Worsening in Ischemic Stroke Patients: Is it Time for a New Strategy?

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What can be more frustrating for physicians (and, of course, for their patients) than deterioration during treatment? Expectations are high that patients will get better when they come to the hospital, not get worse. Unfortunately, worsening is a common occurrence in patients with brain ischemia despite present treatment. In this issue of Stroke, Steinke and Ley show that, among their stroke patients, worsening of motor function, a very important component of disability, was most common among those who had lacunar strokes.1

Categorization of Worsening

The term worsening, as presently used, is arbitrary in that it depends on an extremely variable starting time—entry into medical care. If an individual who becomes considerably more hemiplegic 4 hours after the first symptom of weakness and then stabilizes enters a hospital at hour 2, he or she is classified as worsening. If, instead, the patient enters the hospital at hour 5, he or she would not be classified as worsening. Present designation of worsening then depends on when the clock starts running. I avoid terms based on worsening such as “stroke-in-evolution” and “progressing stroke,” since they depend on a shifting start time. Ideally, physicians should attempt to alter a declining course of illness graph that begins at the time of symptom onset. Worsening during the first few hours often has quite different explanations than worsening during hours 12 to 48. Unfortunately, it is often difficult to quantify deficits present before the patient is seen by a physician experienced in stroke care using only the accounts of the patient and observers.

There are mainly 3 different large categories of worsening: (1) Medical complications, especially febrile illnesses, which affect the patient systemically and may also lead to increased brain ischemia. These complications usually do not develop on the day of admission, and these patients are sick and often febrile. (2) Brain edema—a complication of mostly large strokes, especially hemorrhages. This complication is also delayed for more than 1 day, and headache and decreased alertness are common features. (3) Gradual or stepwise increases in focal deficits while the patient usually remains alert and free of medical complications. It is this last category, which usually begins during the first day of admission, that forms the substance of the study of motor progression in this issue of Stroke1 that I will focus on herein in this editorial.

How Common Is Worsening, and in Which Stroke Subtypes Does it Occur?

The frequency of progression of neurological deficits after onset varies in different series but usually is estimated at between 1 and 2 patients in 5. Frequency of clinical worsening after hospitalization varies depending on the mix of stroke patients and their time of entry into the hospital. In the Harvard Stroke Registry, 95/471 (20%) of stroke patients progressed after onset either gradually (10%) or stepwise (10%).2 Progression was most common in patients with lacunar infarcts (37%) and large-artery occlusive disease (33%) and least frequent in patients with embolism (7%). In the Barcelona Stroke Registry, among >3500 patients, 37% worsened gradually or stepwise after onset.3 In the Lausanne Stroke Registry, among >3000 patients, worsening after admission occurred in 29% of all stroke patients and in 662 (34%) of noncardioembolic ischemic stroke patients.4 Among the noncardioembolic stroke patients who worsened, 58% progressed during the first 24 hours.4 Among 350 Japanese patients in one study, 25% progressed after admission; worsening in the hospital occurred in 26% of lacunar stroke patients.5

A number of studies focused on progression and worsening in series of patients with lacunar strokes. In a Spanish study of 225 lacunar infarct patients, the deficit accrued within hours in 50.5% and within days in 16%.6 In a study from Sweden, among 61 patients with lacunar strokes, all pure motor hemiplegia, 22 (36%) worsened after the first hour of symptoms and 18/22 (82%) progressions occurred during the first 24 hours.7 In the study by Steinke and Ley, 24% of patients had a worsening of motor deficits after hospitalization, and the predominant subtype of stroke was lacunar infarction.1 Progression of deficits in patients with lacunar strokes, even evolving within days after onset, has been noted many times in the past. Mohr, in a 1982 review of lacunar infarcts, commented that “this surprisingly leisure mode of onset” characterizes many lacunar strokes.8

Progression occurs in different patterns and time courses depending on stroke subtype. Patients with intracerebral hemorrhage develop gradual worsening of focal signs usually over minutes, occasionally a few hours, followed by headache, vomiting, and decreased consciousness. Patients with emboli arising from the heart or aorta most often have...
sudden-onset deficits that are maximal at onset (80%); about 20% of patients have a single step of worsening during the next 24 to 48 hours related to distal passage of emboli. The signature of noncardioembolic strokes, in patients with both small penetrating artery and large extracranial and intracranial artery occlusive disease, is a fluctuating changing course. Fluctuations between normal and abnormal, stepwise or stuttering accrual of signs, or gradual development of signs occurred in nearly half the patients with noncardioembolic strokes in the Harvard Stroke Registry. In 37% of patients in the Harvard Stroke Registry who had noncardioembolic stroke, the deficit was maximal at onset, probably indicating an embolus arising from proximal arterial disease.

