REVIEWS

Stroke—a medical emergency

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Abstract

Stroke is the third leading cause of death and number one cause of disability in industrialised countries. A number of new therapeutic approaches are currently in development for use in the acute phase of ischaemic stroke and all trials have, to date, demonstrated the importance of early diagnosis and subsequent initiation of treatment. It is well known that, for most patients, there is a long delay between the onset of symptoms and the start of treatment. A number of factors are responsible for this time delay: signs and symptoms often go unrecognised by patients, relatives, and bystanders and, unlike trauma or myocardial infarction, stroke is not given a high priority by medical staff. Studies into the pathophysiology of acute ischaemic stroke have indicated that treatment options are likely to be optimised when early signs of stroke are recognised and treatment is initiated within six hours of symptom onset. Although a small number of stroke patients are treated as emergencies and attended to by the emergency medical services within this time window, this number could easily be increased by intensified public and emergency personnel education. In the future, it is hoped that treatments which must be administered within the first few hours of acute stroke will be able to be initiated by the emergency medical services. In the same way that hospitals are notified and prepared in advance to receive trauma victims, early notification by the emergency medical services about stroke patients would enable stroke teams to be present at admission, thus improving the likelihood of a better outcome for patients.

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Epidemiology

Stroke is one of the world's major healthcare problems. Between 1985 and 1987 the stroke component of the World Health Organisation Monitoring Trends and Determinants in Cardiovascular Disease (WHO MONICA) project registered 13 597 stroke events in a total background population of 2.9 million

people. In this study, the annual age standardised stroke incidence rates per 100 000 ranged from 101 to 285 in men and from 47 to 198 in women.¹ In Germany, the overall incidence of stroke is estimated to be 127 000/year, 75% of which are first strokes.² Despite some progress in treatment and prevention, stroke remains the third leading cause of death in industrialised countries, often resulting in long term dependency and, concomitantly, enormous treatment costs. In the US, for example, costs due to medical care and lost productivity are estimated to be up to \$ 30 billion/year.³

Classification of stroke**ISCHAEMIC STROKE**

Thromboembolic events and occlusions cause 70–80 % of all strokes, termed ischaemic stroke. Cerebral angiography performed within the first 24 hours after onset of neurological symptoms shows a corresponding vascular occlusion in about 80% of patients.⁴ Thrombi may originate in atherosclerotic lesions of intracranial arteries, or more commonly emboli enter the intracranial circulation from extracranial sources such as atherosclerotic lesions of the carotid bifurcation, aortic arch, or heart.

HAEMORRHAGIC STROKE

Intracerebral haemorrhage is the cause of up to 20% of all strokes. It can be caused by the rupture of cerebral aneurysms or long standing hypertension. Haemorrhagic strokes are far more lethal than ischaemic strokes, causing death in more than 50% of patients.

TRANSIENT ISCHAEMIC ATTACK (TIA)

TIA's are another type of cerebrovascular disease. They are by definition temporary focal neurological deficits that resolve completely within 24 hours. TIA's are often difficult to distinguish from other stroke events.

Despite the existence of several scoring systems and scales,^{5,6} which aim to distinguish between ischaemic and haemorrhagic stroke and which try to predict the outcome of stroke patients, the specificity for the differentiation between ischaemia and haemorrhage is less than 80%. Because of this, diagnosis and prognostic information can at present only be obtained from computed tomography.

The present article focuses on the necessity and rationale for treating acute ischaemic stroke as an emergency.

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Figure 1 Some aspects of the ischaemic cascade.

Pathophysiology of acute ischaemic stroke

BIOCHEMICAL IMPACT OF REDUCED CEREBRAL BLOOD FLOW AND ISCHAEMIA

Although collateral vessels near the cerebral artery occlusion may help to prevent total ischaemia, cerebral blood flow (CBF) close to the infarct zone may still be insufficient to maintain neuronal function and viability. In healthy individuals and in regions unaffected by ischaemia, CBF is maintained at 50 ml/min/100 g.⁷ A regional CBF (rCBF) of at least 15 to 18 ml/min/100 g of brain tissue is required to maintain normal electrical activity. In the zone of infarction, there is usually a rCBF of less than 10 ml/min/100 g, while the penumbra (area surrounding the infarct) have a rCBF of less than 20 to 30 ml/min/100 g.

