Magnetic resonance imaging and ischaemic stroke

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Recent successes in the management of acute ischaemic stroke have emphasized the importance of early diagnosis and treatment. Patients with a 'brain attack' are best managed as a medical emergency. Imaging is vital in identifying infarct as well as tissue at risk and is best done with ultrafast magnetic resonance imaging.

Stroke is the third commonest cause of death in most Western countries and many survivors have substantial disability. Approximately 80% of strokes are thromboembolic in origin. Early spontaneous reperfusion has been shown to be associated with improved clinical state and improved outcome (Barber et al, 1998b).

Published studies of tissue plasminogen activator (tPa) in stroke showed an improved outcome in up to 30% of subjects if the drug was administered within 3 hours of onset of symptoms (Hacke et al, 1995; National Institute of Neurological Disorders and Stroke Study Group, 1995). Clinical trials of anticoagulants, other thrombolytics and a range of neuroprotective agents are currently in progress, following successful trials in animal models. The results in completed trials in humans have so far been disappointing or confusing (Hennerici, 1999).

The aims of these therapeutic manoeuvres are early nutritional reperfusion and neuronal stabilization. There is general agreement, however, that the therapies may benefit only selected subsets of patients. Currently used diagnostic modalities in conventional radiology departments are incapable of separating these subsets. This has led to a demand for a practical, readily available technique for the more sensitive early detection of ischaemic stroke and differentiation between irreversibly damaged and salvageable brain.

THE CURRENT ROLE OF IMAGING IN ISCHAEMIC STROKE

Imaging of any kind in ischaemic stroke is justified only if it is likely to affect clinical management of the patient. Information generally sought from the imaging test includes the following:

1. Confirmation of completed infarct
2. Differentiation of infarct from haemorrhage
3. Exclusion of 'pseudostroke' — clinical presentation resembles that of stroke, e.g. chronic subdural haematoma, slow-growing tumour
4. Detection of multiple strokes in different vascular territories — suggests cardiac rather than carotid source
5. The demonstration of stroke complications, such as haemorrhagic conversion and hydrocephalus
6. Determination of the extent of infarction — administration of thrombolytics is contraindicated if more than one third of middle cerebral artery territory is involved.

Because of its availability, relatively low cost and rapid examination time, computed tomography (CT) has traditionally been the first and usually the only diagnostic modality used. Magnetic resonance imaging (MRI) has been reserved for diagnostically equivocal or difficult cases. However, CT cannot differentiate infarcted brain from potentially salvageable brain and is less sensitive than MRI diffusion-weighted sequences (see below) in the detection of infarction and its extent. Because of the relative subtlety of the signs on CT the presence and extent of infarction was underestimated in the ECASS 2 trial of recombinant tPA (Hacke et al, 1998), leading to an increased rate of haemorrhagic transformation (von Kummer and Forsting, 1993).

CONVENTIONAL MRI STUDIES IN DIAGNOSIS OF STROKE

Conventional MRI studies exploit the conception and widespread distribution of water pro-

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tons in the brain and the relaxation factors T1 (spin lattice relaxation rate) and T2 (spin-spin relaxation rate). T1-weighted studies demonstrate normal and abnormal anatomy particularly well. T2-weighted sequences are particularly sensitive to water distribution. Because almost all pathological processes are associated with abnormal water accumulation, T2-weighted sequences are particularly sensitive to their detection.

Stroke certainly results in the abnormal accumulation of water to produce brain swelling. Cellular swelling, or cytotoxic oedema, occurs within minutes of the ischaemic insult, particularly within the oxygen-dependent neurones. Ischaemic damage to the endothelial cells lining the capillaries of the brain results in loss of the integrity of their normally tight junctions, which is the major component of the blood–brain barrier. Leakage of fluid and electrolytes into the extravascular space results in the extracellular form of oedema known as vasogenic oedema. Because endothelial cells are not as metabolically sensitive as neurones, cytotoxic oedema generally precedes vasogenic oedema.

