

CLINICAL PRACTICE

Acute Ischemic Stroke

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This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.

A 62-year-old man has sudden weakness of the left arm and leg and slurred speech. Except for untreated hypertension, his medical history is unremarkable. He is a current smoker with a smoking history of 45 pack-years. On arrival at the emergency department 1 hour 15 minutes after the onset of symptoms, he reports no headache or vomiting. His blood pressure is 180/100 mm Hg, and his pulse is 76 beats per minute and is regular. Neurologic examination shows dysarthria, a left homonymous hemianopia, severe left-sided weakness, and a failure to register light touch on the left side of the body when both sides are touched simultaneously (left tactile extinction). How should this patient be evaluated and treated in the short term?

THE CLINICAL PROBLEM

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Stroke ranks second after ischemic heart disease as a cause of lost disability-adjusted life-years in high-income countries and as a cause of death worldwide.¹ The incidence of stroke varies among countries and increases exponentially with age. In Western societies, about 80% of strokes are caused by focal cerebral ischemia due to arterial occlusion, and the remaining 20% are caused by hemorrhages.²

Ischemic brain injury is thought to result from a cascade of events from energy depletion to cell death. Intermediate factors include an excess of extracellular excitatory amino acids, free-radical formation, and inflammation.³ Initially after arterial occlusion, a central core of very low perfusion is surrounded by an area of dysfunction caused by metabolic and ionic disturbances but in which structural integrity is preserved (the ischemic penumbra). In the first minutes to hours, therefore, clinical deficits do not necessarily reflect irreversible damage. Depending on the rate of residual blood flow and the duration of ischemia, the penumbra will eventually be incorporated into the infarct if reperfusion is not achieved (Fig. 1).³

Thirty-day case fatality rates for ischemic stroke in Western societies generally range between 10 and 17%.² The likelihood of a poor outcome after stroke increases with increasing age, with the coexistence of diseases such as ischemic heart disease and diabetes mellitus, and with increasing size of the infarct. The likelihood also varies according to the infarct site. Mortality in the first month after stroke has been reported to range from 2.5% in patients with lacunar infarcts⁴ to 78% in patients with space-occupying hemispheric infarction.⁵

STRATEGIES AND EVIDENCE

Acute stroke is typically characterized by the sudden onset of a focal neurologic deficit, though some patients have a stepwise or gradual progression of symptoms. Common deficits include dysphasia, dysarthria, hemianopia, weakness, ataxia, sensory loss, and neglect. Symptoms and signs are unilateral, and consciousness is

generally normal or impaired only slightly, except in the case of some infarcts in the posterior circulation.

INITIAL ASSESSMENT

In the majority of cases of stroke, making the diagnosis is straightforward. However, especially in patients with unusual features (e.g., gradual onset, seizure at the onset of symptoms, or impaired consciousness), the differential diagnosis should include migraine, postictal paresis, hypoglycemia, conversion disorder, subdural hematoma, and brain tumors.

Atherosclerosis (leading to thromboembolism or local occlusion) and cardioembolism are the leading causes of brain ischemia. However, unusual causes should be considered, especially if patients are younger (e.g., below 50 years of age) and have no apparent cardiovascular risk factors. Some clinical clues that suggest alternative diagnoses are ptosis and miosis contralateral to the deficit (carotid-artery dissection), fever and a cardiac murmur (infective endocarditis), and headache and an elevated erythrocyte sedimentation rate in patients older than 50 years of age (giant-cell arteritis).