Ischaemia induces complex metabolic events that result in irreversible damage and neuronal death. After the reduction of CBF, the electrolyte concentration between the intracellular and extracellular spaces changes: voltage sensitive sodium and calcium channels are activated, and the release of the excitatory neurotransmitter amino acid, glutamate, is increased. Subsequently, *N*-methyl-D-aspartate (NMDA) and α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors are activated mediating a massive increase of sodium and calcium influx into the cells. During ischaemia, highly reactive free oxygen radicals are generated which degrade structural molecules, damage cellular membranes, and liberate more free radicals in a chain reaction. The nitric oxide (NO) pathway is also activated. NO promotes oxidative damage by reacting with superoxide anion to form the strong oxidant peroxynitrite, and by perturbing iron metabolism. NO can produce DNA damage and trigger programmed cell death (fig 1).

REPERFUSION INJURY

Cellular necrosis initiated by acute ischaemia may be compounded by rapid reperfusion of ischaemic brain tissue (that is after restoration of blood flow). Animal models have shown that the presence of molecular oxygen in the blood may result in increased concentrations of superoxide and hydroxyl free radicals, in addition to causing an increase in the rates of lipid peroxidation and membrane dissolution. Furthermore, increased glucose delivery leads to higher concentrations of lactate and hydrogen ions which can be damaging to cellular function.⁸ While the mechanisms of reperfusion injury in human ischaemic infarction have not yet been verified, it is likely that the underlying biochemistry will remain the same.

Why should ischaemic stroke be viewed as an emergency?

At the centre of the infarct, brain cell dysfunction occurs within seconds of the onset of ischaemia, and permanent neuronal death occurs within 6–8 minutes.⁹ In the penumbra, tissue will be metabolically impaired, but may be resuscitable for a longer time period of up to six hours. After this period damage to brain cells in the penumbra may be permanent. Ischaemic stroke can, therefore, be considered potentially treatable if treatments restoring CBF and/or providing neuroprotection are administered as soon as possible after the onset of stroke.

New forms of treatment are now being tested extensively to prevent cell death in the ischaemic penumbra and to limit irreversible tissue damage. These therapies are likely to be most effective if initiated early. Animal studies suggest the optimal therapeutic time window to be 4–6 hours from onset of symptoms to start of treatment.¹⁰ The American Heart Association guidelines recommend initiation of thrombolytic treatment (see later in this article) within three hours of onset of symptoms.¹¹ If this therapeutic time window is not taken into consideration during clinical trials, it is likely that potentially effective treatments for cerebral infarction may be falsely shown to be ineffective. Some clinical trials, like that of tirilazad mesylate (see later), have been unable to show positive results in the clinical setting. It is possible that this may be related to the inclusion of patients up to as late as 24 hours after onset of symptoms.¹²

Treating stroke as an emergency

Unfortunately, many stroke patients wait hours before seeking help, as they are not usually suffering pain and do not commonly recognise the warning signs of stroke. Even patients who experience a stroke in hospital do not always receive medical care in time. Additional delay may be caused by pre-hospital stabilisation and transportation, emergency department evaluation, and decisions regarding admission. Identification and arrival of a physician after admission, economic and ethical considerations, as well as transfer to an intensive care unit or even another hospital contribute to further treatment delay. In short, unlike trauma or myocardial infarction, stroke is often not given the

Table 1 Risk factors for stroke

- Age over 55
- Race (blacks and Hispanics are at increased risk)
- Previous stroke or transient ischaemic attack
- Hypertension
- Heart disease, particularly atrial fibrillation
- Diabetes mellitus
- Carotid artery disease
- Smoking
- High serum cholesterol concentration
- Family history
- Excessive alcohol consumption

