Clinical update: management of stroke

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Patients with suspected stroke (ie, "brain attack") require rapid assessment and intervention. Assessment aims to establish the diagnosis of stroke and its pathological and aetiological subtypes, and to forecast the prognosis for complications, recurrent stroke, survival, and handicap. Intervention aims to reverse any ongoing brain ischaemia or haemorrhage, to minimise the risk of complications and recurrent stroke, and to optimise physiological homoeostasis and rehabilitation.

The diagnosis of stroke remains clinical, despite research efforts to identify reliable biomarkers of brain infarction and haemorrhage. The clinical features that favour a diagnosis of stroke are: an exact time of onset; the presence of focal neurological symptoms, lateralising neurological signs, and abnormal cardiovascular findings (eg, atrial fibrillation, heart murmur); and being able to determine a clinical stroke subclassification.[1] Cognitive impairment and abnormal signs in other systems (eg, respiratory, abdominal) suggest a stroke mimic.[1] Diagnosis of stroke and transient ischaemic attack can be facilitated by diffusion-weighted MRI which identifies a relevant abnormality in most patients with recent ischaemic stroke (83%, 95% CI 78–88%) and in about half of patients with recent transient ischaemic attack (figure 1).[2] The diffusion-weighted MRI is more likely to be positive in patients with stroke who score more than 4 on the National Institutes of Health stroke scale and whose lesion is outside the brainstem, and in patients with transient ischaemic attack who have a history of a motor deficit, dysphasia, or dysarthria that lasted longer than 60 min (figure 1).[2]

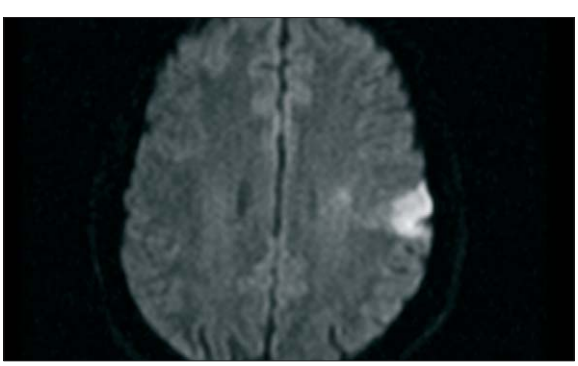

Figure 1: **Diffusion-weighted image MRI**
Figure shows area of restricted diffusion, consistent with ischaemia, in cortex and subcortex of posterior frontal lobe of left cerebral hemisphere in patient with transient ischaemic attack of brain that caused sudden onset of right arm weakness and difficulty speaking for 1 h. Brain CT scan was normal.

Haemorrhagic and ischaemic stroke are rapidly and reliably distinguished by plain CT brain scan.[2] The site of brain haemorrhage or infarction is a clue to the cause. MRI of the brain is more sensitive than CT for detecting the site and extent of focal brain ischaemia,[2] and for showing low-flow vascular malformations (cavernomas) and other vascular abnormalities. Proximal sources of thromboembolism in large arteries can be imaged non-invasively by ultrasound, MRI angiography, and CT angiography (figure 2). Transoesophageal echocardiography is better than transthoracic echocardiography for identifying sources of embolism in the aortic arch and heart; at least one in eight patients with normal transthoracic echocardiography have evidence on transoesophageal echocardiography of a potential source of embolism warranting anticoagulation.[3]

For patients with supratentorial non-aneurysmal intracerebral haemorrhage, early decompressive surgery is associated with a non-significant trend toward a reduction in death (odds ratio 0·85, 95% CI 0·71–1·02) but not dependency.[4] However, early surgery can reduce death and dependency in the subgroup of patients with lobar intracerebral haemorrhage (odds ratio 0·58, 0·36–0·92); a definitive trial in these patients is underway. Early haemostatic therapy with recombinant factor VIIa within 4 h of intracerebral haemorrhage retards growth of the haemorrhage but fails to improve patients' outcomes.[5]

