benefits were seen in patients treated with desmoteplase.[8,135] DIAS-2, a phase III study, did not confirm the clinical benefit of desmoteplase, for reasons that are not well understood.[136] Results of these late thrombolysis trials are encouraging, but much work remains to be done to fully elucidate the role and validity of the diffusion–perfusion mismatch in selecting patients for thrombolysis.[137]

The role of MRI in acute stroke management is an area of intense research. Results from MRI-based clinical trials are helping to refine the mismatch concept, and penumbral imaging is a promising tool that will help us identify individuals who might benefit from thrombolysis beyond the current therapeutic window.[8–10,13,135,136] Developments in the use of arterial spin labeling—a method to measure perfusion using an endogenous tracer, in magnetically labeled blood—make this technique a promising tool for the assessment of brain perfusion in patients with contraindications to gadolinium-based contrast agent.[138,139]

Box 4 | The ischemic penumbra concept

At the onset of ischemic stroke symptoms, cerebral blood flow (CBF) falls. The CBF change in ischemic stroke is a graded reduction. Mild changes in CBF are tolerated because dilation of the vascular bed increases local cerebral blood volume (CBV) to maintain the required delivery of oxygen, glucose and other metabolites (a scenario termed benign oligemia). In locations where severe and prolonged CBF reductions have occurred, CBV cannot be maintained, and a core region of irreversible cell injury and death develops. Intermediate CBF reductions occur in areas between the ischemic core and regions of benign oligemia; such areas comprise the ischemic penumbra. The penumbra is a region of symptomatic, at-risk but potentially salvageable brain tissue with compromised cerebral perfusion. This area has the potential to progress to tissue infarction if blood flow is not restored promptly and, thus, is the hypothetical target of acute stroke therapies.

Penumbral imaging with CT or MRI relies on passage of the injected contrast material through the vasculature to estimate CBF, CBV, and mean transit time (MTT). Since CBF=CBV/MTT, processed parameter maps related to these hemodynamic variables are useful in identifying the penumbra. In practice, parameters related to MTT are most commonly used in delineating the regions of ischemia. Operationally, the core is defined differently with CT and MRI. The CT core is defined as a reduction in CBV, whereas the MRI core is defined as an abnormality on diffusion-weighted imaging, either as increased diffusion-weighted imaging signal intensity or reduced apparent diffusion coefficient values.

Safety considerations

Clinicians should be aware of several safety issues with CT and MRI imaging modalities, some of which are related to the technique (that is, radiation and exposure to magnetic fields) and some of which are related to the contrast materials used.

Findings published over the past 2 years indicate that exposure to radiation in CT studies is higher than was

previously thought.[140–142] Radiation doses vary according to the CT examination and the scanner used, and also differ across and even within institutions.[141] The typical radiation dose for a head CT scan is equivalent to 30 chest radiographs or five mammography series. For CT and CTA (suspected stroke protocol) the radiation is equivalent to 199 chest radiographs.[141] In 2007 alone, ≈29,000 incident cancers in the US were attributed to CT scans.[141]

Excluding human errors—failures to properly screen, or to prevent patients, personnel or equipment containing prohibited metal or electronics from entering the MRI room—the magnetic fields or radiofrequency pulses used in routine clinical MRI scanning carry no known or suspected risks. All patients must, however, be screened for MRI contraindications, including the presence of cardiac pacemakers and other hardware that is not MRI compatible.

In patients with severe chronic kidney disease (CKD), CT and MRI contrast agents are generally contraindicated.[143] The iodinated contrast agents used for CTA and CTP can lead to contrast-induced nephropathy (CIN)—potentially life-threatening acute renal failure. CIN is most common in patients with pre-existing renal disease, particularly that caused by diabetes.[144] The risk of CIN is ≈5% for patients with a glomerular filtration rate (GFR) of 15–40 ml/min/1.73 m^2, and is higher for patients with a GFR of <15 ml/min/1.73 m^2.[145] Several investigators have looked at the occurrence of CIN among patients who underwent CTA or CTP for the evaluation of acute stroke, reporting an incidence of 2–5% in patients who did not have CKD, even when baseline creatinine levels were not measured before the scan.[146–149] Few of the patients who developed CIN (0.2%) from CT contrast required in-hospital dialysis (0.2%), and none developed CKD.[146–149]

In 2006, a link between gadolinium contrast agents and nephrogenic systemic fibrosis (NSF) was identified, and in 2007 the FDA added a boxed warning for these agents.[150] The risk of NSF is highest in patients with moderately severe (stage IV; GFR <15–29 ml/min/1.73 m^2) or severe (stage V; GFR <15 ml/min/1.73 m^2) renal disease.[151] The incidence of NSF in patients receiving dialysis is ≈2.6%, but is lower among patients who are not dialysis dependent.[152] The type of gadolinium-based contrast agent can affect the incidence of NSF.[153] Clinicians are referred to European and North American guidelines for specific management recommendations.[154,155] In general, caution is recommended in giving gadolinium-based contrast agents when the GFR is 30–60 ml/min/1.73 m^2, using agents without reports of associated NSF at the lowest possible dose. Gadolinium should not be used when a patient has a GFR of <30 ml/min/1.73 m^2. The guidelines do not mandate measurement of serum creatinine levels before gadolinium administration unless chronic renal disease is suspected during the screening process. The radiology policies at many institutions require a baseline serum creatinine level for all patients before the scan.[155] A point-of-care handheld system may be used to avoid any delays in obtaining the MRI scan.

Conclusions

Neuroimaging in acute stroke is essential for establishment of an accurate diagnosis, characterization of disease progression, and monitoring of the response to interventions. MRI has demonstrably higher accuracy, carries fewer safety risks and provides a greater range of information than does CT. The latter technique, however, retains pragmatic advantages for acute stroke imaging. Further work is needed to optimize the predictive value of brain perfusion studies and to validate perfusion methods that do not require injection of contrast material. In the near future, we expect to learn whether penumbral imaging or other early imaging features will permit a longer time window for recanalization therapies. Improvements in imaging technologies over the next decade could lead to integration of heart, neck and brain assessments into a single imaging examination for a streamlined work-up of acute stroke and its etiology. High-resolution imaging of arterial plaque components, tracking of inflammatory or stem cells in the brain, and receptor-targeted contrast agents are promising areas of research that could lead to advances in stroke medicine. The ultimate potential of neuroimaging is the provision of certain knowledge of cerebrovascular pathology to direct the management of individual patients with stroke.

Review criteria

PubMed was searched for research and review articles published in English since 1995 using the following terms: "imaging", "magnetic resonance imaging", "computed tomography" and "stroke". Additional papers were identified from the reference lists of papers found on the search of the electronic database, and from our archives. The peer reviewers also suggested papers for consideration.

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Author contributions

Both authors contributed equally to this Review.