Early Stroke: A Dynamic Process

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In the acutely infarcted brain, cytokines are released into cerebrospinal fluid and blood. Interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α, among others, may play a role in the acute increases in plasma adrenocorticotropic hormone, cortisol, epinephrine, norepinephrine, and vasopressin.1–6 Increases in cytokines and hormones may in turn induce changes in other variables. When recorded on admission in acute stroke patients, many variables have been found to be associated with poor outcome in acute stroke. Body temperature7 is one such variable, blood glucose another,8–18 and C-reactive protein (CRP)19–22 and white blood cell count (WBC)20,23 serum cortisol and ferritin24 are further examples. Elevated plasma and cerebrospinal fluid levels of glutamate, glycine,25 ferritin,26 and IL-627 were also associated with deteriorating stroke.

It seems plausible that these variables generally are unaffected at stroke onset and then increase in the early hours after onset, depending on the severity of the stroke. We found this to be the case with temperature,28 which in a large series of patients was normal when measured within 2 hours of stroke onset, but which rose at 4 to 6 hours after stroke onset in patients with severe neurological deficits. At 8 to 10 hours after stroke onset, elevated temperature was associated with poor outcome. This association arose several hours after onset of severe stroke. Thus, the initial severity of the stroke preceded the increase in temperature.

Many studies on blood glucose and stroke prognosis share the same kind of problem. In most studies, blood glucose was measured fairly late after stroke onset and may have changed in the interval between onset of stroke and arrival at hospital. Researchers are divided into 2 groups on this question: those who maintain that elevated blood sugar is a stress response preceded the increase in temperature,28 which in a large series of patients was normal when measured within 2 hours of stroke onset, but which rose at 4 to 6 hours after stroke onset in patients with severe neurological deficits. At 8 to 10 hours after stroke onset, elevated temperature was associated with poor outcome. This association arose several hours after onset of severe stroke. Thus, the initial severity of the stroke preceded the increase in temperature.

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In such series of stroke patients, the timing of blood glucose measurement was not always well specified. Most often, measurements were performed between 12 to 24 hours after stroke onset or even later. A severe stroke may cause blood sugar to rise early after onset, thereby creating a “false” association between elevated blood sugar and poor outcome.

An ongoing study in the United Kingdom29 randomizes stroke patients with blood glucose levels >7 mmol/L to insulin treatment or placebo. This study may help to clarify whether increased blood glucose is harmful or just an epiphenomenon. Serial measurements of blood glucose in the early hours after stroke onset are another way to elucidate the question.

For the other variables claimed to be prognostic markers, such as WBC and CRP, it also seems likely that early changes occur in the interval between stroke onset and arrival at hospital and blood sampling. Peripheral WBC measured within 3 days of stroke onset was associated with poor outcome.20,23 CRP was found to be a prognostic marker in acute stroke by some investigators19,22 and not by others.21 In the cited studies, blood samples were taken too late to determine which came first—the stroke or the elevation of WBC or CRP. Much more clinical research is needed to evaluate the importance of these and other markers of stroke outcome. Plasma ferritin,26 another acute-phase reactant, was significantly elevated in patients with subsequent deteriorating stroke, and elevated ferritin was associated with poor outcome.24 Increased body iron stores were thought to enhance the cytotoxic mechanisms in cerebral ischemia, but the increased ferritin might also reflect an inflammatory reaction to stroke.

A plausible explanation may be that many variables are interrelated: it is likely that severe stroke generates a metabolic as well as an inflammatory response. The inflammatory response may induce fever mediated by IL-1,30 induce systemic inflammation (eg, rise in CRP, WBC, and acute-phase reactants primarily mediated by IL-1, IL-6, and TNF), and enhance excitotoxicity.31,32 The metabolic response may cause an increase in blood sugar, cardiac arrhythmia,33 and a rise in troponins T and I.34 In this hypothesis, all of these variables would be found to be associated with severe stroke and unfavorable outcome; it would only be meaningful to consider them in groups and avoid including them individually in multivariate analysis, because they primarily reflect the size of the inflammatory and the metabolic reactions. Fever, aspiration, elevated blood glucose, and other variables may contribute to worsen the prognosis.

The anatomical brain lesion is usually not fully established before 12 to 24 hours or more after stroke onset. Within this period neuroimaging by MRI, PET and SPECT35–38 may demonstrate penumbral tissue potentially
salvageable or reperfusion of ischemic tissue, which may indicate a fairly good prognosis. The results of such studies are valuable in the acute situation, to guide treatment decision and for information of the patient and the relatives about the outlook. In the majority of patients in whom such studies are not performed, the severity of the neurological deficit, primarily the level of consciousness and the presence of gaze deviation are the immediate, and easily available variables to guide prediction of prognosis. Stroke severity in itself as recorded by one or another of several stroke scales is a major predictor of stroke outcome.

Many researchers, in describing a prognostic marker (be it temperature, blood glucose, CRP, WBC, or other), have adjusted for stroke severity and found that the marker was independent thereof. To do so, rating scales for stroke are often used as if they were interval scales, and not nominal scales with large interobserver and intraobserver variation. This may have contributed to erroneous conclusions. In a biological system, it seems unlikely that so many variables can be causal and predict outcome independently. However, if that is the case, we need to develop models for entering stroke severity—MRI, PET, and SPECT data; temperature; blood glucose; CRP; WBC; plasma cortisol; glutamate; glycine; IL-6; ferritin; and a few others, such as age and prestroke modified Rankin scale score—to estimate the prognosis. Before doing so, we have to reexamine the variables within the first 1 to 2 hours after stroke onset and perform serial measurements to better describe the relationship over time between stroke severity and the variables. To investigate the biological relevance of these variables, we should determine whether they increase as reflections of the brain lesion or whether they are elevated at stroke onset. It is conceivable that the increases reflect the initial severity of the stroke and result from inflammatory or sympaticoadrenergic reactions to severe disease and then contribute to further tissue damage through mechanisms similar to those known from major surgery or septicemia.

References


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