

Brain attack: a new approach to stroke

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ABSTRACT – ‘Brain attack’ is a new term to describe the acute presentation of stroke which emphasises the need for urgent action. The article describes the basis for this new approach to acute stroke treatment. Rational treatment requires individual causes of stroke to be identified early and treatment targeted at the mechanism. Acute stroke treatment aims to preserve the ischaemic penumbra, protect neurons against further ischaemia and enhance brain plasticity to maximise recovery. There is a strong evidence base supporting the routine use of aspirin, but not heparin, in acute ischaemic stroke. There is also convincing evidence supporting intravenous thrombolysis using recombinant tissue plasminogen activator in selected patients within 3 hours of stroke onset. Surprisingly, as many as 33% of suspected-stroke patients arrive in Accident & Emergency departments in the UK within 3 hours of onset. New techniques in MR imaging, particularly diffusion weighted imaging, are transforming the approach to diagnosis of acute stroke. Although neuroprotective drugs have proved disappointing, active neuroprotection in acute stroke should include control of blood pressure within certain limits, antipyretic therapy, maintenance of blood glucose, and early feeding and fluid replacement. Surgical hemicraniectomy should be considered in patients with malignant cerebral oedema. There is good evidence that the best way to enhance recovery from stroke is to admit the patient to a stroke unit. To enable patients to benefit from the early active approach outlined in the article, the following are needed: the development of acute stroke units; imaging protocols; and education of patients, general practitioners and the ambulance services. Stroke care has become a specialised field, requiring input from stroke physicians, as well as the multidisciplinary rehabilitation team. The British Association of Stroke Physicians (BASP) has therefore developed a curriculum which is designed to lead to the development of a new sub-specialty of stroke medicine.

KEY WORDS: stroke, brain attack, cerebral ischaemia, ischaemic penumbra, thrombolysis, neuroprotection, plasticity, stroke unit, British Association of Stroke Physicians

The end of the twentieth century saw a transition in the approach to the treatment of acute stroke from one of therapeutic nihilism to enthusiasm for a new approach. Stroke should now be seen as an emergency, warranting urgent assessment, investigation and treatment. The positive results of major randomised trials of treatment, particularly thrombolysis, have played a major part in stimulating this new approach. This article describes the current and future basis for this new approach to acute stroke treatment, including advances in the understanding of the pathophysiology of stroke, the application of the principles of evidence-based medicine and the use of new magnetic resonance (MR) imaging technology. These advances have transformed the clinical approach to stroke and argue strongly for the development of the sub-specialty of stroke medicine.

New terminology

Stroke is defined, in terms of duration, as an acute focal deficit resulting from vascular disease that lasts for more than 24 hours. However, this definition implies that a patient cannot be considered to have had a stroke until at least 24 hours have elapsed, suggesting an outdated approach of expectant inactivity while awaiting the inevitable outcome. Brain attack is a new term to describe the acute presentation of stroke, which removes the requirement for a delay of 24 hours and emphasises the need for urgent therapeutic action. The term also emphasises that when a patient presents with symptoms suggesting stroke, other diagnoses need to be considered, eg hypoglycaemia. We should completely abandon the old-fashioned term cerebrovascular accident, because it implies that the stroke is a chance event for which little can be done. It is important to recognise that the term stroke describes the clinical presentation, and should not be regarded as a sufficient diagnosis on its own. It requires a description of the anatomical territory involved, the underlying pathology (ie infarction or haemorrhage), the mechanism (eg embolism), the underlying aetiology (eg atherosclerosis) and the underlying risk factors (eg smoking). There is a wide variety of underlying pathological causes and mechanisms of stroke, and it is clear that rational treatment requires the individual causes to be identified early so that treatment can be targeted at the mechanisms. However, until

now, most acute treatment trials have assumed that the majority of strokes are caused by thromboembolism from atherosclerotic plaque or cardiac sources. In this article I will concentrate on ischaemic stroke, although many of the treatments, particularly neuro-protection and rehabilitation, apply equally to cerebral haemorrhage.

