Early neurological deterioration in acute ischaemic stroke: predictors, mechanisms and management

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ABSTRACT

Early neurological deterioration (END) in acute ischaemic stroke is a common event. The underlying mechanisms are heterogeneous. The clinical predictors of END include severity of the initial stroke, large vessel occlusion, diabetes mellitus, hypotension, and atrial fibrillation. Serial observations and detailed assessment by the trained staff in specialised stroke units are key to the successful management of these patients. Advances in brain and vascular imaging have provided insight into the underlying mechanisms, enabling clinicians to use preventative and therapeutic interventions specifically targeted at them, though several questions still remain unanswered. END has potentially serious consequences on the short term (morbidity and death) and long term (recovery from stroke) outcomes for the patient. Therefore, attempts to prevent and treat END should be made promptly and aggressively.

Worsening of acute stroke early in its course (within 48–72 h of its onset) is a common occurrence and has potentially serious short term and long term consequences for the patient. The underlying mechanisms are mostly neurologic as opposed to the worsening in the later part of stroke when systemic factors (for example, infection, electrolyte disturbances, myocardial ischaemia, venous thromboembolism, etc) tend to play a greater role.1 In primary intracerebral haemorrhage, worsening is often related to continuous bleeding whereas recurrence of bleeding and vasospasm account for most of the worsening in aneurysmal subarachnoid haemorrhage. In ischaemic stroke, several possible mechanisms exist that can lead to worsening. The issues surrounding the use of terminology, role of potential predictors and underlying mechanisms, and management of early worsening in ischaemic stroke shall be discussed.

HOW COMMON IS END?

The incidence of END in ischaemic stroke among hospitalised patients varies widely in different studies. In a recently published Australian study, 19% of acute stroke patients had END.3 Incidence was greater in haemorrhagic stroke subtype than in non-haemorrhagic subtype (22% vs 7%). In the Harvard Cooperative Stroke Registry that included haemorrhagic and non-haemorrhagic strokes, early worsening was noted in ~20% of patients.6 In the Barcelona Stroke Registry of 3577 consecutive patients hospitalised with stroke (all types), 57% showed END.7 Rates of 29% and 25%, respectively, were reported for all acute strokes in Swiss2 and Japanese4 studies. In a study that excluded haemorrhagic strokes, 256 out of 1964 (13.0%) consecutive patients admitted within 4 h of the onset of acute cerebral ischaemic symptoms had an increased score of one point or more on the NIHSS scale after 48–72 h.8 According to the authors, a lower frequency of END in this study could partly be explained by the inclusion of 18 patients with transient ischaemic attacks. Similar figures (16.1%) have been reported in a recent study.1 It could be argued that the availability of modern treatment (for example, thrombolysis and interventional recanalisation procedures) and stroke units might account for the lower frequency in the recent studies.

The differences in the time scale of assessments after acute stroke, diagnostic criteria used for END, and the case mix of stroke patients could account for the wide variations reported in the studies. Even among ischaemic subtypes, strokes differ in rates of END.4 **
PREDICTORS OF END

Several studies have looked into the clinical and radiological factors that could possibly predict END in acute stroke (Table 1).

<table>
<thead>
<tr>
<th>Clinical predictors</th>
<th>Radiological predictors</th>
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<tbody>
<tr>
<td>Initial stroke severity</td>
<td>Large vessel occlusion</td>
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<tr>
<td>History of diabetes mellitus</td>
<td>Hypodensity &gt;33% in the MCA territory</td>
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<tr>
<td>Low blood pressure</td>
<td>Hyperdense MCA sign on brain CT</td>
</tr>
<tr>
<td>Raised blood pressure</td>
<td>Cerebral oedema on early brain CT</td>
</tr>
<tr>
<td>Lacunar infarction</td>
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<tr>
<td>Atrial fibrillation</td>
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</table>

**Table 1** Predictors of early neurological deterioration in ischaemic stroke

**PREDICTORS OF END**

Several studies have looked into the clinical and radiological factors that could possibly predict END in acute stroke (Table 1).

Age, gender, and pre-stroke level of independence do not generally appear to be significant risk factors for END, though age was recognised as a risk factor for END in some studies.

