IMAGING OF ACUTE STROKE AND TRANSIENT ISCHAEMIC ATTACK

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It is increasingly recognised that both stroke and transient ischaemic attacks (TIA) are medical emergencies and that rapid clinical and radiological evaluation underpin the urgent management of cerebrovascular disease. The arbitrary duration based separation of stroke from TIA is felt by many to be redundant in the era of stroke treatment, and the term acute ischaemic cerebrovascular syndromes (AICS) is a suggested alternative analogous to cardiological terminology changes. However, presentation with an acute stroke syndrome diagnosed clinically is not synonymous with an AICS, since there are a number of pathologies that can produce identical clinical pictures, and many stroke mimics. Imaging is an essential component of diagnosis.

The need for increasingly early imaging has led to new emphasis on hyperacute changes on plain computed tomography (CT) and has also seen the widespread use of more complex imaging modalities in acute stroke.

Immediate brain imaging with CT for all stroke patients on admission is more cost effective than deferred imaging, even when the possible interventions are limited to aspirin use and stroke unit care. A cost effectiveness analysis has not yet been done to take into account thrombolytic treatment or modalities other than routine CT.

ACUTE STROKE

Around 85% of cases of stroke fulfilling the 1976 World Health Organization definition are ischaemic in origin, with 10% caused by focal haemorrhage and 5% by subarachnoid haemorrhage (SAH). Since SAH rarely presents with sudden focal symptoms, this review will ignore SAH.

Many ischaemic strokes exhibit rapid early improvement, leading clinicians to apply the term “TIA” when strictly speaking this label is attached only when symptoms resolve entirely within 24 hours. Most true TIAs last minutes, and the longer the symptoms last, the greater the likelihood of a causative lesion being identified on imaging.

Haemorrhage

Computed tomography

Non-contrast CT (NCCT) remains the gold standard means of detecting intracranial haemorrhage in acute stroke. Blood is hyperdense because of its high electron density (fig 1). As blood is broken down, density on CT declines by approximately 1.5 Hounsfield units (HU) per day. Old haemorrhage appears hypodense on CT within a time scale determined by the volume of the initial haematoma. Small bleeds may be indistinguishable from infarcts within days of the event.

Anatomical location is relevant in determining the aetiology of primary intracerebral haemorrhage (PICH)—for example, small vessel disease most commonly causes basal ganglia haemorrhage, while lobar haematoma is most commonly caused by amyloid angiopathy in the elderly. Lobar haemorrhage in younger patients may be due to underlying pathology—for example, bleeds secondary to arteriovenous malformations (AVMs) typically extend from the cortical surface to the lateral ventricles, superior sagittal sinus thrombosis often gives bilateral parasagittal haemorrhages, and thrombosis of the vein of Labbe causes temporal lobe haemorrhage. Cavernomas may cause pontine or supratentorial lobar bleeds.

It is now recognised that a high proportion of haematomas expand within the first hours after onset (fig 1), and that expansion is associated with poorer outcome. With the preliminary demonstration that recombinant factor VII not only reduces haematoma expansion but also improves clinical outcomes in PICH treated within three hours of onset, early recognition of PICH is likely to become an important diagnostic goal of acute imaging in its own right, and not simply a necessary step in exclusion before considering treatment for an ischaemic event.
Vascular imaging
Surgical evacuation may still be considered for some haematomas, particularly superficial lobar haematomas, and there may be a need to undertake cerebral angiography in order to seek an underlying AVM before surgical decompression or evacuation can be planned. If surgery is not anticipated, it is usually advisable to defer vascular imaging studies for some months after an acute intracerebral haemorrhage since mass effect from any residual haematoma may obscure small low pressure AVMs. External carotid studies may need to be included in addition to selective catheterisation of the internal carotid system in order to identify small dural arteriovenous shunts.

Magnetic resonance imaging
Susceptibility weighted MRI sequences have been compared to CT in acute stroke and results to date suggest that MRI is a good alternative for the detection of haemorrhage. However, further comparative evaluation is needed before MRI can be regarded as a substitute.