Deficits should be assessed by careful neurologic examination. Several scales have been developed to quantify the severity of the neurologic deficit, mainly for use in research studies; the National Institutes of Health Stroke Scale⁶ is most often used. An irregular pulse suggests atrial fibrillation. A very high blood pressure may signal hypertensive encephalopathy and precludes thrombolysis if sustained at or above 185/110 mm Hg. Carotid bruits lack sufficient sensitivity and specificity for a diagnosis of severe carotid stenosis.⁷

Laboratory testing during the acute phase should include measurement of the glucose level (since hypoglycemia may also cause focal neurologic deficits), a complete blood count, and measurement of the prothrombin time and partial-thromboplastin time, particularly if thrombolysis is considered. An electrocardiogram may reveal atrial fibrillation or an acute or previous myocardial infarction as potential causes of thromboembolism. Because stroke may be complicated by myocardial ischemia and arrhythmias, cardiac monitoring is recommended for at least the first 24 hours.⁸ Echocardiography in the first hours after the onset of stroke is necessary only in

rare cases, such as if infective endocarditis is suspected. In the days thereafter, transthoracic echocardiography or, preferably, transesophageal echocardiography may be indicated to rule out cardioembolism.

IMAGING

Cerebral infarction cannot be distinguished with certainty from intracerebral hemorrhage on the basis of symptoms and signs alone. In all patients with suspected ischemic stroke, computed tomography (CT) or magnetic resonance imaging (MRI) of the brain is therefore required. Noncontrast CT may suffice (Fig. 2); as compared with MRI, it is more widely available, faster, less susceptible to motion artifacts, and less expensive. Both CT and MRI have a high sensitivity for acute intracranial hemorrhage, but MRI has a much higher sensitivity than CT for acute ischemic changes, especially in the posterior fossa and in the first

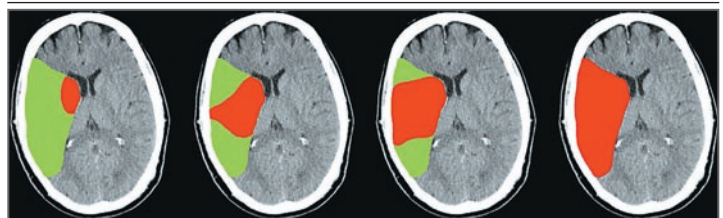


Figure 1. Progression over Time (Left to Right) of the Infarct Core (Red), with Irreversible Damage at the Expense of the Ischemic Penumbra (Green).

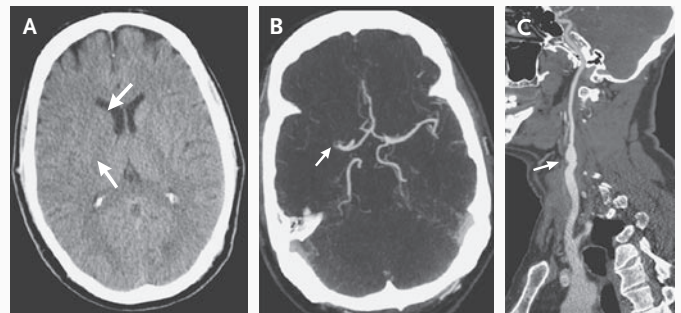


Figure 2. CT Scans Obtained 1 Hour 40 Minutes after the Onset of Symptoms Suggestive of Cortical Stroke in the Territory of the Right Middle Cerebral Artery.

An unenhanced CT scan (Panel A) shows a slight loss of differentiation of gray and white matter in the basal ganglia (arrows). A CT angiographic image shows occlusion of the first segment of the right middle cerebral artery (Panel B, arrow) and atherosclerotic lesions in the carotid bifurcation (Panel C, arrow). The external carotid artery is not shown.

hours after an ischemic stroke.⁹ Cytotoxic edema is detectable within minutes after the onset of ischemia, with a reduced apparent diffusion coefficient on diffusion-weighted imaging (Fig. 3).¹⁰ However, it remains unclear whether early visualization of ischemia has important implications for management.

