acute ischaemic stroke [created by Paul Young 03/11/07]

general

- the rationale for acute ischaemic stroke treatment is that when arterial occlusion occurs there is an area of infarcted brain the is surrounded by a region of that has reduced blood flow impairing function but not sufficiently severe to result in irreversible infarction
- this is the 'ischaemic pendumbra' and if adequate blood flow can be restored within a critical time frame this area may return to normal function

pathophysiology

- ischaemic strokes are generally classified as:
(i) large vessel thrombotic
(ii) small vessel thrombotic
(iii) embolic
- large vessel thrombotic strokes are often preceded TIAs
- clinical deficits typically correspond to the territory of a major cerebral artery or their border zones
- in embolic strokes, the onset is usually sudden
- the presence of AF, rheumatic heart disease or a recent myocardial infarction increase the probability of embolism
- several clinical syndromes are attributable to small vessel or lacunar strokes including pure motor stroke, pure sensory stroke, ataxic hemiparesis and dysarthria/clumsy hand syndrome
- clinical determination is unreliable and imaging is required

emergent stroke evaluation

general assessment:
- emergent assessment of the stroke patient begins prehospital and mechanisms are required for early notification if aggressive early therapies are feasible
- initial assessment should be performed rapidly and targetted towards assuring adequate airway and ventilation [particularly in obtunded or comatose patients]
- hypoxaemia should be corrected [aspiration is a major cause of morbidity in these patients]
- arrhythmias are common in stroke patients [particularly AF] and bradycardia may signal increased intracranial pressure
- hypotension should be corrected
- seizures should be controlled with anticonvulsants
- hypoglycaemic may mimic stroke and should be treated

blood pressure management:
- hypertension commonly accompanies stroke & in most cases treatment is not recommended due to the risk of causing further impairment of perfusion to ischaemic penumbra
- when thrombolytic therapy is considered, SBP should be controlled to less than 185mmHg or diastolic less than 110mmHg

triage & laboratory studies:
- immediate concern for the emergency department after initial stabilisation is confirming the diagnosis of stroke, excluding stroke mimics & established whether acute intervention is warranted
- establishing time of onset is crucial and if rapid intervention is needed then CT should be performed rapidly
- additional blood tests include coagulation studies, full blood count & electrolytes

glucose:
- evidence from animal models of stroke suggests that hyperglycaemia increases the severity of ischaemic injury & initial blood glucose in acute stroke is correlated with outcome independent of initial stroke severity
- although studies have not been performed to demonstrate a beneficial effect on outcome of controlling blood glucose, it seems reasonable to control glucose to reasonable levels

temperature control:
- fever is clearly associated with worse outcomes after stroke
- hypothermia reduces stroke severity in animal models of stroke but no randomised trials have been completed in humans
- despite the uncertainty or benefit, maintenance of normothermia is advised after stroke

stroke team:
- a stroke team consists of individuals from multiple disciplines with specialised knowledge and interest in acute ischaemic stroke. The stroke team is usually responsible for evaluating the CT scan, establishing the diagnosis and making the decision about treatment

imaging

- evaluation of patients with acute stroke depends heavily on imaging

CT:
- CT excludes haemorrhage as the aetiology in recent stroke
- subtle abnormalities may indicate the presence of acute ischaemic stroke including subtle hypodensity, loss of insular ribbon and hyperacute artery signs
- CT angiography also allows evaluation of vessels and may have potential to determine which patients will benefit fromintervention (based on the burden and distribution of thrombus)although studies are currently lacking
- xenon CT can be used to determine cerebral perfusion and may identify the size of the ischaemic penumbra; its use to guide therapy has yet to be elucidated

MRI:
- the major drawbacks of MRI are difficulty with performance on an emergent basis and the problems with identification of hyperacute haemorrhage
- diffusion weighted imaging shows early ischaemia and in combination with perfusion imaging may identify reversibly ischaemic tissue

anticoagulation

- RCTs to date include trials of low molecular weight heparin & heparin
- overall, the studies do not show a reduced recurrence of ischaemic stroke from anticoagulation commenced 24-48 hours after stroke & haemorrhage rates varied from 1-2.5%; even in patients with atrial fibrillation the role of early anticoagulation is uncertain

antiplatelet therapy

- Chinese Aspirin Stroke Trial and IST trial combined include more than 40000 patients and demonstrated a small but significant reduction in recurrent stroke (7 per 1000) or death/dependency (12/1000) at 28 days

surgical options

- cerebral herniation is the most common cause of death from stroke in the 1st few days
- surgical decompression of large hemispheric infarcts causing oedema and can prevent herniation and death; randomised trials have not been performed
- cerebellar infarction is a special case where surgical intervention may be clearly indicated. In these patients compression of the brainstem and 4th ventricle leads to hydrocephalus or severe pontomedullary compromise which may be reversed by rapid surgical decompression of the posterrior fossa leading to survival with minimal residual deficit

neuroprotectives

- multiple neuroprotective agents have been trialled; however, results have been universally disappointing

mechanical devices

- mechanical devices have been shown to increase recanalisation rates (MERCI trial); however, clinical data are lacking at present