During the first 6 hours of ischaemic stroke in which cellular (cytotoxic) oedema predominates conventional T1- and T2-weighted MRI studies are often normal. In fact, plain CT is more frequently abnormal than non-contrast enhanced MRI at this stage. As vasogenic oedema develops, MRI T2-weighted sequences detect infarction more sensitively than CT. This is not usually until about 6 hours after the onset of the occlusive event. If a paramagnetic contrast medium such as gadolinium diethylene-amine-pentaacetic-acid (gadolinium DTPA) is administered intravenously, the sensitivity improves as a result of enhanced signal from slow-flowing blood in the infarcted region and leptomeningeal collateral vessels (*Figure 1*). These phenomena last up to 1 week.

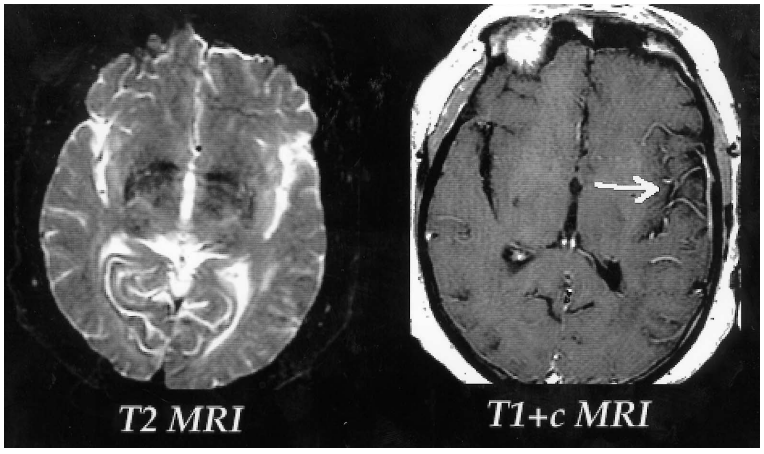

Figure 1. T2-weighted and contrast-enhanced T1-weighted magnetic resonance images (MRIs) (enhanced signal, arrow) of a stroke patient with left middle cerebral arterial territory infarction at 5 hours after stroke onset.

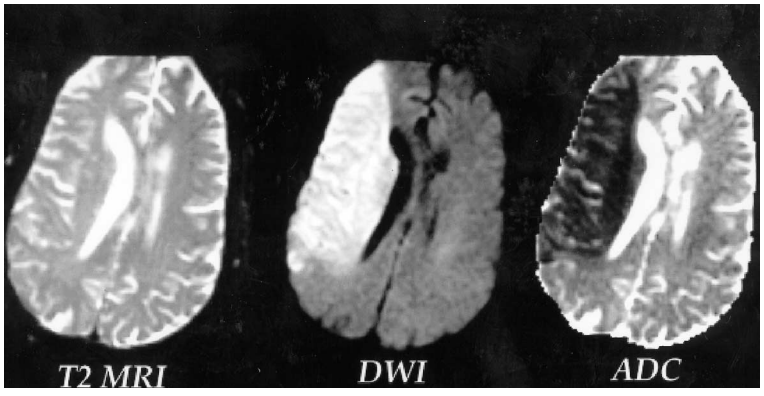

Figure 2. T2-weighted magnetic resonance image (MRI), diffusion weighted imaging (DWI) and apparent diffusion coefficient (ADC) map of a large right middle cerebral artery territory infarction at 4.5 hours after stroke onset.

DIFFUSION-WEIGHTED IMAGING

Ultrafast echoplanar imaging (EPI) MRI sequences (Mansfield, 1984; Edelman et al, 1994) utilize scan times of as little as 30 msec, allowing actual water diffusion (Brownian motion) to be detected and quantified (Moseley et al, 1990a). These sequences can be obtained in standard MRI scanners modified to apply rapid steep magnetic gradients to the imaging field. Top end scanners from most suppliers are now supplied with this hardware as standard proprietary equipment. The images are processed almost instantaneously and are available with standard images for immediate perusal and management decisions.