For patients with ischaemic stroke, reperfusion within 3 h of onset with intravenous recombinant tissue plasminogen activator (alteplase), 0·9 mg/kg over 1 h, reduces death and dependency (odds ratio 0·64, 95% CI 0·5–0·8) despite an increase in brain haemorrhage.[6] Alteplase also seems to be safe and effective in routine clinical use.[7] Preliminary studies suggest that intravenous desmoteplase, 125 μg/kg 3–9 h after ischaemic stroke onset, is acceptably safe and can be effective for patients with MRI evidence of an ischaemic penumbra as defined by diffusion/perfusion mismatch.[6] Ongoing trials aim to resolve uncertainty about: the duration of the therapeutic time window; the optimum thrombolytic drug, route and dose; the independent baseline predictors of a response to thrombolysis; the role and timing of concomitant antithrombotic therapies; and the use of complementary therapies such as transcranial doppler

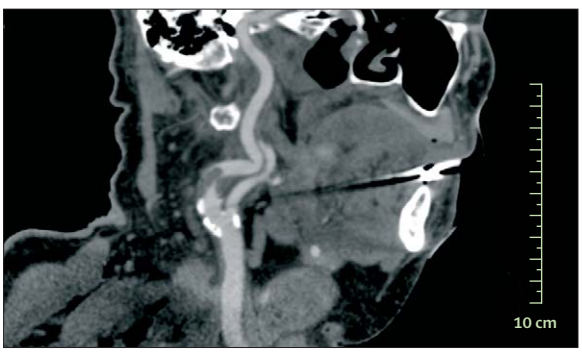

Figure 2: **CT angiogram**
Figure shows left common, internal, and external carotid arteries, with calcification (white) in terminal left common carotid artery, and calcification (white) and thrombus (black) causing very severe stenosis at origin of left internal carotid artery.

ultrasonography and mechanical clot penetration (with a microwire or microcatheter) and disruption (by balloon angioplasty, stent deployment, or snare device).[6] Early decompressive surgery within 48 h of onset of large, space-occupying, hemispheric ischaemic stroke reduces mortality and improves functional outcome in carefully selected patients.[8] Neurovascular protection with the free-radical scavenger NXY-059 was reported to improve functional outcome after ischaemic stroke, but a reanalysis of the data and subsequent larger trial[9] indicate this was a false positive. Ongoing trials continue to evaluate other strategies of neurovascular protection (eg, hypothermia) and treatments for complications of stroke (eg, graduated compression stockings for venous thromboembolism prophylaxis).[6]

After a transient ischaemic attack or minor ischaemic stroke, the overall risk of a recurrent stroke is about 5% within the first 2 days, 10% within the first week, and 18% within the first 3 months.[10] Risk factors for early recurrence are age 60 years or more, systolic blood pressure above 140 mm Hg or diastolic blood pressure above 90 mm Hg, clinical features of unilateral weakness or speech disturbance, duration of focal neurological symptoms over 60 min, and diabetes ($ABCD^2$).[10] Other possible adverse prognostic factors include recent symptomatic large artery atherosclerosis, multiple recent transient ischaemic attacks, embolic signals on transcranial doppler sonography, and a new clinically relevant lesion on CT or MRI brain scan.