In investigation of stroke with delayed presentation, gradient echo MRI is the investigation of choice for exclusion of old haemorrhage. On gradient echo MRI, old bleeds are of low signal. Gradient echo MRI increasingly identifies microhaemorrhages in the brain in individuals with no clinical history to suggest intracerebral haemorrhage (fig 2). These microbleeds may be a risk factor for spontaneous bleeds after thrombolytic treatment, and offer an explanation for the occurrence of haematomas that are remote from the site of ischaemia for which treatment was given. It remains to be established definitively whether the presence of microbleeds on gradient echo MRI represents a contraindication to systemic thrombolysis for ischaemic stroke, although some investigators believe that it does.
Acute ischaemic stroke
Computed tomography
NCCT remains the mainstay of emergency imaging of stroke in order to exclude intracranial haemorrhage. NCCT may also identify other intracranial pathologies that mimic stroke such as tumour or encephalitis.

Ischaemic tissue on NCCT appears hypodense because of a combination of reduced blood volume and cytotoxic oedema. The rate of decline of tissue density is dependent upon severity and duration of ischaemia (fig 3). Within the three hour window for systemic thrombolytic treatment, hypodensity is usually subtle if visible at all. More clearly visible hypodensity should always prompt reappraisal of the history around time of onset, since it suggests a greater duration of ischaemia.

Early ischaemic change (EIC) on NCCT (table 1, fig 4) is a term encompassing changes that almost certainly represent a number of different pathological processes in acute ischaemia whose significance varies. Previous radiological prejudice that CT within a few hours of stroke onset has low sensitivity is unfounded, at least in middle cerebral artery (MCA) occlusions, where EICs are present in around 70% of cases within three hours of onset. While the sensitivity of these changes is compromised by their subtlety, inter-observer reliability can be improved by systematic CT scan evaluation using systems such as the Alberta stroke programme early CT score (ASPECTS). Inter-observer agreement is improved significantly by clinical information being available. A recent large multi-observer comparative study found inter-observer agreement to be greater among neuroradiologists than stroke neurologists or general radiologists.

Most defined EIC on CT, and systems such as ASPECTS are concerned exclusively with stroke caused by occlusion of the carotid artery, the main trunk of the MCA, or the major branches of the MCA. The sensitivity of CT to ischaemia within small penetrating artery territories, the posterior circulation, or scattered multifocal small infarcts that are often encountered in embolic stroke, is not established, and technical limitations mean that CT sensitivity in these scenarios is likely to be poor.

Vessel hyperdensity
Increased density of the MCA or other intracranial vessels on NCCT is indicative of thrombus partially or completely occluding the vessel. The plane of section of CT means that main trunk MCA occlusions are seen as a linear hyperdensity in the sylvian fissure, while internal carotid artery (ICA) or branch MCA occlusions may be seen as hyperdense “dots” in cross section. “False positive” hyperdense MCAs may be seen, particularly in conditions associated with increased haematocrit (for example, polycythaemia) or where hypo-
density of brain parenchyma leads to increased contrast with normal vessels (for example, herpes encephalitis).

Contrast CT
Routine use of contrast enhanced CT is of limited additional diagnostic value in acute stroke and is not recommended, although concerns that blood–brain barrier breakdown would lead to contrast extravasation with risk of stroke worsening are not supported by evidence. Increased conspicuity of ischaemic lesions within six hours of onset on source images from CT angiography (CTA) examinations has been reported, but in effect the high dose contrast administration for CTA yields an image representing cerebral blood volume (CBV). Decreased CBV corresponds with infarct core. CT using routine doses of contrast is not validated in this respect, and in general the use of contrast agents should be to acquire additional information from CTA or CT perfusion (CTP), or to address specific diagnostic concerns about alternative pathologies.

CT angiography
CTA of intracranial vessels can identify the site of vessel occlusion, which may be of value in clinical management decisions. For example, the response to intravenous thrombolytic treatment of tandem occlusions of the ipsilateral ICA and MCA, carotid “T” occlusions, or of basilar artery thrombosis, is poor compared to isolated MCA occlusion, and in many centres is considered a potential indication for rescue therapy with intra-arterial thrombolytics or mechanical embolus removal.