Diffusion is more rapid in the extracellular space than the intracellular space and more rapid in liquids than solids. Within minutes of experimental arterial occlusion reduced diffusion can be extremely sensitively detected (Moseley et al, 1990b) as a result of failure of the energy dependent sodium pump, which normally maintains a 10:1 ratio of extracellular to intracellular sodium. The immediate result is a shift of extracellular sodium, calcium and water into the intracellular space (cytotoxic oedema) and a reduction in the volume of the extracellular space. Both these factors are thought to contribute to regional reduced diffusion. This is depicted in diffusion weighted imaging (DWI) as a local increase in signal hours before conventional MRI becomes positive (*Figure 2*). Diffusion can be quantitatively evaluated by calculation of the apparent diffusion coefficient (ADC) on a pixel basis.

In clinical practice abnormal signal intensity has been obtained in 100% of acute stroke patients within the first 24 hours. The signal remains hyperintense for a maximum of 2 weeks (Burdette et al, 1998). Acute DWI lesions correlate well with clinical outcome and final infarct volume (Barber et al, 1998a).

If the ischaemic insult is short lived and normal brain perfusion rapidly restored, as is thought to occur during transient ischaemic attacks, diffusion will not be grossly affected and DWI sequences will show no abnormality. DWI is now an extremely sensitive and practical test in the differentiation of stroke from transient ischaemia, migrainous hemiplegia and Todd's palsy after seizures.

PERFUSION IMAGING

The intravenous injection of a bolus of paramagnetic contrast medium causes protons in the immediate vicinity of blood vessels to experience a transiently different magnetic field, resulting in loss of spin phase coherence of resonance and signal diminution. The relative signal loss can be graphed against time on a pixel by pixel basis and a number of indices of cerebral blood perfusion obtained (Belliveau et al, 1990; Kucharczyk et al, 1993).

These include cerebral blood volume (CBV), cerebral blood flow (CBF) and mean transit time (MTT). These maps can be constructed with good spatial resolution (*Figure 3*). More images in unit time can be collected by MRI scanners capable of EPI sequences, but the perfusion images are generally processed off line on an alternative workstation with specialized software and can be available for examination within half an hour.

Acute perfusion imaging lesions correlate well with acute neurological state, as well as clinical outcome and final infarct volume (Barber et al, 1998b).

THE ISCHAEMIC PENUMBRA

Previous electrophysiological (Astrup et al, 1981) and positron emission tomography (Wise et al, 1983) studies have confirmed that many infarcts initially consist of zones of irretrievably damaged brain and other areas in which cerebral blood flow is reduced but the tissue is capable of recovery if early reperfusion is achieved. This latter zone has been entitled the 'ischaemic penumbra', analogous to the half shaded zone surrounding a solar eclipse (Astrup et al, 1981).

In MRI studies, the ischaemic penumbra is thought to be that portion of the brain with compromised blood flow, as depicted by perfusion imaging, minus the zone of reduced diffusion, as seen in DWI scans (*Figure 4*). In short, it is a region with perfusion deficits but no DWI abnormalities (Barber et al, 1998a). Studies designed to more accurately define the threshold of perfusion and diffusion abnormalities in stroke and the ischaemic penumbra are under way.

MAGNETIC RESONANCE ANGIOGRAPHY

A variety of subtraction methods is available for differentiating rapidly moving protons in blood from the relatively static protons in brain parenchyma. The intracranial vertebral, basilar and internal carotid arteries and their first order branches can be depicted in as little as 2 minutes using standard MRI sequences. Occlusions of major intracranial vessels can be non-invasively demonstrated (Masaryk et al, 1989) (*Figure 5*). An ischaemic penumbra is more likely to be present in the presence of occlusion (Rordorf et al, 1998).