Initial stroke severity increases the risk of END. In a study to determine the value of initial NIHSS score for risk stratification in ischaemic stroke, patients with an initial NIHSS ≤7 experienced lower frequency of worsening (14.8%) than those with a score >7 (65.9%), with a dichotomy in early outcome surrounding an initial NIHSS score of 7. A reduced level of consciousness on admission is associated with greater END.

Severe strokes were independently related to the greater frequency of worsening in another study. Different subtypes of ischaemic strokes differ in the rates of END, with non-cardioembolic strokes being more likely to deteriorate than cardioembolic, and lacunar types more than the non-lacunar types. Also, significantly more patients (67% vs 5%) with total anterior circulation strokes worsen than those with partial anterior circulation stroke.

Hyperglycaemia is noted on admission in approximately one third of patients with stroke and is associated with poor outcomes after ischaemic stroke, including among patients treated with thrombolytic agents. High serum glucose values and history of diabetes have been associated with END. In a case–controlled study, previous history of diabetes along with elevated admission systolic blood pressure predicted END. Persistent hyperglycaemia during the first 24 h after stroke independently predicted expansion of the volume of ischaemic infarct and poor neurological outcomes. The detrimental effects of hyperglycaemia have been attributed to tissue acidosis secondary to anaerobic glycolysis, lactic acidosis, free radical production, disruption of the blood–brain barrier, the development of brain oedema, and increased risk of hemorrhagic transformation. Hyperglycaemia may be marker of a more severe stroke. It is not known whether treatment of hyperglycaemia in acute stroke has a beneficial effect on patient outcome. In the recently published UK Glucose Insulin in Stroke Trial (GIST-UK), glucose–potassium–insulin infusion in patients with hyperglycaemia in the acute stroke setting was associated with a reduction in blood glucose and blood pressure, but there was no significant effect on the 90 day mortality. However, the study was underpowered to reach a definitive conclusion regarding the mortality outcome.

A history of elevated admission systolic blood pressure along with diabetes mellitus has been suggested to predict early deterioration. The independent role of hypertension as a predictor of END has not been established. On the contrary, it is suggested that the rates of neurologcal worsening, poor neurological outcomes, or death increase with a baseline systolic blood pressure <100 mm Hg or a diastolic blood pressure <70 mm Hg. The current stroke guidelines, therefore, do not advise treatment of hypertension in acute stroke, except when thrombolysis is contemplated or in the presence of extremely severe hypertension. It is not clear whether there are high and low thresholds of optimal blood pressures in ischaemic stroke. Three ongoing studies—Controlling Hypertension and Hypotension Immediately Post-Stroke (CHHIPS), Efficacy of Nitric Oxide in Stroke (ENOS), and Continue or Stop post Stroke Antihypertensives Collaborative Study (COSSACS)—aim to provide an answer to the blood pressure dilemma in acute stroke.

The presence of large vessel occlusion has been recognised as a major independent risk factor for END in several studies. In a study of early magnetic resonance imaging (MRI) and outcomes of patients with ischaemic stroke, 10% of patients eligible for acute reperfusion therapy excluded on the basis of mild or rapidly improving symptoms showed END with infarct expansion within 48 h. Authors comment that persisting large vessel occlusion substantially increases risk of END. Sequential angiographic changes in patients with neurologic worsening show progression of arterial stenosis. Interestingly, a history of prior transient ischaemic attacks is negatively related to END. Since severe stenosis is associated with a greater risk of transient ischaemic attacks, it is possible that mechanisms other than embolisation may operate for END in vessel occlusion.

Atrial fibrillation and high serum urea have also been shown to increase risk of END. Extent of hypodensity >33% in the middle cerebral territory, hyperdense middle cerebral artery sign, and brain swelling on computed tomography (CT) scan at 24 h are associated with END. These may simply reflect severe initial stroke.

MECHANISMS OF END

Several mechanisms have been proposed to explain END in acute ischaemic stroke. They include failure of collateralisation, clot progression, recurrent (local or remote) stroke, raised intracranial pressure, seizures, and haemorrhagic transformation. Advances in the brain and vascular imaging techniques have provided great insight into their role in END in acute stroke.