CT perfusion
Multidetector CT scanners allow the acquisition of several slices of brain repeatedly during the intravenous passage of high doses of iodinated contrast medium. The changes in the density–time curve for each pixel allow calculation of a number of parameters reflecting tissue perfusion by mathematical calculations based around the central volume principle. Typical derived parameters include mean transit time (MTT), time to bolus peak (TTP), and CBV, from which cerebral blood flow (CBF) can be calculated (as MTT/CBV). TTP and MTT in the first 3–6 hours after stroke onset are predictive of final infarct volume in the absence of repulsion, and represent tissue at risk. Diminished CBV probably represents failure of autoregulatory responses and therefore tissue infarction. The difference between CBV and TTP or MTT lesions can be taken as an estimate of the “ischaemic penumbra”, the volume of tissue at risk of infarction but still viable (fig 5).^ PCT has been validated against other techniques such as diffusion and perfusion MRI, and quantitative PET. Claims that CTP is itself capable of quantitative blood flow measurement are not universally accepted.

High dose contrast administration for CTA or CTP carries a risk of renal impairment and also necessitates discontinuation of metformin in diabetics to avoid precipitating lactic acidosis, a rare complication. There is also a risk of allergic reactions. The additional time required for the examination, and the need for a patient to lie still during scanning, may present problems with acutely ill patients.

Magnetic resonance imaging
Conventional MRI sequences such as T2 weighted images carry little advantage over NCCT in sensitivity to stroke within the first hours. However, newer sequences, notably diffusion weighted MRI (DWI) and dynamic contrast bolus tracking perfusion MRI (generally referred to as “perfusion weighted imaging”; PWI) offer considerable increases in diagnostic sensitivity and are at present better validated than CT techniques in defining pathophysiological parameters such as tissue viability in acute ischaemic stroke.

DWI is based on the detection of the mobility of water molecules, measured as the apparent diffusion coefficient (ADC) of water. In ischaemia, energy failure compromises cellular ion pumps that normally extrude sodium, with resultant entry of sodium and extracellular water into cells (cytotoxic oedema). This is evident as reduced ADC signal (intracellular water can diffuse less freely than extracellular

Figure 4 Two examples of early ischaemic changes on CT in sub-three hour ischaemic stroke. (A) Acute left middle cerebral artery (MCA) ischaemia with loss of insular ribbon, and hypodensity of tail of lentiform nucleus. (B) Similar changes in a different patient, with hypodensity of entire lentiform nucleus, some hemispheric sulcal effacement, and compression of lateral ventricle caused by hypodensity of caudate head.
space water) and this is processed to show as bright on DWI (fig 6).

DWI is highly sensitive to ischaemia, perhaps greater than 95% within the first hours, and changes are documented within 40 minutes of symptom onset in humans (and within two minutes of onset in animal models). Lesion conspicuity is greatly improved compared to other sequences or imaging modalities (fig 7). DWI changes are not specific, however, and can be seen in focal seizures, encephalitis, and possibly also migraine. Interpretation should also take into account the phenomenon of T2 shine through, a term denoting visibility on DWI of non-acute lesions that are bright on T2 weighted sequences. In order to confirm whether a DWI lesion represents acute ischaemia, an ADC map should be examined to ensure ADC is reduced correspondingly. The increased DWI signal gradually fades over around 7–10 days (dependent on severity of ischaemia and on lesion volume) to an isointense background, so DWI is most useful in differentiating recent from remote ischaemia. Persistence of DWI lesions in some patients after TIA or minor stroke is reported, extending out to several months after symptoms. The significance of protracted DWI lesions is not known.