combination therapy

- involves intravenous tPA followed by angiography and intraarterial tPA if persistent thrombus is present
- in a small study, this approach lead to greater recanalisation in the combined group than the intra-arterial alone group (81 vs 50%); however, it was associated with a slight risk of increased bleeding and the study was not powered to lookfor differences in functional outcome

intra-arterial thrombolysis

general:
- an alternative approach to intravenous thrombolytics is direct delivery of thrombolytic agents by a microcatheter embedded in the clot
- the advantage is direct visualisation of the occluded artery and knowledge of the recanalisation status as thrombolysis proceeds; while the disadvantage is the additional time required

trials:
- the PROACT II trial showed that intra-arterial thrombolysis with urokinase at up to 6 hours from the onset of symptoms in patients with M1 or M2 segment occlusions led to improved functional outcome at 90 days; however, symptomatic haemorrhage occurred in 10% of patients compared with 2% of controls (control group received direct arterial injection of saline)
- evidence for thrombolytics in basilar artery thrombosis comes only from case series; good outcomes have been reported with intra-arterial thrombolysis of basilar thrombosis well beyond the usual 6 hour time limit

tpa in specific subgroups

general:
- further analysis of the NINDS study did not identify any specific subgroups with a greater or lesser likelihood of responding to tPA; however, clinical experience has raised questions about treatment of several subgroups

age and risk of thrombolytics:
- elderly patients have a higher incidence of cerebral amyloid angiopathy which might predispose to haemorrhage after tPA
- in the NINDS study, older patients were less likely to have a favourable outcome but fared better with tPA than without it
- in ECASS II, older patients had a greater risk of haemorrhagic transformation
- advanced age is not a contraindication to thrombolysis but requires consideration of a lower probability of good outcome and higher risk of haemorrhage

CT findings on baseline scan:
- before RCT tPA trials, several studies suggested that the presence of early changes on CT predicted a greater risk of haemorrhagic transformation
- in ECASS II early hypodensity was an independent risk factor for intracranial haemorrhage
- in the NINDS study the odds ratio of symptomatic haemorrhage was increased (2.9 vs 1.5) with hypodensity of >1/3rd the MCA territory; however, few patientshad this finding on baseline scan and the increased risk of haemorrhage did not reach statistical significance
- analysis of the Australian Streptokinase study failed to show any significant relationship between ischaemic changes on baseline CT (within 4 hours of symptom onset) and intracerebral haemorrhage

aspirin pretreatment:
- may individuals at risk of stroke are treated with aspirin or other antiplatelet agents
- whether aspirin increases the risk of thrombolytic therapy is unclear
- in MAST-I, patients treated with aspirin and streptokinase had a higher incidence of death from intracerebral haemorrhage
- aspirin pretreatment was not associated with intracerebral haemorrhage in the NINDS trial
- aspirin therapy is not a usually regarded as a contraindication to thrombolytics

severe stroke:
- in most studies of thrombolysis, prognosis and risk of haemorrhage are strongly related to the severity of stroke
- despite poorer outcomes and increased risk of haemorrhage, more patients had good outcomes with tPA than without in the NINDS trial
- severe stroke is not a contraindication to thrombolytics

other thrombolytics

- 3 large double blinded placebo controlled trials of streptokinase in stroke (multicentre acute stroke trial - Europe MAST-E ; Australian Streptokinase Trial (ASK) & the multicentre acute stroke trial - Italy (MAST-I))
- all three demonstrate a significant increase is risk of haemorrhage NNH to cause death or disability = 5

tPA

- European cooperative acute stroke study (ECASS) trial was one of the first large RCTs to test rtPA administered within 6 hours of stroke onset. Patients with clinically severe hemispheric strokes were excluded & CT was allowed to show no or early signs of ischaemia only. No difference in outcome and increased risk of bleeding. Subgroup analysis of target population showed statistically significant benefit in favour of rtPA for good outcome.
- ECASS-II designed with strict exclusion of patients with greater than 1/3rd MCA infarct on CTB. Also failed to demonstrate benefit - NNH to cause haemorrhage was 18.
- NINDs was designed to assess very early rtPA (<3 hours). Total of 624 patients in 2 parts. Demonstrates NNT to have minimal or no disability at 3 months is 8. NNH to cause symptomatic ICH is 14. No significant difference in mortality (24 vs 28% respectively). No difference in outcomes at 24 hours.
- Canadian Altepase for stroke effectiveness study which is a cohort study of all patients receiving rt-PA in Canada over a 2 and half year period shows similar benefit to NINDs with a lower risk of ICH (only 4.6%). This study includes at total of 1135 patients An earlier metanalysis of 15 publications from post NINDs era using NINDs criteria show a stroke deficit reduction (37% achieved a very favourable outcome) similar to NINDs but a lower risk of bleeding (5.2%). This study includes 2639 patients and results were achieved despite protocol deviations in 19.8% of patients.
- ATLANTIS part A was another North American study of rtPA which enrolled patients up to 6 hours was stopped early because of safety concerns. Study showed increased risk of haemorrhage and no favourable outcome.
- ATLANTIS part B aimed to assess efficacy within 5 hours - results indicated no significant benefit. Subgroup in ALTANTIS treated within 3 hours of onset had trend towards better outcome but this only constituted 62 patients.
- Metanalysis of all of the above studies (and others) with total of 5216 patient shows significant improvement in good outcome at 3 months and significant increase in ICH