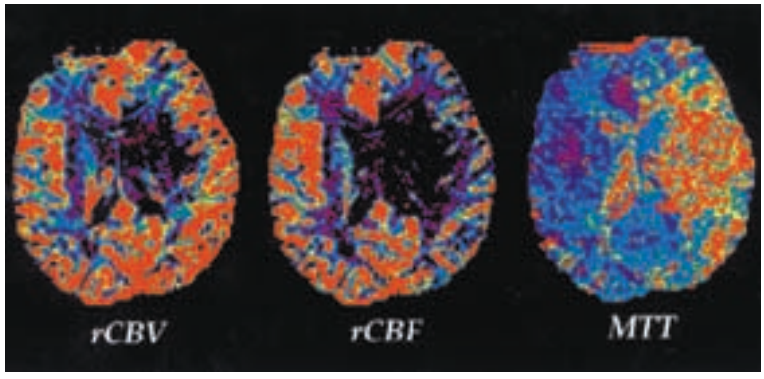

Figure 3. Relative cerebral blood volume (CBV), cerebral blood flow (CBF) and mean transit time (MTT) maps of a left middle cerebral artery territory infarction at 5 hours after stroke onset.

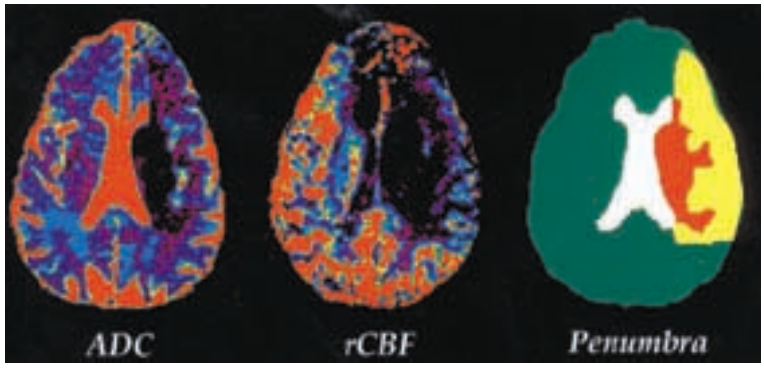

Figure 4. Apparent diffusion coefficient (ADC) and relative cerebral blood flow (CBF) maps of a left middle cerebral artery territory infarction at 4 hours after stroke onset. The right-hand image delineates the infarct core (red), ischaemic penumbra at risk of infarction (yellow) and normal tissue (green).

Figure 5. Phase-contrast magnetic resonance angiography of the same stroke patient as in Figure 1.

MAGNETIC RESONANCE SPECTROSCOPY

Nuclear magnetic resonance spectroscopy (MRS) in vitro has been available as a biochemical tool for the identification of a variety of metabolites in tissue from soon after the discovery of the phenomenon of nuclear magnetic resonance in 1946. The technique, with the name shortened to MRS, has been used in vivo from as early as 1983 in the identification of phosphorus containing molecules, but is limited by the relative insensitivity of phosphorus compared with hydrogen, which is both highly sensitive and ubiquitous within the brain.

MRS can be performed on the same magnets used for MRI, after the magnets have been 'shimmed' or adjusted to the degree of homogeneity required for spectroscopy. Protons in different chemical environments experience slightly different magnetic fields and thus spin or process at very slightly different frequencies. The shift in parts per million relative to tetramethylsilane proton spin frequency identifies key metabolites.

The results are displayed as a graph of signal strength *vs* chemical shift (*Figure 6a*). In the stroke context the most important metabolites are N-acetyl-aspartate (NAA), which is found almost entirely in neurones, and lactate, a measure of anaerobic metabolism (Ricci, 1998). Infarcted tissue shows initial rapid increase in lactate levels, followed by marked loss of all metabolites, particularly NAA (Moseley et al, 1990a) (*Figure 6b*). Early MRS studies of stroke in animal studies suggest that tissue in the ischaemic penumbra may show lactate elevation, but no or minimal reduction in NAA (Gillard et al, 1996) (*Figure 6c*).