Ischaemic penumbra

The symptoms of stroke result from ischaemia, irrespective of the underlying cause and mechanism. New drug treatments for stroke are derived from an understanding of the pathophysiology of cerebral ischaemia, and illustrate the fruits of neuroscience research started over 20 years ago. It has been shown that where the infarction occurs depends critically on the level of blood flow in the ischaemic area of brain¹. The size of the eventual infarct depends on the size of the vessel occluded, the extent of collateral supply, whether there is reperfusion as a result of spontaneous or therapeutic thrombolysis, and, if reperfusion does occur, the duration of the ischaemia. Early animal studies showed that the fate of neurons in an animal model of stroke depended on the extent to and duration for which blood flow was reduced in an ischaemic area². Normal cerebral blood flow is about 50 ml/100 g/minute in the cortex, but it is striking that the brain can tolerate a reduction in blood flow to about 20 ml/100 g/minute without obvious adverse effects. This is because haemoglobin provides a good reserve of oxygen, and the reduction in blood flow is accompanied by an increase in oxygen extraction. Below about 20 ml/100 g/minute neurons stop working, so that, in animal experiments, evoked potentials disappear. In a patient, we would expect a focal deficit to develop because the neurons are not working. At blood flows of below about 10 ml/100 g/minute there is rapid membrane failure: potassium leaks out of the cells, while water and calcium enter. This results in cell death within about 10 minutes of ischaemia. In contrast, at blood flows between about 10 ml/100 g/minute and 20 ml/100 g/minute the membranes remain intact: there is no potassium leakage, and the cells remain alive for some time, although they are not able to generate electrical activity. Restoring blood flow to areas with flows between 10 ml/100 g/minute and 20 ml/100 g/minute allows neuronal activity, as represented by evoked potentials, to recover. This has led to the concept of the ischaemic penumbra: an area of brain surrounding the core of an infarct in which intermediate levels of blood flow can be salvaged by treatment. The core of the infarct will die within a few minutes if blood flow has fallen below the threshold of 10 ml/100 g/minute, and it is unlikely that we will ever be able to prevent cell death in the core unless we can pretreat patients at high risk of stroke.

Animal studies have demonstrated a complex sequence of events after cerebral ischaemia, which lead to cell death in both the core and the penumbra³. One fundamental feature of this ischaemic cascade appears to be the failure of the calcium channels to maintain calcium balance. The rise in intracellular calcium activates enzymes that destroy the cell membrane and result in free-radical production. Neuroprotective agents, which

Key Points

Acute stroke treatment aims to preserve the ischaemic penumbra, protect neurons against further ischaemia and enhance brain plasticity to maximise recovery

There is a strong evidence base supporting the routine use of aspirin; intravenous thrombolysis in selected patients within 3 hours of stroke onset; and admission to a stroke unit

Neuroprotection in acute stroke should include maintenance of physiological variables, and early feeding and fluid replacement. Surgical hemicraniectomy should be considered in patients with malignant cerebral oedema

New techniques in MR imaging are transforming diagnosis

Stroke care has become a specialised field, requiring input from stroke physicians as part of a multidisciplinary team. The British Association of Stroke Physicians has developed a curriculum designed to lead to the development of the sub-specialty of stroke medicine

block one of the stages of the cascade, reduce the size of infarction in animal models. However, to reverse the chemical process leading to cell death, and save the penumbra, requires rapid treatment. In animal models, such treatment has to be given within about 2 hours of the onset of ischaemia if the outcome is to be improved. In humans, this interval may be a little longer in some patients, but the evidence from thrombolysis trials is that the penumbra lasts no longer than 3 hours in the majority of patients.