Perfusion MRI is most commonly applied as bolus tracking during the intravenous administration of gadolinium, with the same principles as those governing CTP imaging allowing the derivation of TTP, MTT, CBV, and CBF. The signal intensity is reduced as gadolinium passes through tissue, rather than the increased density with iodinated contrast in CTP. PWI has the advantage of acquisition of perfusion data for the entire brain, whereas the physical size of the CT detector is limited to smaller volumes (generally 20 mm slice thickness) in most systems in current clinical use. More widely spaced detectors will enable the entire brain to be imaged simultaneously. MRI PWI is also a better validated technique with respect to acute stroke, and is more widely available. Arterial spin labelling, a newer technique that measures perfusion without contrast agents, remains experimental at present.

The DWI–PWI mismatch hypothesis
In the first hours after stroke, DWI signal change is postulated to represent irreversible tissue injury, and therefore indicate the infarct core. By comparison with the perfusion defect on PWI, it is possible to define a “diffusion–perfusion mismatch” that is proposed to represent
an MRI signature of the ischaemic penumbra. In perhaps as many as 70% of acute strokes caused by MCA occlusion imaged within six hours of onset, a DWI–PWI mismatch is present, the PWI lesion (hypoperfused) being larger than the DWI (“infarct core”). Over time, the DWI lesion expands to eventually incorporate most of the PWI defect (fig 8). This evolution over time is consistent anatomically with the progression of penumbra to final infarct. The mismatch appearance is therefore a potential tool to select patients in whom there is evidence of potentially salvageable tissue, either for clinical trials, or for individualised treatment. In the small DIAS trial, intravenous thrombolytic treatment given to patients selected on the basis of a mismatch improved clinical and radiological outcomes even though treatment was between 3–9 hours after stroke onset. Confirmation of the clinical utility of the mismatch hypothesis will come from further trials that are planned or ongoing. Recent studies comparing DWI–PWI mismatch with PET have shown, however, that, while the mismatch tissue overlaps considerably, it does not correspond with PET defined metabolic abnormalities signifying the penumbra, and metabolic patterns within the mismatch region are complex.7

MR angiography (MRA) in the early stages of stroke can identify the site of arterial occlusion in much the same manner as CTA. Time of flight MRA does not require contrast, but is longer to perform, and therefore often difficult in acute stroke patients. Shorter time of flight sequences are of poorer quality. Contrast enhanced MRA improves quality of imaging and shortens imaging time.

Other MR sequences such as spectroscopy are of research value only at the present time.

Patient tolerability may be a limiting factor in acute stroke MRI: in addition to the conventional MR compatibility issues such as ferromagnetic implants, pacemakers, and metallic foreign bodies, duration of examination is a concern since patient monitoring is compromised by the physical constraints of the scanner. While vital signs can be monitored with MRI compatible equipment, it is difficult to deal with a patient vomiting while undergoing an MRI scan. Claustrophobia can be problematic, but more often in convalescent patients and those with minor strokes. Despite these concerns, careful selection of sequences ensures that multiparametric MRI is well tolerated and widely used in acute stroke, and is the investigation of first choice in many stroke centres worldwide.

Single photon emission computed tomography (SPECT)

SPECT blood flow imaging uses tracers tagged to molecules that are delivered to tissue and fixed in proportion to blood flow (for example, hexamethylpropylene amine oxime (HMPAO), ethyl cysteinate dimer (ECD)). This produces qualitative CBF data, and has the advantage that uptake reflects blood flow at the time of injection; the scan itself can be deferred for several hours without affecting the ability to image this snapshot of perfusion. The duration of a full SPECT scan acquisition (around 40 minutes) is too long for routine clinical use, but SPECT has produced valuable research data.

Specific ligands such as the neuronal marker iomazenil or the NMDA receptor tracer CNS 1261 are of research value only at present.

Positron emission tomography (PET)

Multi-tracer PET has been invaluable in defining the pathophysiology of acute stroke, but the technique is confined to research use because of several factors, including the requirement for a cyclotron to produce radiotracers in close proximity to clinical activity, and need for arterial access to produce quantitative data—increasingly difficult in the thrombolytic era.

Both PET and SPECT are unsuited to serial imaging in individual patients because of the radiation dose involved.