CONCLUSIONS

The first reported success of thrombolysis in the treatment of ischaemic stroke and the very real prospect of other thrombolytics and neuroprotective agents proving effective has already changed the clinical management of ischaemic stroke. Earlier clinical and radiological diagnosis has become vital if active therapy is to be initiated in the subset of patients most likely to benefit. Magnetic resonance techniques, all of which can be utilized in a scanning session of approximately 35 minutes, will be central to acute stroke management. DWI detects the presence and

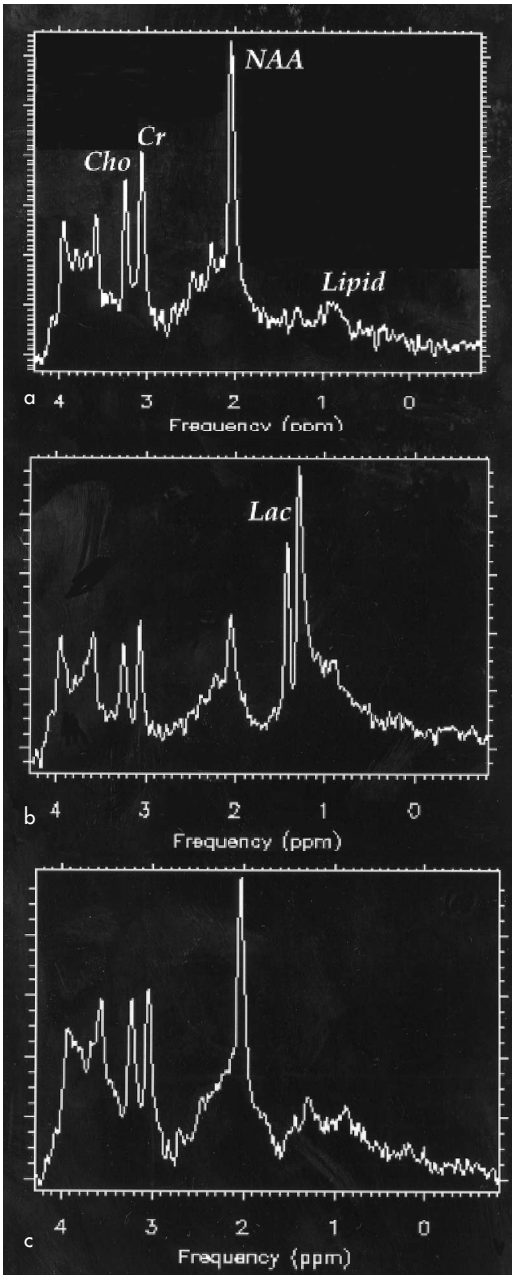

Figure 6. In vivo 1H MRS acquired with TE=35 ms in (a) normal tissue, (b) infarct core, and (c) ischaemic penumbra.

extent of infarcted tissue within minutes of vessel occlusion. Perfusion imaging rapidly provides an index of CBF with excellent spatial resolution.

The presence of an ischaemic penumbra can be deduced by demonstrating that the area of compromised perfusion is greater than that in which impaired diffusion indicates irreversible infarction. MRS may provide an alternative method of identification of an ischaemic penumbra by its ability to detect increased lactate as an indicator of anaerobic metabolism in the presence of normal NAA. These techniques can equally well be applied to non-invasive serial monitoring of the effectiveness of the various therapeutic regimens. **HM**

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KEY POINTS

- Recent success in the treatment of acute stroke with thrombolytic drugs has emphasized the need for a readily available, non-invasive test for the detection of the presence and extent of acutely infarcted brain.
- Both computed tomography and conventional magnetic resonance imaging (MRI) have limited sensitivity in the diagnosis of acute stroke and cannot identify brain tissue at risk.
- The refinement of ultrafast MRI techniques has facilitated the diagnosis of infarction within minutes by the detection of reduced water diffusion in the infarcted zone.
- Perfusion deficits can be detected and mapped by rapid MRI after the injection of a bolus of paramagnetic contrast media.
- The tissue at risk, named the ischaemic penumbra, is identified as that portion of the brain with compromised perfusion but no diffusion restriction. The ability to rapidly determine the presence or absence of an ischaemic penumbra is likely to determine whether or not active therapy is likely to be effective.