Antithrombotic treatments

The process that initiates thrombosis in patients with atherosclerotic stroke is likely to be plaque rupture. This stimulates platelet aggregation, which leads to thrombosis and then ischaemia. Atherosclerosis also leads to vessel stenosis, which may reduce blood flow and contribute to ischaemia. However, it is likely that the main mechanism by which stenosis leads to stroke is by causing turbulence, which itself activates platelets. Similar mechanisms may be involved in cardioembolic stroke. It is therefore logical to investigate the use of antiplatelet agents and anticoagulation in acute ischaemic stroke. As well as interfering with thrombus generation in the cerebral circulation, these might also prevent deep vein thrombosis and pulmonary embolism. Aspirin has been tested in two very large multi-centred randomised trials, the International Stroke Trial (IST)⁴ and the Chinese Acute Stroke Trial (CAST)⁵. A total of 40,000 patients were included in these trials, illustrating the number of patients needed to show effective treatments in stroke. Both trials showed a small benefit of aspirin given within 48 hours of stroke, primarily in preventing early recurrence⁶. Overall, there was a significant reduction in the incidence of recurrent ischaemic stroke of about 1% in treated patients, which caused

a similar benefit in long-term outcome. Thus, treating 100 patients with aspirin within 48 hours of onset will save one patient from early death or residual disability. This may seem a very small benefit, but as there are about 100,000 ischaemic strokes annually in the UK, aspirin (300 mg once daily) given within 48 hours of onset will save 1,000 patients from death and disability every year, at a very small cost. This requires all patients to have a CT scan, preferably on admission but certainly within 48 hours, because aspirin is contraindicated in cerebral haemorrhage. Other antiplatelet regimes might be more effective in acute stroke but have not yet been tested extensively.

In many parts of the world, anticoagulants, particularly intravenous heparin, are used extensively in the acute treatment of ischaemic stroke on the assumption that they must be beneficial. However, several randomised trials of both standard and low-molecular-weight heparin have shown no overall benefit in acute stroke⁶. This is primarily because any benefit of heparin in reducing early recurrence is balanced by an increased risk of intracerebral haemorrhage and secondary haemorrhage into the infarct. Heparin treatment should, therefore, be limited to selected cases. My own practice is to use it acutely in stroke only in patients who have had a small infarct associated with a definite cardiac source of embolism, those with demonstrated thrombus in the carotid- or vertebral-artery system, in acute arterial dissection and in patients with cerebral venous thrombosis. However, none of these indications are supported by randomised-trial data.

The trials of aspirin and anticoagulation were rather disappointing. In contrast, the positive results of the National Institute of Neurological Diseases and Stroke (NINDS) study have revolutionised the approach to stroke treatment in forward-looking centres. The NINDS trial examined the benefits of intravenous alteplase, a recombinant tissue plasminogen activator⁷. The trial was conducted in 48 hospitals in North America, and included 624 patients randomised within 3 hours of stroke onset. This is still the only published trial to have addressed the narrow window of opportunity, suggested by animal studies, during which there is likely to be a salvageable penumbra. All patients had CT and blood tests before randomisation; if necessary, blood pressure was carefully controlled using intravenous agents. The results were impressive. The outcome was statistically significantly better in the alteplase-treated patients, with 52% of patients making a good recovery at 3 months (Barthel index, 95 or 100), compared with 38% of those treated by placebo. As expected, the risk of intracranial haemorrhage after treatment was higher in the alteplase-treated group (6%, compared with 1% in the placebo group). However, this increase in intracranial haemorrhage did not translate into an overall increase in the death rate, which was very similar in both groups.

In contrast to the strongly positive results of the NINDS study, the two European Co-operative Acute Stroke studies (ECASS I and ECASS II) failed to show a statistically significant difference in the primary analysis between placebo and intravenous-alteplase treatment^{8,9}. Both showed a trend towards benefit, which reached significance in ECASS I when patients with