Table 2 Acute stroke symptoms

- Alterations in consciousness
- Sudden weakness or numbness of the face, arm and/or leg, especially if on the same side of the body
- Facial weakness or asymmetry
- Sudden double vision or loss of vision in one or both eyes
- New imbalance, sense of spinning or trouble walking, loss of coordination
- Trouble speaking or understanding
- Unilateral hearing loss
- Vertigo, nausea, vomiting

highest priority in treatment. However, in order to favour the outcome of stroke patients, stroke should be treated as an emergency. Although therapeutic concepts for emergency treatment have been published recently,^{3 8 13} transporting the stroke patient to the place of treatment in time remains a problem. An obvious solution would be to initiate appropriate treatment as soon as the tentative diagnosis is made. Initiation of treatment in the pre-hospital setting could save time and certain European emergency medical services do potentially have the capacity and the structural resources to handle stroke as a medical emergency.

Recognition of signs and symptoms—the value of education

Over the past few years, some progress has been made in the prevention of stroke, and in reducing stroke related mortality. Identification and modification of risk factors (table 1) are in part responsible for this improvement. Nevertheless, it is important for the general public, particularly those who are at increased risk, to recognise the clinical features of stroke, as early recognition is vital for stroke treatment to be successful. It should be stressed that this condition is an emergency, that it is potentially treatable, and that the emergency medical services should be called. Promotional programmes on television, radio, and in newspapers dealing with the signs and symptoms of stroke (table 2), as well as the importance of timely treatment should be developed. Regional educational campaigns concerning signs and symptoms of stroke and acute stroke treatment have already increased public awareness. Alberts *et al.*, for example, have demonstrated the efficacy of educational campaigns in cutting down the time delay to hospital admission.¹⁴

Intensified education, not only of the public but also of the emergency medical services, is likely to increase the number of stroke patients able to be treated at an earlier stage. The attitude of emergency service personnel—that nothing specific can be done in stroke treat-

ment during emergency care—needs to be changed. Initiation of treatment after a pre-hospital diagnosis by the emergency medical services or continuation of treatment started by them, may avoid unnecessary time delay.

Involvement of the emergency medical services

EMERGENCY MEDICAL SERVICES ASSESSMENT OF THE POTENTIAL STROKE PATIENT

In addition to providing life support and giving the patient a general examination, the emergency personnel should be able to perform a brief neurological evaluation to provide an initial evaluation within a few minutes, though they will not need to differentiate subtle, unusual, or isolated neurological signs. Differential diagnoses like cardiovascular disease and head or neck trauma must be excluded. After evaluation and a tentative diagnosis, initial stabilisation should begin as soon as possible to avoid time delay, which may hinder adequate treatment.

PRE-HOSPITAL DIAGNOSIS

Kothari *et al* investigated an emergency medical system in Ohio as a model for pre-hospital stroke evaluation, and compared management by basic life support (BLS) and advanced life support (ALS) units. For all patients attended to by the emergency medical services, 2% were given a pre-hospital diagnosis of stroke or TIA; 51% of these patients were managed by BLS and 49% by ALS units. A subsequent confirmed diagnosis of stroke or TIA was made for almost three quarters of these patients. BLS and ALS units were compared:

- The mean time to hospital arrival was 41 minutes for BLS treated patients *v* 45 minutes for ALS treated patients.
- Physician consultation was 63 minutes for all BLS treated patients and 58 minutes for all ALS treated patients.
- Computed tomography was 94 minutes (ALS) and 112 minutes (BLS) after the emergency call.¹⁵

The study concluded that it is feasible for the emergency service to carry out pre-hospital diagnosis, and emphasised the importance of rapid patient evaluation and transport to hospital, though it is a pity that the study did not report on the time delay between onset of symptoms and the 911 call.

