Plasma Cortisol as a Measure of Stress Response in Acute Stroke

To the Editor:

Mulley et al.1 suggest that hyperglycemia following stroke is an epiphenomenon reflecting a stress response and may not independently predict outcome. I would argue to the contrary that hyperglycemia in the acute phase of stroke indicates an underlying diabetic state, which makes the outcome worse in these patients. We can diagnose diabetes (i.e., a patient has sustained abnormal levels of blood glucose over weeks or months) by measuring glucose binding to the hemoglobin A molecule. Of the three major glycosylation sites, HbA1a, HbA1b, and HbA1c, the fraction of the latter predominates. HbA1b sites are a possible source of error in the diagnosis of diabetes, which can be avoided by utilizing an isoelectric focusing chromatographic technique. This technique eliminates elevated glycosylated fractions produced by transient blood glucose elevations such as the short duration “stress” effects of hyperglycemia.

An earlier study of patients with acute myocardial infarction showed a highly significant correlation between glycosylated HbA1c measurements and frankly diabetic glucose tolerance tests obtained 3 months later.2 Using the isoelectric focusing technique, we studied glycosylated HbA1c levels in 100 consecutive acute stroke admissions3 and demonstrated a highly significant correlation between the random blood sugar and the HbA1c value (p<0.0001). This result strongly supports the existence of diabetic glucose levels for several weeks before the stroke and not acutely in the days surrounding the event.

Of those patients with HbA1c values in the clearly diabetic range, 27% had not been previously diagnosed with the condition and 64% died within the first week, compared with 16% of the nondiabetic group (p<0.001). The stroke scores and demographic profiles of the two groups showed no statistically significant differences. Therefore, the poorer prognosis of the high blood sugar group was more likely to depend on premorbid diabetic state than on stroke severity. This result led us to speculate that HbA1c measured by isoelectric focusing could be a useful predictor of stroke outcome and that a measurement of 7.8% or above definitely predict outcome. I would argue to the contrary that hyperglycemia in the acute phase of stroke indicates an underlying diabetic state, which makes the outcome worse in these patients.

We respectfully suggest that the concept of stress hyperglycemia has outlived its usefulness.

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References


Animal Models in Stroke

To the Editor:

In a recent editorial, Wiebers et al. noted the failure of several pharmacologic studies to translate from the experimental cerebral ischemia model to the clinical setting. The authors suggested that deficiencies in current animal models of stroke were primarily responsible for these shortcomings. In our view, a principal and obvious deficiency in most current stroke models is that they rely on mechanical occlusion of brain arteries and therefore do not simulate the clinical condition of this disease. To model stroke per se requires the induction of thrombotic occlusions at suitable arterial sites, resulting in the generation of cerebral infarction.

Over the past several years, we have developed models of photochemically induced vascular thrombosis for the purpose of investigating the consequences of thrombotic stroke on brain structure and function.4–6 These studies have shown that thrombotic events in cerebral vessels produce not only cerebral infarction, but also widespread hemodynamic, metabolic, and structural abnormalities, which may be absent in more conventional infarct models yet potentially important in terms of stroke outcome. For example, we have shown that thrombosis of the common carotid artery releases circulating humoral factors, which acutely alter cerebral vascular permeability and blood flow at remote sites.3–5 These findings have recently been duplicated for the case of heat-mediated arterial thrombosis (photoagulation), further indicating that thrombosis per se is involved intrinsically in generating remote consequences (unpublished observations). In a recent pharmacologic study, the remote hemodynamic consequences of acute cortical thrombotic infarction were inhibited without affecting infarct size.6 Thus, although the size of a pathological lesion is an important indicator of stroke outcome, we also need functional and behavioral probes to assess pharmacologic trials adequately.9

Finally, recent data demonstrate that ischemic brain injury may be enhanced when ischemia is induced by arterial thrombosis, in comparison to ischemia induced by mechanical arterial occlusion.10,11 Our findings also suggest that the temporal profile of neuronal and vascular injury may be different from that induced by ischemia alone and may help explain the current clinical inadequacy of drugs found to be protective in animal models. We therefore believe it useful to call attention to these experimental findings, inasmuch as this work demonstrates the consequences of a methodology that was invented to simulate stroke directly, thereby facilitating a direct approach to developing strategies to alleviate this widespread clinical problem.