Failure of collaterals

Occlusion of major cerebral vessels is one of the most important independent predictors of END. Vascular occlusion leads to distal hypoperfusion with its potential to compromise perfusion of the affected region unless effective collateral circulation develops. Development of collaterals appears to be the mechanism underlying transient ischaemic attacks and rapid recovery from an ischaemic stroke. Diabetic microangiopathy and chronic hypertension impair microvascular function, reducing the potential for collateral development. This leads to reduced oxygen delivery and regional metabolic disturbances, which may aggravate cellular damage by enhancing brain oedema and free radical injury. Insufficient collaterals with the adverse metabolic consequences on the ischaemic penumbra appear to be the most common mechanism for END. Initially, clinical worsening is due to synaptic dysfunction with preserved cell membrane integrity and is potentially reversible with vessel recanalisation. Serial transcranial Doppler studies may be useful for haemodynamic evaluation in acute stroke and large vessel patency can be evaluated by duplex ultrasound, magnetic resonance angiography, and CT angiography.
Clot progression
In the past, END in acute ischaemic stroke had been attributed to clot progression, though this had never been demonstrated. Recent studies of early MRI in acute stroke have shown large vessel occlusion and failure of collaterals rather than clot progression as the main mechanism of END. Hypoperfusion due to occluded vessels may impair washout of distal emboli and the two may act synergistically to cause END.

Recurrent stroke
Patients with acute ischaemic stroke are at a high risk of recurrent stroke in the first week. However, most of the recurrent strokes detected on diffusion weighted MRI scans do not produce clinical deficit. Weimer et al reported recurrent cerebral ischaemia as the cause of END in 11.5% of cases. Recurrent embolism can occur in the original region or in a remote location. Transcranial Doppler can detect microembolic signals and may be useful for identifying patients at risk of early recurrent stroke.

Cerebral oedema
Raised intracranial pressure accounts for ~19% of cases of early deterioration in ischaemic stroke. The overall risk of brain swelling in patients with anterior circulation stroke is low and is estimated to be 10–20%. In patients with an occluded stem of the middle cerebral artery, cerebral oedema tends to appear 4 days after the onset of stroke. The term “malignant” has been used to describe brain oedema in patients with a large territorial infarct that swells within 24 h, causing signs of brain herniation. Clinical features such as a deteriorating level of consciousness, bilateral ptosis and involvement of the non-dominant hemisphere may suggest a high risk of deterioration. In middle cerebral infarcts, NIHSS score >20, involvement of two thirds or more of the artery on initial brain imaging, concomitant anterior and posterior cerebral artery infarction, and lesion volume >145 ml on diffusion weighted imaging scan predict evolution to fatal cerebral oedema. Cerebral oedema in ischaemic stroke tends to be cytotoxic and does not respond to osmotic diuretics.

Haemorrhagic transformation
Haemorrhagic transformation in ischaemic stroke is common and ranges from small asymptomatic petechiae to a large haematoma with pressure effects. Symptomatic transformation occurs only in 0.6% of patients treated with supportive care, whereas the incidence is higher in those treated with intravenous recombinant tissue plasminogen activator (rt-PA). Haemorrhagic infarction is defined as small petechiae along the margins of the infarct or more confluent petechiae within the infarcted area, but without space occupying effect. Parenchymal haematoma is defined as blood clot with space occupying effect. Only parenchymal haematoma type 2 (large haematoma >30% of ischaemic lesion volume) are considered to be associated with adverse outcome. Haemorrhagic infarction 1 and 2 may represent reperfusion injury (and successful recanalisation) leading to reduction in infarct size and improved clinical outcome. The risk factors for thrombolysis related intracerebral haemorrhage include old age, severe initial stroke, high serum glucose values, and signs of mass effect on pre-treatment imaging. Though thrombolysis with rt-PA increases risk of haemorrhage, it requires 100 patients to be treated with rt-PA to get one significant adverse outcome. Secondary haemorrhage accounted for ~10% of cases of END in one study.

Re-occlusion of a recanalised artery
With the advent of thrombolysis and mechanical recanalisation procedures in stroke treatment, re-occlusion has been increasingly recognised as a cause of END. Early re-occlusion occurs in 34% of rt-PA treated patients with any initial recanalisation, accounting for two thirds of deterioration following improvement. Stroke severity, partial recanalisation after rt-PA, and ipsilateral severe carotid artery disease independently predict re-occlusion after rt-PA induced recanalisation of the middle cerebral artery. Real-time use of transcranial Doppler in such patients may identify re-occlusion and help to predict which patients will benefit from intra-arterial thrombolysis or mechanical embolectomy.