The Mainz emergency medical service carried out a prospective study over 18 months on all their patients who had been given a tentative pre-hospital diagnosis of stroke. When the results were compared with those obtained using computed tomography, the scan showed that 112 of the 225 patients tentatively diagnosed as stroke had actually suffered an acute stroke: 27 had an acute haemorrhage and 85 had signs of acute ischaemia. Forty five per cent of the patients who had actually suffered a stroke were treated by the mobile life support unit and, therefore, had their first time physician at the scene. Forty three per cent of patients were treated in less than two hours after onset of symptoms, 72% of all stroke patients received treatment in less than six hours.¹⁶ This study shows that the critical time

window for early intervention can be met by the emergency medical services and illustrates the important part which the emergency team plays in patient care.

PATIENT STABILISATION

The first priority is to establish airway control, adequate gas exchange, and ventilation. It is important to avoid hypoxia in stroke patients, as this can increase the extent of brain injury. Causes of hypoxia in acute stroke patients are partial airway obstruction, hypoventilation, and atelectasis. In some patients, especially those with impaired consciousness, it will be necessary to protect the airway and to give ventilatory assistance. Supplementary oxygen should be administered to all stroke patients, with oxygen saturation being maintained above 95%. Blood pressure should be maintained stable without the use of hypotensive drugs unless systolic blood pressure is <220 mm Hg (mean arterial pressure <130 mm Hg, diastolic arterial pressure <120 mm Hg). Hyperglycaemia should be treated early. Some studies have shown poor outcome after stroke accompanied by hyperglycaemia. The serum glucose concentrations should be maintained below 7.8 mmol/l; and glucose infusions should be avoided. Body temperature should be maintained below 37°C and the patient's position should be semisitting, with the head raised at an angle of 30°.

In-hospital confirmation of diagnosis

The primary in-hospital diagnosis is a diagnosis by exclusion usually verified by neurologists. The differentiation between intracerebral haemorrhage and ischaemic stroke is important because of different subsequent therapeutic strategies.

Computed tomography of the brain is the diagnostic gold standard, with a success rate of nearly 100% in the detection of intracerebral haemorrhage. Other lesions causing focal neurological signs such as tumours and abscesses can also be detected by computed tomography. Absence of bleeding on computed tomography supports the diagnosis of ischaemic stroke. However, ischaemic lesions may not be visualised within the first hours after acute stroke. Early stroke signs on computed tomograms are hypodensities, mass effects, dense middle artery signs, effacement of cortical sulci, compression of the insular cisternae, loss of the internal capsule definition, and focal loss of grey/white matter differences.¹¹ New diffusion weighted image techniques in magnetic resonance imaging are able to perform all necessary images in less than 10 minutes, and are more sensitive than computed tomography in detecting symptoms of cerebral ischaemia within the first hours after onset of symptoms, although detection of haemorrhaging is not as sensitive.

Further diagnostic procedures consist of blood samples, electrocardiography, Doppler ultrasound, chest radiography, and lateral cervical spine radiography if necessary. Blood samples should be initiated as early as possible in order to plan further treatment. These could be taken during emergency medical service treatment, which would further decrease time delays.

Early treatment strategies—new therapies

The classic treatments used in the early stages of stroke have relied on prevention of further strokes through the use of antithrombotic and antiplatelet agents.^{17 18} Newer strategies actively remove the occlusion to restore cerebral blood flow (thrombolytics) or protect the neurones in the penumbra (neuroprotectants). In haemorrhagic stroke, early initiation of surgical intervention (decompression, aneurysmal surgery) to treat mass effects, reduce intracranial pressure, and restore CBF is frequently used for individual patients.

THROMBOLYTIC AGENTS

Spontaneous thrombolysis is common, which suggests that thrombolysis resistant thrombi are unusual in the acute phase. Vascular recanalisation is a result of endogenous fibrinolysis, dependent on the generation and release of plasmin from endogenous fibrin and platelet bound tissue plasminogen activator (t-PA) and single chain urokinase plasminogen activator within the thrombus. The infusion of exogenous thrombolytic agents has been used in many settings to achieve thrombolysis. Agents used for thrombolysis include streptokinase, urokinase, t-PA, and anisoylated plasminogen streptokinase activator.