For patients in whom acute invasive treatment strategies (such as intraarterial thrombolysis or mechanical clot retrieval) are considered, urgent CT or magnetic resonance angiography is useful to identify the site of arterial occlusion (Fig. 2). Either method can provide complete visualization from the aortic arch to the circle of Willis and beyond.¹⁰ Carotid duplex ultrasonography and transcranial Doppler ultrasonography have also been used to detect the site of occlusion.¹⁰

INTRAVENOUS THROMBOLYSIS

The National Institute of Neurological Disorders and Stroke Recombinant Tissue Plasminogen Activator (NINDS rt-PA) Stroke Study, a multicenter, randomized trial, has demonstrated the efficacy of treatment with intravenous rt-PA (alteplase) started within 3 hours after the onset of symptoms.¹¹ Among patients treated with rt-PA (0.9 mg per kilogram of body weight, with 10% of the dose administered as a bolus and the rest infused over 1 hour and a maximum total dose of 90 mg), 31 to 50% had a favorable neurologic or functional outcome at 3 months (depending on the scale used), as compared with 20 to 38% of patients given placebo; mortality rates were similar in the two groups. Symptomatic intracranial hemorrhage

occurred in 6.4% of patients treated with intravenous rt-PA and in 0.6% of controls. Four other trials of intravenous rt-PA therapy given within 6 hours after the onset of symptoms (with few patients treated within 3 hours) failed to find a benefit of thrombolysis separately, but if analyzed in combination, they provided support for a benefit of treatment administered within the first 3 hours after stroke.^{12,13} Even within the 3-hour time frame, the benefit of rt-PA is greater the sooner treatment is started.¹³

The risk of symptomatic intracranial hemorrhage after thrombolysis is higher in patients with more severe strokes and with increased age.¹⁴ However, a post hoc subgroup analysis of the NINDS rt-PA Stroke Study found no significant differences in the benefit from rt-PA therapy across these and other subgroups,¹⁵ but the numbers of patients in each subgroup were small. Similar concerns have been raised about the efficacy and safety of rt-PA in patients with early ischemic changes on CT. Other post hoc analyses of data from the NINDS rt-PA Stroke Study showed that in the first 3 hours after the onset of symptoms, the appearance of ischemic changes on CT was not an independent predictor of an increased risk of symptomatic intracranial hemorrhage or other adverse outcomes after treatment with rt-PA.¹⁶ Several observational studies have suggested that intravenous thrombolysis with rt-PA can be used in the community setting with efficacy and safety similar to that found in the randomized trials.^{17,18}

OTHER TREATMENTS

Aspirin

In two large randomized trials, the use of aspirin (160 or 300 mg per day), initiated within 48 hours after the onset of stroke and continued for 2 weeks or until discharge, led to reduced rates of death or dependency at discharge or at 6 months,^{19,20} probably by means of reducing the risk of recurrent ischemic stroke. In both trials, the routine use of aspirin was recommended as secondary prevention after the first few weeks. Although the benefit was small (77 patients would need to be treated to prevent a poor outcome in 1 patient), aspirin is inexpensive, has a good safety profile, and appears to be effective across the range of patients with ischemic stroke.²¹ Because the effect of aspirin in combination with rt-PA is uncertain, it seems wise to withhold aspirin for 24 hours in

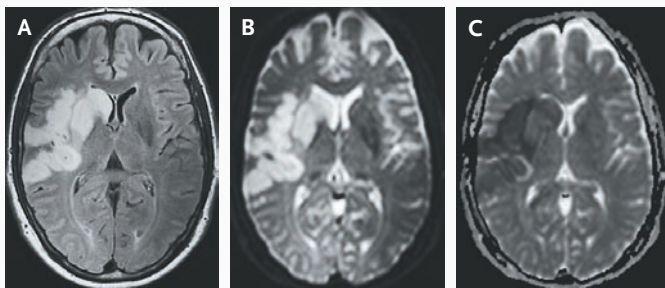


Figure 3. MRI Scans Obtained 2 Days after the Onset of Ischemic Stroke in the Territory of the Right Middle Cerebral Artery.