Seizures
Seizures are common in large cortical ischaemic infarcts and may account for END in ~5% of patients with ischaemic strokes. Seizures often cause only temporary worsening, though prolonged partial seizures can lead to persistent worsening. Non-convulsive seizures, difficult to detect clinically and requiring electroencephalography (EEG) to diagnose, may account for worsening in some cases.

MANAGEMENT OF END
Given the significantly high frequency of END, all patients with acute stroke should be admitted to specialised stroke units with trained multidisciplinary staff capable of carrying out detailed and frequent assessments of the general and neurological status of patients. Those patients with risk factors for END and those with overt signs of deterioration should be admitted to the high dependency or intensive care areas. Since there are several causes of END, no single intervention is likely to be effective for all patients. Good supportive care and attention to temperature, oxygenation, hydration, intercurrent infections, thromboprophylaxis, positioning, pressure areas, bowel and bladder care, etc, is essential to the care of all patients with acute stroke. Specific interventions for prevention and treatment of END depend upon the underlying mechanism. A detailed work-up with serial neurological assessments using NIHSS and appropriate selection of diagnostic tests—for example CT, MRI, MR angiography, duplex and transcranial Doppler, and EEG—is required to elucidate the cause(s) of END.

Large vessel occlusion and failure of collaterals is the most common mechanism of END. Recanalisation interventions—for example, thrombolysis with rt-PA or mechanical embolectomy in appropriate cases—may reduce frequency of END, though direct evidence for this is lacking. In a series of patients where thrombolysis was not given in view of rapidly improving symptoms or minor symptoms, END occurred in 58% of patients with large vessel occlusion but in only 5% of those with no occlusion. In future, general availability of penumbral imaging combined with vascular imaging might help in selecting patients who would benefit from late recanalisation therapies.

An alternative approach is collateral augmentation. In patients where a drop in blood pressure or reduced cerebral perfusion is the likely mechanism of deterioration, head down position and pressor therapy (with fluids or pressor agents) may...
Box 1: Some of the unanswered questions in relation to the early neurological worsening in acute stroke

- Does treatment of hyperglycaemia in acute stroke improve survival?
- What is the optimum control of blood pressure in acute stroke?
- What is the ideal method for improving collateral circulation in acute stroke?
- How to reduce the risk of potentially detrimental haemorrhagic transformation (parenchymal haematoma) in acute stroke?
- What is the best medical treatment for cerebral oedema in acute stroke?

be appropriate. However, evidence for pressor therapy is insufficient. In a pilot randomised trial of 15 patients with acute ischaemic stroke and >20% diffusion–perfusion mismatch on MRI, significant improvement in NIHSS, cognitive score and volume of hypoperfused tissue (152 to 58 ml) on perfusion weighted imaging was reported in patients given phenylephrine as a pressor agent.86 No significant untoward effects were observed. However, no large scale studies are available to draw definitive conclusions. In an approach to augment cerebral blood flow by partial aortic obstruction using a double-balloon device in patients with vasospasm complicating aneurysmal subarachnoid haemorrhage, Lylyk et al reported improvement in neurological deficits.87

In the Early use of Existing Preventive Strategies of Stroke (EXPRESS) trial, early initiation of preventive treatments after transient ischaemic attacks or minor stroke was associated with an 80% reduction in the risk of early recurrent stroke.88 Antiplalet agents are used to reduce recurrent embolism in ischaemic stroke. A combination of aspirin and dipyridamole is superior to aspirin alone.89 Clopidogrel can be used in patients with genuine aspirin allergy. An ongoing study is aiming to compare the efficacy of aspirin plus dipyridamole versus clopidogrel in stroke prevention.89 A recent study suggested superiority of combination of aspirin and clopidogrel over aspirin alone in reducing stroke recurrence (7% vs 10.8%) when given early after a transient ischaemic attack or minor stroke.90 The authors comment that the benefit was not negated by the increased risk of haemorrhage with the combination treatment.