Pilot studies during the 1980s and early 1990s provided encouraging data on the potential efficacy of thrombolysis in anterior or posterior circulation strokes and, recently, large scale studies using intravenous t-PA have been carried out. These include the European Cooperative Acute Stroke Study (ECASS), where patients received recombinant t-PA (rt-PA) within six hours of a hemispheric stroke¹⁹ and the National Institute of Neurological Disorders and Stroke (NINDS) study,²⁰ in which patients received rt-PA within three hours of the onset of cerebral ischaemia. In both of these trials, positive effects on neurological and functional outcome were observed at 90 days, though in the ECASS trial, efficacy was limited to a defined subgroup whose identification was complex and dependent on prompt recognition of computed tomography signs of early infarction. t-PA was approved by the Food and Drug Administration in 1996 for the treatment of acute ischaemic stroke provided that this could be administered within three hours of onset and that there were no signs of intracranial bleeding on computed tomography.

Clinical trials using streptokinase, for example Multicenter Acute Stroke Trial–Europe (MAST–E),²¹ Multicenter Acute Stroke Trial–Italy (MAST–I)²² and the Australian Streptokinase (ASK) trial²³ were all terminated early because of safety concerns: haemorrhagic transformation (MAST–E) and unacceptable mortality rate (MAST–I, ASK).

In conclusion, it appears that intravenous thrombolysis in acute ischaemic stroke is effective in improving outcome in some subgroups of stroke patients, though identification of these subgroups may be difficult and dependent on computed tomography and there are a

Table 3 Exclusion criteria for thrombolytic therapy in acute ischaemic stroke²

- Use of oral anticoagulants, prothrombin time >15 sec
- Use of heparin <48 hours
- Platelet count <100 ×10⁹/l
- Previous stroke, serious head injury <3 months
- Major surgery <14 days
- Pretreatment systolic blood pressure >185 mm Hg
- Pretreatment diastolic blood pressure >110 mm Hg
- Rapidly improving neurological signs
- Isolated mild neurological deficits
- Prior intracranial haemorrhage
- Blood glucose <2.8 mmol/l or >22.2 mmol/l
- Seizure at stroke onset
- Gastrointestinal or urinary bleeding <21 days
- Recent myocardial infarction

Table 4 Neuroprotective agents

Ion channel blockers
Nimodipine
Nicardipine
Lifarizine
Glutamate receptor antagonists
Aptiganel
YM90K
Glutamate release inhibitors
BW619C89
Fos-phenytoin
Scavengers of free radicals
21-aminosteroids (for example tirilazad mesylate)
Superoxide dismutase
Modulation of NO pathway
Lubeluzole
Others
Citicoline

number of exclusion criteria that must be strictly adhered to (table 3). As the benefits of thrombolysis are offset by their potential to produce haemorrhagic complications and because of the very short therapeutic window, thrombolysis is generally only advisable in centres with specialised teams who are able to intervene quickly.

NEUROPROTECTANTS

A large number of experimental drugs are currently under investigation as neuroprotectants (table 4). Ischaemia induces the release of excitatory amino acid neurotransmitters such as glutamate, which acts at several receptor sites to play a pivotal part in neuronal cell death. Additionally, ischaemia induces entry of extracellular calcium into the neurones via ionotropic receptors, which is extremely detrimental to the cell, eventually resulting in cell death. However, studies using calcium channel blockers, such as nimodipine and nicardipine, aimed at inhibiting the huge influx of calcium into the neurone, have been disappointing.²⁴

Glutamate receptor antagonists

Blockade of the NMDA receptor has been shown to reduce infarct volume in experimental models. Aptinagel is a non-competitive NMDA antagonist, currently undergoing phase III clinical trials. Two others, Selfotel (competitive antagonist; Ciba Pharmaceuticals) and Eliprodil (which acts at the NMDA polyamine site; Lonex Pharmaceuticals) have both failed clinical trial scrutiny; Selfotel due to concerns about the risk/benefit ratio and Eliprodil due to lack of efficacy.²⁵

There has been recent characterisation of other glutamate receptors (the AMPA and kainate receptors), in addition to elucidation of

the mechanisms of presynaptic glutamate release. This is prompting the investigation into new compounds, for example the glutamate release inhibitor, BW619C89, which is currently in phase II clinical trials.