prespecified exclusion criteria, particularly CT changes of infarction, were excluded. ECASS II also showed a significant benefit in a *post hoc* analysis examining the numbers of patients who recovered without serious disability. The main difference between the NINDS and the ECASS trials was that the latter allowed patients to be randomised within 6 hours of onset and included very few patients within the 3-hour window. The results in the patients in all three trials randomised within 3 hours of stroke onset have been combined in a meta-analysis¹⁰. This has confirmed a highly significant benefit to intravenous-alteplase treatment at under 3 hours, with a significant reduction in unfavourable outcomes. In keeping with the proposal that the difference between the trials was primarily related to differences in the interval to treatment, a fourth trial of intravenous alteplase in acute stroke, the Alteplase Thrombolysis for Acute Non Interventional Therapy in Ischaemic Stroke study (ATLANTIS), which randomised patients between 3 hours and 5 hours after onset, had a neutral result¹¹. A meta-analysis of patients randomised in ECASS I, ECASS II and ATLANTIS more than 3 hours after onset of stroke confirmed no significant benefit of late treatment, although there was a trend to benefit (G Ford, personal communication). Arterial thrombolysis, which has the advantage of targeting sites of persistent occlusion, has been shown to be beneficial for up to 6 hours after stroke onset, but is limited in applicability¹². Therefore, it is possible that some patients will benefit from intravenous thrombolysis between 3 hours and 6 hours after stroke onset, if they have a persisting penumbra. Another ongoing trial of intravenous thrombolysis delivered less than 6 hours after stroke onset, the International Stroke Trial 3 (IST-3), will provide data about which patients benefit most from thrombolysis and which are most at risk from iatrogenic haemorrhage. Alteplase has a licence for use in the treatment of acute stroke in the USA and Canada, but discussions are continuing about the granting of a European licence.

Many hospital physicians think that thrombolysis is impractical because they never see patients within 3 hours of stroke onset. In fact, a remarkable number of patients in the UK get to hospital within 3 hours. The ASIST study, which was carried out in 13 district general hospitals in the UK, recorded the time at which patients arrived in accident and emergency departments, and discovered that 33% of suspected-stroke patients arrive within 3 hours of stroke onset and 26% arrive within 2 hours (unpublished observations). However, few were examined and none were scanned within these time periods. There is clearly a potential benefit to patients from introducing thrombolysis in centres that have not yet done so. This requires the development of acute-stroke response teams and imaging protocols. It is essential that patients considered for thrombolysis are assessed by an experienced team familiar with the early diagnosis of stroke, the interpretation of early imaging in stroke and the inclusion and exclusion criteria for thrombolysis. CT-scanning departments need to be reorganised to accept emergency requests in stroke, and treatment needs to be administered as early as possible within the 3-hour time window. It is essential to maintain a low rate of intracranial haemorrhage, which requires

Careful early monitoring of the patient and a prospective audit of the results. Enthusiastic centres are showing that up to 10% of acute-stroke patients can be treated with thrombolysis. To reach this target, education of patients, general practitioners and the ambulance services about the symptoms of stroke and the need to respond quickly is needed. This requires a change in ambulance priorities, so that stroke is responded to as quickly as a myocardial infarct and the patient is taken direct to an acute-stroke service. It has been shown that this can be achieved by the ambulance service taking suspected stroke patients directly to an acute-stroke unit, bypassing assessment in an accident and emergency department, which often leads to delay¹³.

Advances in MR Imaging

New techniques in MR imaging are transforming the approach to diagnosis in acute stroke in those centres where the new MR sequences are available¹⁴. In the future it is likely that these new MR techniques will help us to select patients for thrombolysis and other acute treatments. The most helpful new MR technique is diffusion-weighted imaging (DWI). This measures the diffusion of free water molecules in the brain, mainly in the extracellular space. In acute ischaemia the cells swell and the space available for diffusion is restricted. Acute infarction produces a very bright signal in the area of ischaemia on DWI within a few minutes of onset, in contrast to CT, which is often normal in the first few hours after onset or shows only subtle abnormalities visible only to experienced observers. This 'light-bulb sign' on DWI is easily seen by inexperienced observers (Fig 1). In general, diffusion in areas of infarction is restricted for about 14 days after the onset of stroke. Thereafter, presumably as the cell walls lyse, diffusion is enhanced. This reversal of signal intensity on DWI allows acute and chronic infarcts to be easily distinguished, which is particularly useful in patients with more than one area of abnormality on conventional imaging. The other new MR-imaging modality that is likely to prove particularly useful in selecting patients for treatment is