A hyperintense lesion in the temporal and frontal lobes and in the basal ganglia is shown on fluid-attenuated inversion recovery (Panel A) and diffusion-weighted imaging (Panel B), corresponding to a reduced apparent diffusion coefficient (Panel C). Similar changes may be observed on diffusion-weighted imaging in the first hours after the onset of symptoms.

patients treated with the use of intravenous thrombolysis. The use of dipyridamole or clopidogrel in the acute phase of ischemic stroke has not been tested in randomized trials.

Anticoagulant Therapy

A meta-analysis of six randomized trials involving 21,966 patients found no evidence that the use of anticoagulants (unfractionated heparin, low-molecular-weight heparins, heparinoids, thrombin inhibitors, or oral anticoagulants) in the acute phase of stroke improves functional outcomes.²² According to this analysis, nine fewer cases of recurrent ischemic stroke would be expected per 1000 patients treated, but so would nine more cases of symptomatic intracranial hemorrhage.²² A meta-analysis of seven trials similarly failed to show improvement in functional outcome with the use of anticoagulant therapy in patients with acute cardioembolic stroke.²³

PREVENTION AND MANAGEMENT OF COMPLICATIONS

Nutrition is often compromised in patients admitted to the hospital with stroke. However, in randomized trials, neither the routine use of oral nutritional supplements²⁴ nor early tube feeding²⁵ to prevent or treat undernutrition in hospitalized patients with stroke resulted in improved long-term functional outcome.

Patients with acute stroke are at increased risk for deep venous thrombosis and pulmonary embolism, and the risk increases with increasing age and stroke severity.²⁶ Although the use of anticoagulants does not improve overall functional outcomes, the use of subcutaneously administered low-dose unfractionated heparin or low-molecular-weight heparin has been recommended in patients at high risk for deep venous thrombosis, such as patients who are immobile (e.g., due to paralysis of a leg).^{8,27}

In patients with large supratentorial infarcts, space-occupying brain edema may lead to tentorial or uncal herniation, usually between the second and fifth days after the onset of stroke.⁵ Case series of such patients in intensive care units have reported early case fatality rates of up to 78%.⁵ No medical therapy has proved effective.²⁸ In a pooled analysis of three randomized trials comparing surgical treatment (hemicraniectomy and duraplasty, the insertion of a dural patch to enlarge the intradural space) with medical treat-

ment in 93 patients 60 years of age or younger with space-occupying infarction in the territory of the middle cerebral artery, surgical treatment in the first 48 hours after the onset of stroke reduced both the case fatality rate (22%, vs. 71% in the medical-management group) and the rate of moderately severe or severe disability or death (57% vs. 79%).²⁹ Surgery appeared to be less beneficial for patients with aphasia (vs. those without aphasia), patients older than 50 years of age (vs. those 50 years of age or younger), and patients in whom surgery was performed on the second day after the onset of stroke (vs. the first day after onset); however, the numbers of patients in these subgroups were small.

Data from randomized and other trials indicate that patients who receive care in a stroke unit are more likely to survive, regain independence, and return home than are those who do not receive such organized care.³⁰

STRATEGIES TO REDUCE RISK OF RECURRENT STROKE OR OTHER CARDIOVASCULAR EVENTS

In patients presenting with stroke, attention to secondary prevention of stroke and other cardiovascular complications is routinely warranted. Although space limitations preclude a detailed discussion of recommended strategies, they include the use of low-dose aspirin and dipyridamole in patients with ischemic stroke of arterial origin³¹; oral anticoagulation in patients with cardiac embolism; treatment of hypertension; statin therapy for the lowering of lipid levels; glucose control in patients with diabetes; smoking cessation; and carotid endarterectomy in patients with substantial ipsilateral carotid stenosis. These issues have been discussed in detail elsewhere.^{32,33}

AREAS OF UNCERTAINTY

Even in high-income countries such as the United States, only a small minority of patients with acute ischemic stroke receive intravenous rt-PA.³⁴ Its use is currently restricted to a 3-hour time window after the onset of symptoms, on the basis of results of the NINDS rt-PA Stroke Study,¹¹ but a pooled analysis of six randomized trials has suggested a potential benefit within up to 6 hours after the onset of stroke.¹³ Trials assessing treatment in this extended time frame among broad populations of patients with ischemic stroke are under way.