Magnesium salts

These are thought to be neuroprotective by acting, in part, as antagonists to the NMDA receptor.²⁶ The Intravenous MAGnesium Efficacy in Stroke (IMAGES) trial in Glasgow is currently investigating the neuroprotective properties of magnesium sulphate.

Free radical scavengers

Results from phase III clinical studies with Freedox (tirilazad mesylate; Pharmacia & Upjohn), a free radical scavenger believed to have neuroprotective properties,²⁷ have, to date, been inconclusive.²⁸

Lubeluzole

Lubeluzole (Prosynap; Jansen Research Foundation), a novel benzothiazole neuroprotectant, is thought to prevent the increase in extracellular glutamate concentration in the ischaemic penumbra.²⁹ It also appears to inhibit the glutamate activated nitric oxide pathway, although precisely where in the pathway is as yet unknown. The results of phase II double blind, placebo controlled trials showed that lubeluzole was well tolerated and significantly reduced mortality in ischaemic stroke patients. Lubeluzole has been studied in two large multicentre phase III trials and results of these studies will soon be published.

Stroke unit and the stroke team

New approaches to the management of acute ischaemic stroke require streamlining of appropriate care facilities, where computed tomography, magnetic resonance imaging, Doppler ultrasound, electrophysiological and intracranial pressure monitoring devices are immediately available. Emergency medical services personnel, emergency physicians, neurologists, neuroradiologists, neurosurgeons, and nurses need to cooperate closely and, where possible, form a cohesive stroke team. If necessary, acute stroke patients should be rapidly transferred to a hospital that has a specialised stroke unit. A stroke unit should be equipped like an intensive care unit; personnel should include specialised nurses, neurologists, neuroradiologists, and internists. Close monitoring of vital and neurological signs and early mobilisation should be possible and, in addition, measures should be taken to prevent the secondary complications of stroke. Alternatively, a stroke team could be formed through a collaboration of different specialists, enabling patients to be treated by a stroke team on any appropriate hospital ward. Emergency departments and non-specialised intensive care units might also be able to take over some of the functions of a stroke unit.¹³ Development of acute stroke protocols adapted to local needs would increase the effectiveness of all units and teams caring for acute stroke patients.

Conclusion

Early initiation of novel treatments (thrombolytics and neuroprotectants) in patients with acute ischaemic stroke is likely to improve the outcome for these patients. However, both of these types of treatment must be given as early as possible for optimal effect and safety. While the administration of thrombolytics requires a definitive diagnosis, it is hoped that in the future, it may be possible to treat patients with neuroprotective treatments before the patient arrives in hospital. In order for this to happen, emergency service personnel should be able to evaluate a stroke patient promptly, and be aware of the need to treat stroke as an emergency. Additionally, the general public needs to be educated to recognise the signs and symptoms of stroke and to react quickly to them by calling the emergency number.

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Recent advances in the acute management of ischaemic stroke

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Stroke is the third commonest cause of death and the commonest cause of adult disability in the western world. Approximately 1.5 million patients in Europe and America suffer acute stroke each year¹ and 85% of these are ischaemic. This is an enormous burden to patients, their families, and also to health care systems. Although the incidence of stroke has declined in recent years,² it is likely to become more prevalent in the future as the population ages.

Recent licensing of the thrombolytic agent, recombinant tissue plasminogen activator (rt-PA) in the United States for treatment of

selected stroke patients has focused attention on active stroke management. However the restoration of blood flow to ischaemic brain is only one of several approaches currently being investigated to improve stroke outcome. Advances in the understanding and manipulation of the cellular derangements which occur in the ischaemic brain offer other possibilities for active treatment. Development of investigations which differentiate between ischaemic and infarcted tissue will allow new therapies to be directed towards those patients most likely to benefit.