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References


The following is in response:

To the Editor:

We thank Doctors Watson and Dietrich for their letter. They have made several useful points, which may further assist in understanding the disparity between animal stroke models and the human situation.

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Gonadotrophins, Livedo Reticularis, and Strokes

To the Editor:

Sneddon’s syndrome is an entity characterized by idiopathic livedo reticularis and recurrent strokes. Its pathogenesis is unknown, and the part played by antiphospholipid antibodies remains controversial. Recently Rautenberg and coworkers reviewed 16 patients (15 female) with Sneddon’s syndrome, all of them with negative tests for anticardiolipin antibodies. Bruyn et al., reviewing the literature, found that many patients were cigarette smokers, oral contraceptive users, or both. Thus, it is likely that multiple factors interact, at least in some cases, to produce this peculiar dermal and cerebral vasculopathy. We wish to report the case of a woman with Sneddon’s syndrome whose first stroke was probably triggered by gonadotrophin therapy.

This 27-year-old patient had a past history of migraine and heavy tobacco use. Livedo reticularis over all four limbs and Raynaud’s phenomenon were present since puberty. Anoreulasion was the cause of infertility and a first course of gonadotrophins was administered in November 1980. The patient received 21 intramuscular injections of human menopausal gonadotrophins and then 5,000 IU human chorionic gonadotropin (HCG). The day following the last injection she complained of pain in the right foot, which was cold and livid. The symptoms resolved spontaneously in 2 hours. Three days later, she developed the sudden onset of expressive aphasia and right hemiparesis. Brain computed tomography was consistent with left middle cerebral artery territory infarction. Cardiovascular examination and routine laboratory tests were unremarkable. Chest X-ray, echocardiography, electrocardiographic monitoring, right cardiac angiography, and bilateral carotid Doppler examination were normal. Platelet hyperaggregability to ADP was noted. Neurologic symptoms resolved within the following 6 months.

We maintained the patient on anticoagulant therapy until June 1989, and then changed to aspirin (250 mg daily) and dipyrindamole. In November 1989, she presented with left facial and arm weakness that regressed over 48 hours. We also noted a diffuse pyramidal syndrome and a slight slowing of mentation, but without cognitive impairment. Normal or negative values were obtained for ESR, full blood counts, serum glucose, renal and liver function tests, rheumatoid factor, cryoglobulins, circulating immune complexes, antinuclear antibody (ANA), IFA anti-DNA, C3, C4, CH50, VDRL, TPHA, protein C and S, antithrombin III, and prothrombin time. On repeated examinations using different reagents, partial thromboplastin time was normal, and the search for anticardiolipin antibodies by ELISA was twice negative. Biopsy of the livedo reticularis revealed a small inflammatory infiltrate in the dermis, but no vasculitis, and immune-fluorescence studies were negative. The patient refused permission for cerebral angiography. Magnetic resonance imaging of the brain using T2-weighted sequences showed multiple white matter hyperintensities in both centrum-semiovale.

Although our patient had other vascular risk factors (i.e., migraine and tobacco use), we believe that because of the close temporal relationship, gonadotrophin administration triggered the first stroke. Strokes related to gonadotrophin therapy are extremely rare although its use is widespread. Previously reported cases have been linked with the ovarian overstimulation syndrome, which causes a rapid shift in body fluid balance, abdominal pain, ascites, pleural effusions, hemoconcentration, and blood hypercoagulability. In this case, although clinical features of ovarian overstimulation were absent, it is possible that gonadotrophin-induced hyperestrogenism favored thrombosis via a transient increase in clotting factors (VII, IX, XI) or in platelet aggregability. This observation also suggests that women with livedo reticularis could be at risk for stroke when treated with gonadotrophins and should probably have a careful dermatological examination before their prescription.

Sneddon’s syndrome is known to show a marked female preponderance (sex ratio 3:1), Moreover, long-lasting periods of hormonal changes, such as pregnancy and oral contraceptive use, have both been linked to a possible increased risk of stroke in women with Sneddon’s syndrome. Thus, we should pay attention to the putative involvement of hormonal factors in the pathogenesis of this cerebral-dermal vasculopathy, particularly when the presence of anticardiolipin antibodies cannot be demonstrated.

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