Xenon inhalation CT (Xe-CT)

This is a theoretically attractive technique since it is able to produce quantitative CBF data, based on the inhalation of known concentrations of xenon and changes in tissue density that are dependent on tissue concentration. While some useful research data have accrued from Xe-CT, difficulties in administration of xenon (which has anaesthetic properties) in acute patients have limited the use of this modality of investigation.

Figure 6  Apparent diffusion coefficient (ADC) map and diffusion weighted MRI (DWI) of subacute stroke (day 3). Restricted diffusion of water leads to decreased signal on ADC, increased signal on DWI.
Figure 7  Improved lesion conspicuity of DWI in acute ischaemic stroke. (A) DWI and (B) CT in acute right MCA occlusion. CT shows early ischaemic changes (sulcal effacement, loss of grey-white differentiation, compression of lateral ventricle, loss of posterior lentiform nucleus definition, anterior insular ribbon loss). (C) DWI and (D) conventional T2 weighted MRI in multifocal (post-thrombolytic treatment) right MCA infarction.

Figure 8  Diffusion–perfusion mismatch in sub-six hour acute stroke. (A) DWI (degraded by movement artefact) shows signal change confined to basal ganglia (MCA perforator) territory and a small area of abnormal signal in posterior cortical MCA territory. (B) Mean transit time (MTT) perfusion MRI shows prolonged MTT throughout entire left MCA territory. (C) Day 3 infarct on DWI showing expansion of lesion to fill hypoperfused lesion volume.
Transcranial Doppler ultrasound (TCD)

Pulsed wave 2 MHz ultrasound via the temporal bony window in TCD can provide diagnosis of occlusive disease of the major branches of the circle of Willis, and lends itself well to continuous monitoring in the acute phase—for example, during thrombolytic treatment to determine whether (and when) recanalisation occurs.

Recent reports support the proposal that diagnostic TCD may enhance clot lysis by recombinant tissue plasminogen activator (rt-PA) with higher recanalisation rates in the CLOTBUST clinical trial, and are backed by experimental evidence. Higher energy ultrasound systems have led to poorer outcome because of higher rates of intracerebral haemorrhage.

However, TCD is very user dependent, and confident identification of the major intracranial vessels may be difficult, particularly so when one is occluded.

NON-ACUTE STROKE

CT shows structural changes reflecting tissue loss after stroke, but has notable limitations in clinical use: these include poor lesion visibility in the posterior fossa caused by surrounding bone, poor ability to delineate small cortical infarcts adjacent to cerebrospinal fluid (CSF) spaces, and inability to distinguish old ischaemic stroke from old haemorrhage. In addition, in the subacute phase (around 10–14 days after the ictus), the phenomenon of “fogging” may obscure a recent infarct; in some instances the CT may appear normal, even after large hemispheric lesions. The isodense appearance is probably caused by a combination of petechial bleeding, and tissue infiltration by macrophages and other inflammatory cells.

MRI avoids many of these problems, provided some thought is given to the sequences that will provide clinically relevant information: routine T2 weighted fast spin echo, T1 weighted and proton density images share many of the limitations of CT. A CSF suppressed sequence such as fluid attenuated inversion recovery (FLAIR) improves lesion conspicuity, notably for lesions adjacent to CSF spaces, and may distinguish enlarged Virchow-Robin spaces in the basal ganglia and capsule from lacunar infarcts by demonstrating gliotic signal change. FLAIR on some scanners is less sensitive to posterior fossa lesions, where a routine T2 sequence may be superior. Gradient echo MRI is sensitive to haemoglobin degradation products and so will reliably detect old areas of haemorrhage.