Preliminary data have suggested that the identification of patients who would benefit from thrombolysis beyond a 3-hour interval might be improved by quantification of the ischemic penumbra with the use of diffusion–perfusion MRI or perfusion CT techniques (Fig. 4).^{35–37} This suggestion requires further study.

Although the intent of intravenous thrombolysis is to recanalize occluded arteries, none of the pivotal clinical trials tested whether recanalization actually occurred. Other studies have shown that complete recanalization of an occluded middle cerebral artery 2 hours after the start of thrombolysis was achieved in only up to one third of patients.^{38,39} In one controlled trial, continuous 2-MHz transcranial Doppler ultrasonography applied for 2 hours augmented the rate of rt-PA–induced arterial recanalization.³⁸ Limited data suggest that the addition of intravenous galactose–based microbubbles to this treatment strategy may further increase rates of recanalization.³⁹ Because it is still uncertain whether additional measures to improve perfusion also improve functional outcome, these techniques cannot be recommended for use outside clinical trials.

As compared with intravenous thrombolysis, intraarterial thrombolysis may increase the likelihood of recanalization, but the two strategies have not been directly compared in a sufficiently large randomized trial. In a small randomized trial, the administration of both intraarterial recombinant prourokinase and intravenous heparin, as compared with intravenous heparin alone, within 6 hours after the onset of stroke resulted in a higher rate of recanalization of the middle cerebral artery (66% vs. 18%) and a higher rate

of a favorable functional outcome (no disability to slight disability) at 3 months (40% vs. 25%, $P=0.04$).⁴⁰ However, the procedures required to deliver the thrombolytic agent to the site of vascular occlusion involve more time than does intravenous therapy. Thrombolytic “bridging therapy,” in which intravenous thrombolysis is followed by intraarterial thrombolysis,⁴¹ could permit more rapid treatment and improved rates of recanalization but is resource intensive, limiting widespread application. Mechanical thrombectomy in patients with acute intracranial occlusion of the intracranial carotid artery has resulted in a high rate of recanalization in case series,⁴² but controlled trials are lacking.

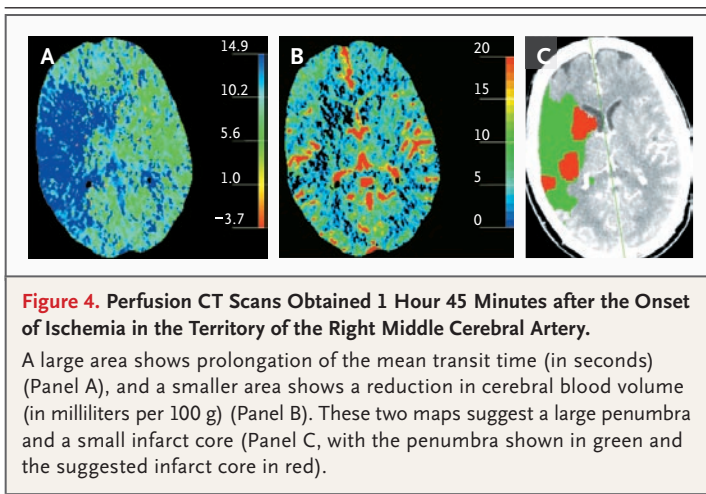
OTHER TREATMENTS

High blood pressure,⁴³ a high serum glucose level,⁴⁴ and a high body temperature⁴⁵ in the first hours to days after ischemic stroke have all been associated with poor long-term outcomes. The effects of the early lowering of blood pressure and maintenance of normothermia and normoglycemia are currently being tested in large randomized trials.^{43,46,47}