Anticoagulation with heparin is sometimes used in ischaemic stroke to reduce recurrent embolism, though evidence for its efficacy is not proven and safety concerns exist. The International Stroke Trial tested two doses (5000 U/day or 25 000 U/day) of subcutaneously administered heparin within 48 h of stroke.91 Although heparin was effective in lowering the risk of early recurrent stroke, an increased rate of bleeding complications negated this benefit. The recommendation from current guidelines from the American Heart Association/ American Stroke Association92 says “urgent anticoagulation with the goal of preventing early recurrent stroke, halting neurological worsening, or improving outcomes after acute ischaemic stroke is not recommended for treatment of patients with acute ischaemic stroke”. There is no evidence for use of glycoprotein IIb/IIIa inhibitors in ischaemic stroke.

Cerebral oedema in ischaemic stroke is cytotoxic and is unresponsive to steroids, hyperventilation, and osmotic agents. Decompressive surgery, including hemicraniectomy and durotomy with temporal lobe resection, may be considered in selected patients with pronounced ischaemic brain swelling.93 In patients with malignant middle cerebral artery infarction, decompressive surgery undertaken within 48 h of stroke onset reduces mortality and has a favourable effect on the functional outcome.94

No intervention is currently available to reduce the risk of haemorrhagic transformation except that patients for thrombolysis should be appropriately selected. Space occupying haematoma resulting from thrombolysis may require neurosurgical evacuation.

There is no evidence for prophylactic use of antiepileptic agents. Patients with evident seizures should be treated with antiepileptic agents.

CONCLUSION

Early neurological deterioration in ischaemic stroke is common and is associated with poor outcome and death. Development of stroke units has evidently improved outcomes in acute stroke and it is possible, though not proven, that recent reports of decline in the rates of early worsening may partly be attributed to the increasing care in stroke units. Recognition of the predictors of early worsening may help in selecting patients for admission to the high dependency units equipped with intensive monitoring and treatment of these ill patients and prompt initiation of appropriate therapy. Prompt institution of antithrombotic treatment may help in reducing risk of recurrent stroke. Recognition and appropriate management of raised temperature, hyperglycaemia, hypotension, atrial fibrillation, and large vessel occlusion may prevent early worsening and improve patient outcome.

Despite advances in the treatment of acute stroke, several questions remain unanswered (box 1). Hyperglycaemia is a recognised predictor of early worsening but the evidence for a beneficial effect of treating hyperglycaemia in acute stroke on outcomes is lacking. Similarly, direct evidence for reducing frequency of early worsening with recanalisation interventions—for example, thrombolysis with rt-PA or mechanical embolectomy—is not available. Blood pressure management in acute stroke is still a matter of debate and is a subject of ongoing studies (COSSACS, ENOS). Craniotomy for large ischaemic infarctions associated with cerebral oedema is applicable for

Key learning points

- Worsening of acute stroke early in its course is a common occurrence and is associated with increased morbidity and mortality.
- The underlying mechanisms include failure of collaterals, clot progression, recurrent (local or remote) stroke, raised intracranial pressure, seizures, and haemorrhagic transformation of the ischaemic infarct.
- Clinical predictors of early worsening include severity of initial stroke, large vessel occlusion, diabetes mellitus, hypotension, and atrial fibrillation.
- Radiological predictors include extent of hypodensity >33% in the middle cerebral territory, hyperdense middle cerebral artery sign and brain swelling on CT scan at 24 h.
- Modern imaging techniques are very useful for the assessment, risk stratification, and management of these patients.
- As the patient’s condition can deteriorate rapidly, urgent and aggressive approach to diagnose, assess and treat these patients is warranted.
selective patients only and optimal treatment of cerebral oedema in acute stroke remains unknown. Future studies looking into these questions may improve our understanding of the phenomenon of early worsening in acute stroke and hence improve patient outcomes.

Competing interests: None.

REFERENCES

Transcendental meditation and hypertension

A 58-year-old woman was referred to our clinic for advice on the management of hypertension. As part of her pre-clinic assessment a 24 h ambulatory blood pressure measurement was performed (fig 1). This revealed a striking dip in blood pressure at around 17:00 with her systolic and diastolic measurements both being lower than when she was asleep. On review in clinic it transpired that this dip corresponded to the patient practising transcendental meditation. There is some evidence to suggest that regular transcendental meditation may reduce blood pressure in hypertensive patients, although at around 5/3 mm Hg, this is considerably less than the striking, acute reduction in blood pressure seen in our patient.

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