Extracranial vascular imaging

Doppler ultrasound of the carotid arteries remains the mainstay of extracranial vascular imaging in the UK since it is non-invasive and available in most hospitals. However, correct identification of the carotids is operator dependent, and grading of stenosis—being dependent upon measurement of flow velocity—may be imprecise. Few departments check the validity of local Doppler estimates of stenosis against more objective techniques, particularly as conventional angiography is now seldom performed even pre-operatively. The anatomical coverage of ultrasound is limited to the region of the carotid bifurcation and therefore omits intracranial stenosis and aortic arch disease. Visualisation of the vertebral arteries by ultrasound is poor and limited in range. Ultrasound may be a reasonable screening test to identify patients with conventionally defined “surgical” carotid stenosis of > 70%. Surgical practice in confirming ultrasound measurements with other techniques is varied, with MRA being the most common second modality. CTA offers greater anatomical coverage than ultrasound, being able to include the vascular tree from the arch of the aorta to the circle of Willis in a single examination. This offers the potential to screen for potentially relevant clinical factors, such as intracranial stenosis (fig 9), that may impact upon the assessment of perioperative risk, and also identify vertebrobasilar disease and patterns of collateral supply that may be clinically important. On the negative side, CTA requires large intravenous contrast doses with attendant risks (see above) and involves processing by a radiologist.
MRA offers similar anatomical coverage to CTA without the need for contrast, if time of flight sequences are used. This may overestimate the degree of stenosis since turbulence in the region of a severe stenosis leads to loss of signal. Signal dropout adjacent to calcific atheroma may also interfere with assessment. Contrast MRA may avoid some of these problems at the expense of being more invasive.

Although intra-arterial angiography is the conventional standard for vascular imaging, concerns over the associated morbidity (probably 1–5% in older patients with atherosclerotic disease) have led to its replacement by the less invasive techniques of CTA and MRA. However, the dynamic quality of angiography does yield information that may be difficult to obtain from other techniques—for example, the immediately characteristic appearance of Moya Moya disease, or characterisation of arteriovenous fistulae. In most cases this technique is now reserved for particular diagnostic or technical difficulties, most of which can be resolved by CTA or MRA.

**TIA (AND MINOR STROKE)**

The majority of patients with true TIA (that is, complete resolution of all symptoms within 24 hours) and minor stroke have delayed presentation and attend as outpatients. Recognition of the high early risk in some patients, and the advent of thrombolytic treatment, is changing the pattern of presentation to a greater proportion being seen early and admitted to hospital, and is also increasing the pressure to investigate rapidly.

NCCT is of limited value, since haemorrhage is very rarely a cause of TIA, and most ischaemic episodes are caused by very small or scattered lesions to which CT has poor sensitivity. Immediate MRI, particularly DWI, performed early is of much greater potential value since the yield of causative lesions is far greater (fig 10). This has both immediate clinical value in assisting localisation—often very difficult based upon history alone, and of considerable importance in decisions about surgical endarterectomy—and has recently been recognised as having prognostic value. Those patients with DWI lesions (particularly with evidence of intracranial vessel occlusions) had a far higher risk of subsequent stroke than those without in a prospective series of TIA and minor stroke patients.

Extracranial vascular imaging is of particular importance in these patients, both because carotid stenosis appears to have a higher early recurrence risk than other stroke aetiologies, and also because endarterectomy has greatest absolute benefit if performed within two weeks of the event.

**Abbreviations**

- ADC: apparent diffusion coefficient
- ASPECTS: Alberta stroke programme early CT score
- CBF: cerebral blood flow
- CBV: cerebral blood volume
- CSF: cerebrospinal fluid
- CT: computed tomography
- CTA: CT angiography
- CTP: CT perfusion
- DWI: diffusion weighted MRI
- ECD: ethyl cysteinate dimer
- EIC: early ischaemic change
- FLAIR: fluid attenuated inversion recovery
- HMPAO: hexamethylpropylene amine oxime
- ICA: internal carotid artery
- MCA: middle cerebral artery
- MRA: magnetic resonance angiography
- MRI: magnetic resonance imaging
- MTT: mean transit time
- NCCT: non-contrast CT
- PET: positron emission tomography
- PWI: perfusion weighted MRI
- SPECT: single photon emission computed tomography
- rt-PA: recombinant tissue plasminogen activator
- TCD: transcranial Doppler ultrasound
- TTP: time to peak
- Xe-CT: xenon inhalation CT

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