For patients with ischaemic stroke or transient ischaemic attack due to atherothromboembolism, immediate and long-term aspirin reduces the relative risk of recurrent stroke and other serious vascular events by about 13% (95% CI 6–19%).[6] Oral anticoagulation is not more effective than aspirin because any possible protective effect against ischaemic events is offset by increased bleeding complications.[11] Long-term clopidogrel reduces the relative risk of serious vascular events by about 9% (0·3–16·5%) compared with aspirin.[6] Any benefits of clopidogrel combined with aspirin, compared with aspirin or clopidogrel alone, are offset in the long-term by cumulative risks of bleeding.[6,12] The combination of aspirin and extended-release dipyridamole is significantly more effective than aspirin (odds ratio 0·82, 0·74–0·91) and does not cause excessive bleeding.[13] Dipyridamole-induced headache can be reduced by starting with a low dose and gradual titration. A large trial comparing clopidogrel with the combination of aspirin and dipyridamole in more than 20 000 patients with recent (<120 days) atherothrombotic ischaemic stroke is expected to report in 2008.[14] Carotid endarterectomy is most effective for elderly men with a recent (within 2 weeks), non-disabling, carotid territory ischaemic stroke or transient ischaemic attack of the brain and an irregular or ulcerated symptomatic carotid plaque that is causing severe stenosis of the lumen.[15] Carotid angioplasty and/or stenting is associated with a non-significant trend toward a greater risk of perioperative stroke or death within 30 days compared with carotid endarterectomy (odds ratio 1·2, 0·9–1·6).[6,16,17] Whilst awaiting the results of long-term follow-up in ongoing trials comparing carotid stenting with endarterectomy, the use of carotid stenting (with an embolism-protection device) should probably be restricted to patients with recently symptomatic severe carotid stenosis and coexisting conditions that increase the risk of carotid endarterectomy, thereby precluding carotid endarterectomy.[6] Long-term reductions in systolic blood pressure by about 10 mm Hg and LDL-cholesterol by about 1 mmol/L are associated with significant reductions in risk of recurrent stroke and other serious vascular events by about 30% and 20%, respectively.[6,18] The effect of modifying other "newer" risk factors for stroke remains uncertain. Twelve trials to date show no evidence that B-vitamin supplementation (folic acid, vitamin B12, vitamin B6) significantly reduces the risk of serious vascular events, despite effectively lowering plasma homocysteine concentrations.[19] The results of ongoing trials of B vitamins in larger samples are awaited.

For patients with ischaemic stroke or transient ischaemic attack due to cardiogenic embolism, oral anticoagulation with warfarin (international normalised ratio 2·0–3·0) remains the most effective thromboprophylactic. The combination of clopidogrel plus aspirin is less effective than warfarin for prevention of serious vascular events in patients with atrial fibrillation, particularly those who are already taking warfarin (relative risk 1·44, 95% CI 1·2–1·8).[20] The direct thrombin inhibitor ximelagatran is not inferior to warfarin in efficacy but has an unacceptably high rate of adverse effects on liver function which has precluded its further development in atrial fibrillation. Warfarin is being compared with other direct thrombin inhibitors and with factor Xa inhibitors in ongoing trials.

For patients with aneurysmal subarachnoid haemorrhage in whom the aneurysm is considered suitable for both surgical clipping and endovascular coiling, the outcome is better with coiling.[6] Oral nimodipine (60 mg every 4 h) reduces the risk of delayed cerebral ischaemia and improves outcome.[6] Magnesium sulphate may also be effective in reducing the risk of delayed cerebral ischaemia (hazard ratio 0·66, 0·38–1·14) and a poor outcome at 3 months (risk ratio 0·77, 0·54–1·09). However, acetylsalicylic acid 100 mg suppositories, started within 4 days of aneurysm treatment and continued for 14 days, do not reduce delayed cerebral ischaemia (hazard ratio 1·83, 0·85–3·9).

Organised inpatient care and rehabilitation of stroke patients by a dedicated multidisciplinary team in a stroke unit reduces death and dependency.[6] Most deaths prevented would have occurred between 1 and 4 weeks after stroke due to recurrent cardiovascular events and the complications of immobility (eg, venous thromboembolism) and dysphagia (eg, aspiration pneumonia).[6] Stroke patients with mild to moderate disability who are discharged earlier than usual from hospital (by about 8 days) and continue their rehabilitation at home with a coordinated specialist multidisciplinary team have a lower risk of long-term dependency and admission to institutional care than similar patients who continue their rehabilitation in hospital.[6]

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I have received honoraria from Sanofi-Aventis, Bristol-Myers-Squibb, Boehringer-Ingelheim, AstraZeneca, Bayer, and Pfizer for serving on advisory boards and speaking at sponsored scientific symposia.

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