What Factors Are Present in Patients With Noncardioembolic Strokes Who Worsen?

Three factors, in my opinion, warrant emphasis in predicting and explaining progression and significant worsening: (1) presence of a severe flow-reducing arterial lesion supplying the ischemic zone, (2) chronic hypertension, and (3) a diminished frequency of transient ischemic attacks (TIAs) preceding the stroke.

Bang et al found that severe middle cerebral artery stenosis was an important predictor of progression in Korean patients with striatocapsular infarcts. Among patients who worsened in the Michael Reese Stroke Registry, severe large-artery occlusive disease and lacunar infarcts predominated, and chronic hypertension and a relatively low frequency of TIAs were also noted. Lacunar infarcts are caused in the great majority of patients by occlusive disease, either lipohyalinosis or atheromatous branch disease, involving the penetrating artery (and sometimes also adjacent penetrating arteries) supplying the territory involved in the small, deep infarcts. These penetrating arteries are widely considered to be end arteries with little potential for collateralization. Recent studies using newer magnetic resonance technology show that patients whose perfusion-weighted images (PWI) show a larger area of involvement than the diffusion-weighted images (DWI) who have occlusive lesions on magnetic resonance angiography and do not reperfuse develop larger infarcts and more severe clinical deficits than those patients with open arteries and no PWI/DWI mismatch. The situations that most often cause progressing noncardioembolic infarcts—severe stenosis or occlusion of large arteries and penetrating artery disease—have in common severe flow reduction to ischemic brain areas. Hypoperfusion and distal embolization are the 2 mechanisms that lead to progressive infarction. These 2 mechanisms are interrelated since hypoperfusion also diminishes clearance and washout of any emboli. When perfusion is adequate, microemboli are often cleared efficiently.

Chronic hypertension, and also likely diabetes and hyperviscosity, impair microvascular function and blood flow. This likely reduces the potential of the microvasculature to provide collateral circulation to ischemic areas. Experimental animals made hypertensive develop larger infarcts when arteries are occluded than normotensive animals.

By definition, TIAs are reversible. This means that circulation was somehow restored to a previously ischemic area. Circulation was improved either by passage of emboli (implying the potential for washout) or by collateral circulation providing adequate blood flow. Thus the presence of TIAs implies the potential for reversal of abnormal perfusion.

Progression thus is most likely explained by decreased perfusion and/or decreased potential for rapid development of adequate collateral blood flow to ischemic zones.

How Should Patients With Nonembolic Brain Ischemia Be Managed?

If the problem is that there just isn’t enough blood getting there, then the intuitive obvious solution is simply to try to augment blood flow. Other solutions—eg, altering coagulation (using either heparins or antiplatelet drugs) and using neuroprotective agents—have been unproductive and are unlikely to make a large impact as long as blood flow is deficient. Reduced blood flow likely has a “Mack truck effect,” ie, it overrides all other factors. Although thrombus formation and propagation may play a role in progression, reducing coagulability while blood flow is still deficient is unlikely alone to impact progression and has not been effective in past trials. Neuroprotectants likely will not reach ischemic zones in sufficient quantities to be effective when the blood itself isn’t getting there.

Improving blood flow can be accomplished in 2 broad ways: opening arteries or augmenting collateral blood flow by systemic strategies. Opening arteries can be accomplished mechanically (by surgery or angioplasty and/or stenting) or by thrombolysis. However, many arteries either cannot be opened or have been occluded long enough that reopening would have a high complication rate of reperfusion hemorrhage and edema.

There is now accruing evidence that manipulation of the systemic circulation to augment cerebral blood flow can be therapeutic and can limit brain ischemia. In patients with positional ischemia, simply having them assume a supine or Trendelenburg position can reverse ischemic deficits. Pharmacologically raising blood pressure and expanding the circulation in experimental animals and humans using albumin infusions have been shown to limit the size of brain infarcts. Constriction of the abdominal aorta in experimental animals also augments cerebral blood flow.

The only treatment shown to be effective in patients with progressing lacunar infarcts is augmentation of cerebral blood flow. Frey, in a small preliminary study of 10 consecutive patients with lacunar strokes, found that reducing blood pressure often led to worsening. Furthermore, augmenting blood flow by giving a volume expander (intravenous hetastarch) was uniformly effective in improving worsening and induced improvement in all patients. Unfortunately, this treatment has not been tested in a controlled trial.

The first and most important goal should be to get more blood flow to the ischemic zone. While anticoagulants and antiplatelets and neuroprotectants may be useful, their utility is probably limited if there is persistent perfusion failure.

References

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