Data from randomized trials are needed to guide the management of blood pressure in the context of acute stroke. Given concerns about adverse effects of the short-term lowering of blood pressure on cerebral perfusion, current guidelines based on consensus opinion recommend withholding antihypertensive therapy during the acute phase of stroke unless the diastolic blood pressure exceeds 120 mm Hg or the systolic blood pressure exceeds 220 mm Hg in patients who are not candidates for rt-PA.⁸ Blood-pressure monitoring is recommended before, during, and after rt-PA therapy, and intravenous antihypertensive therapy is recommended to maintain the systolic blood pressure below 180 mm Hg and the diastolic blood pressure below 105 mm Hg.

NEUROPROTECTION

Hundreds of neuroprotective strategies have been shown to improve outcome in animal models of focal cerebral ischemia,⁴⁸ but thus far only rt-PA and aspirin have been shown to be clearly efficacious in patients. Although early data suggested a possible benefit of the free-radical-trapping agent NXY-059 in acute ischemic stroke,⁴⁹ a large multicenter trial reported on by Shuaib et al. in this issue of the *Journal* showed no improvement in



functional outcomes of patients who were treated with this agent within 6 hours after the onset of symptoms.⁵⁰

Hypothermia has been shown to reduce infarct volume and improve neurologic outcomes in animal models of focal cerebral ischemia⁵¹; it has also improved functional outcomes in randomized clinical trials involving patients with global cerebral ischemia after cardiac arrest,^{52,53} but the improvement was not consistent among those with traumatic brain injury.⁵⁴ Large clinical trials testing the effect of hypothermia in patients with acute ischemic stroke are warranted.

GUIDELINES FROM PROFESSIONAL SOCIETIES

Practice guidelines have been issued by the Stroke Council of the American Heart Association and the American Stroke Association⁸ and by the European Stroke Initiative.⁵⁵ The recommendations in this article are generally consistent with those guidelines.

CONCLUSIONS AND RECOMMENDATIONS

The patient described in the vignette had a sudden left-sided hemiparesis, strongly suggestive of a right hemisphere stroke. CT or MRI of the brain should be performed promptly; MRI is more sensitive for early ischemic changes, but either method can fully rule out hemorrhage. In the absence of bleeding or other contraindications to thrombolysis (e.g., spontaneous, complete clearing of the deficits or an increase in blood pressure to 185/110 mm Hg or more) (Table 1), since the pa-

Table 1. Main Contraindications to Intravenous Thrombolysis in Patients with Acute Ischemic Stroke.*

Onset of symptoms >3 hr before start of treatment
Intracranial hemorrhage on CT or MRI
Head trauma or stroke in previous 3 mo
Myocardial infarction in previous 3 mo
Gastrointestinal or urinary tract hemorrhage in previous 21 days
Major surgery in previous 14 days
History of intracranial hemorrhage
Systolic blood pressure ≥ 185 mm Hg or diastolic blood pressure ≥ 110 mm Hg
Evidence of active bleeding or acute trauma on examination
Use of oral anticoagulants and an INR ≥ 1.7
Use of heparin in previous 48 hr and a currently prolonged aPTT
Platelet count <100,000 per cubic millimeter
Blood glucose level <50 mg/dl (2.7 mmol/liter)
Seizure with postictal residual neurologic impairments

* Adapted from Adams et al.,⁸ which provides a more complete overview of indications and contraindications. INR denotes international normalized ratio, and aPTT activated partial-thromboplastin time.

tient presented within 3 hours after the onset of symptoms, we would recommend therapy with intravenous rt-PA. We would start aspirin after 24 hours (300 mg daily for the first 2 weeks) and would then administer lower-dose aspirin and dipyridamole for secondary prevention. Aggressive management of other cardiovascular risk factors — including encouraging the patient to stop smoking, treating his hypertension, and initiating statin therapy — is also warranted.

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