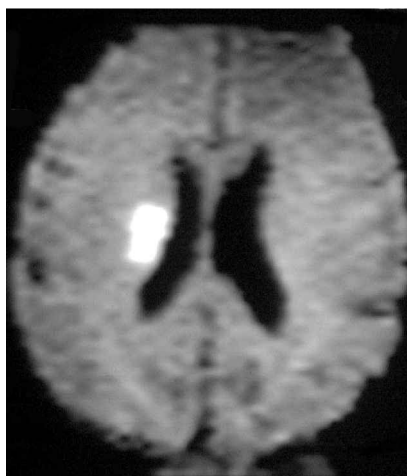


Fig 1. Diffusion-weighted MR image showing an acute infarct as a bright area ('light-bulb sign').

perfusion imaging. In this technique, the transit time of intravenously injected gadolinium can be mapped to produce images of cerebral blood volume and perfusion. In some cases, perfusion imaging may show a much larger area of reduced blood flow than is shown by DWI. This mismatch between a large area of reduced perfusion and a smaller area of cell death, indicated by the abnormal DWI signal, may indicate the presence of a penumbra and tissue at risk of infarction. Areas showing an abnormal DWI signal are usually destined to permanent infarction, while thrombolysis with early reperfusion has been shown to prevent extension of the area of infarction throughout the territory shown to be ischaemic on perfusion imaging¹⁵. DWI and perfusion imaging combined with intracranial MR angiography (multimodal imaging) can thus elucidate the pathophysiology of acute stroke, improving our understanding of the mechanisms of stroke, and may help to select appropriate patients for thrombolysis. These new MR techniques are already being used in clinical trials of new agents to select patients with perfusion–diffusion mismatch for neuroprotective treatment.

Neuroprotection

The concept of neuroprotection plays an important part in the new approach to stroke. A large number of neuroprotective drugs have been tested in randomised trials but, despite major benefits in animal models of stroke, none have proved effective in human stroke to date¹⁶. It is likely that the failure of neuroprotective agents in clinical trials reflects the fact that none of the human studies have appropriately mimicked the circumstances in which neuroprotective agents have been shown to work in animals. For example, none of the clinical trials have limited randomisation to patients within 2 hours of stroke onset, which has been necessary to demonstrate benefit in animal models. It is also logical to combine thrombolysis with neuroprotective agents.

Although, as yet, no neuroprotective drugs have been shown to be effective in acute ischaemic stroke, the active management of acute stroke includes a number of measures to protect the brain from further ischaemia and extension of infarction. For example, we use appropriate treatment to maintain systolic blood pressure within a given range, give antipyretic drugs and keep blood glucose between 4 mmol/l and 10 mmol/l. We also feed and replace fluid in acute-stroke patients as soon as they arrive in hospital. This requires early assessment of swallowing ability, with feeding and fluid replacement given by nasogastric tube if swallowing is impaired. We also sit patients up and mobilise them early. None of these measures are yet supported by the results of randomised clinical trials, but there are strong arguments in favour of their neuroprotective value.

Surgical craniectomy is an aggressive neuroprotective treatment, which we have recently applied with impressive results. Malignant cerebral oedema usually develops after occlusion of the middle cerebral or internal carotid artery in younger patients with large areas of infarction. Untreated, malignant cerebral oedema leads to swelling of the hemisphere with brain-stem compression, progressive coma and, often, death. Removal

of a large portion of the skull vault allows the brain to expand externally, preventing compression and secondary ischaemia of the surrounding brain, and limiting extension of the area of infarction and brain-stem coning. A case series of craniectomy in selected patients with malignant middle cerebral artery infarction has shown a large reduction in mortality and a slightly better outcome in survivors¹⁷.

If reperfusion achieved using thrombolytic therapy is beneficial, it is logical to consider the role of reperfusion achieved using surgery or endovascular techniques in carotid stenosis, which is responsible for about 10% to 20% of strokes. Currently, treatment for carotid stenosis is indicated in patients with recent symptoms associated with severe carotid stenosis to prevent recurrent stroke, but it is usually recommended that there should be a delay of a few weeks in patients with significant infarction. The Carotid and Vertebral Artery Transluminal Angioplasty study (CAVATAS) has recently reported very similar major risks and long-term efficacies of both endovascular treatment and surgery for carotid stenosis, but endovascular treatment avoided much of the minor morbidity of surgery¹⁸. Improvements in carotid stenting technology, particularly the introduction of protection balloons placed distally in the carotid artery to provide neuroprotection during stenting, will almost certainly reduce the risk significantly. At present, both surgery and endovascular techniques are thought to be too hazardous in acute stroke, but this may not be the case if they could be applied within a few hours of stroke onset. Further clinical trials of carotid stenting are required, but in the future it is likely that carotid stenting to improve cerebral perfusion, perhaps in combination with intra-arterial thrombolysis, will have a part to play in the acute treatment of stroke, as well as in long-term stroke prevention.

Enhancing plasticity

Almost all patients who survive a stroke show a variable degree of recovery over time. There is considerable evidence that much of this recovery occurs as a result of the reorganisation of neural activity. The process underlying functional reorganisation is known as neural plasticity. We are beginning to understand the process of neural plasticity by using functional imaging techniques, but we currently know little about how to manipulate the process directly, which is an important avenue for future research¹⁹. On the other hand, there is good evidence that the best way to enhance recovery from stroke is to admit the patient to a stroke unit. Randomised trials have shown that organised stroke-unit care can produce significant benefits to patients compared with routine care on a general medical ward²⁰. Part of the benefit is due to a reduction in mortality, but there is also a significant reduction in disability. A meta-analysis of the stroke-unit trials has shown that for every 100 patients receiving stroke-unit care, three additional patients survive, three avoid long-term institutional care and an additional six return home compared with patients receiving routine medical care²⁰. The benefits of stroke-unit care are very similar in males and females, and are independent of the age of the patient and the

severity of the stroke. It is, therefore, clear that all stroke patients should be admitted to an organised stroke unit. However, organising a stroke unit is not just a matter of putting beds together and labelling them as a stroke unit. Successful stroke units have a number of characteristics, including physicians and nurses interested in stroke and a multidisciplinary team whose work is coordinated by at least weekly multidisciplinary meetings.

For patients to benefit from the early aggressive approach I have outlined in this article they must be admitted to an acute-stroke unit immediately after the onset of stroke. At University College London Hospitals we have developed an acute brain injury unit, which takes acute stroke and head-injury patients directly from the accident and emergency department, with the aim of providing acute assessment, neuroprotective treatments and early therapy to enhance plasticity. The highest standard of medical care for stroke patients must be provided by a team including neurologists, care-of-the-elderly physicians, neurosurgeons, neurorehabilitation experts and access to cardiology as well as nurses, therapists and psychologists. This allows patients immediate access to specialised assessment and treatment, as well as providing seamless transfer to long-term rehabilitation if necessary.

Introducing change

How should we ensure that patients benefit from these advances? It is clear that we need to develop comprehensive services for all stroke patients. Fortunately, this concept has recently been supported by the National Service Framework for Older People, which has made stroke a key target for NHS service development in England, and requires all hospitals caring for stroke patients to develop a specialised stroke service according to the Royal College of Physicians' clinical guidelines for stroke care. This article illustrates the extent to which stroke care has become a specialised field, requiring input from stroke physicians as well as the multidisciplinary rehabilitation team. The Stroke Association recently carried out a nationwide survey and reported that only about a quarter of stroke patients in the UK are admitted to a specialised stroke unit, and only about 3% of patients are seen by a physician who admits to having an interest in stroke. This is clearly not in the best interests of the patients, and many more stroke physicians are needed if patients are going to benefit from specialised care. The recently established British Association of Stroke Physicians (BASP) aims to address this need by encouraging physicians to develop a specialised interest in stroke. BASP has recently developed a modular curriculum for subspecialty training in stroke medicine, which will be open to specialist registrars from a variety of other specialties, reflecting the membership of BASP, which includes neurologists, care-of-the-elderly physicians, clinical pharmacologists and rehabilitation experts interested in stroke. It is hoped that many specialist registrars will be attracted to this new subspecialty, which incorporates the approach outlined in this article.

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