

Research letter

Biochemical markers in acute ischemic stroke

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The diagnosis of ischemic stroke remains a clinical one, with confirmatory evidence obtained through neuroimaging. Early ischemic changes may be subtle or absent on CT scans. Analogous to the role that the creatine kinase (CK) MB fraction or troponin testing plays in the management of acute coronary syndromes, a biochemical test or panel of tests may be useful in the management of acute ischemic stroke.

We designed a preliminary prospective cohort study to test a panel of biochemical markers (neuron-specific enolase [NSE], myelin basic protein [MBP], S-100 β protein and thrombomodulin [Tm]) in blood samples from patients with acute ischemic stroke. These markers were chosen because they cover important cellular components of the brain that might be damaged in acute stroke. Adult patients with a persistent neurological deficit due to ischemic stroke were eligible. Twenty-eight nonconsecutive patients admitted at 2 hospitals with a diagnosis of acute ischemic stroke confirmed by CT scanning were evaluated. Their National Institutes of Health Stroke Scale (NIHSS) score on admission and their modified Rankin Scale (mRS) score on discharge were recorded. All patients provided informed consent. Blood samples were drawn on days 1 (admission), 3, 5 and 7 at one hospital and on days 1, 2 and 3 at the second hospital. Samples were immediately centrifuged and sera stored at -70°C . The 4 biochemical markers were as-

sayed using enzyme-linked immunosorbent assay.¹ Normal values were obtained through analysis of blood samples from healthy blood donors; thresholds for elevated levels were defined by the 98th percentile values for each marker. Analysis of the serum levels from healthy subjects showed no relation to age or sex.¹

The mean age of the 28 patients was 65 years (range 27–90); 18 were men. Stroke types were classified using the Oxfordshire Community Stroke Project classification:² partial anterior circulation stroke (PACS) in 10 patients, lacunar stroke (LACS) in 8, posterior circulation stroke (POCS) in 4 and total anterior circulation stroke (TACS) in 1; the type was unknown in 5. The time from stroke onset to initial phlebotomy was not controlled and varied from 3 to 24 hours.

On admission, elevated levels of NSE were found in 89% of the patients, Tm in 43%, MBP in 39% and S-100 β in 32%. At least one of the markers was elevated on admission in 93% of the patients (Table 1). By stroke type, 100% of the patients with LACS, 100% of those with POCS and 90% of those with PACS had elevated NSE levels on admission. Conversely, none of the patients with LACS had an elevated S-100 β level initially or subsequently. Peak levels of NSE, S-100 β and MBP, but not of Tm, were significantly correlated with admission NIHSS scores ($p < 0.05$). Similarly, peak levels of NSE, S-100 β and Tm, but not of MBP, were significantly correlated with discharge mRS scores ($p < 0.05$).

These preliminary results confirm an important conclusion: brain proteins are released into the blood after stroke, they can be easily measured, and they correlate with outcome. Others have examined these questions with a variety of markers.^{3–6} One advantage of using a panel of markers may be improved sensitivity.

Time after stroke onset to initial phlebotomy was not controlled in this preliminary study. Given the recent use of thrombolytic therapy within 3 hours of acute stroke onset,⁷ biochemical markers will be of most use if they are elevated in the first hours after stroke. In addition, the specificity of the test was arbitrarily fixed by values from a group of healthy blood donors. Thresholds for test interpretation may differ in a population of patients with non-neurological acute illnesses.

Table 1: Proportion of patients with acute ischemic stroke who had a positive test result for biochemical markers on admission

Biochemical marker	Proportion of patients with positive results (and 95% CI)
NSE	0.89 (0.72–0.98)
MBP	0.39 (0.22–0.59)
S-100 β	0.32 (0.16–0.52)
Tm	0.43 (0.24–0.63)
≥ 1 marker on panel	0.93 (0.76–0.99)

Note: CI = confidence interval, NSE = neuron-specific enolase, MBP = myelin basic protein, S-100 β = S-100 β protein, and Tm = thrombomodulin.

Several new hypotheses deserve further testing. Use of the panel of markers may make it possible to identify stroke subtypes biochemically. Although we did not show it in this small sample, a panel of biochemical markers may have greater diagnostic utility than any single marker alone. We are proceeding to address these questions at defined times in the first hours after stroke onset.

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References

1. Takahashi M, Chamczuk A, Hong Y, Jackowski G. Rapid and sensitive immunoassay for the measurement of serum S100 β using isoform-specific monoclonal antibody. *Clin Chem* 1999;45:1307-11.
2. Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. Classification and natural history of clinically identifiable subtypes of cerebral infarction. *Lancet* 1991;337:1521-6.
3. Fassbender K, Schmidt R, Schreiner A, Fatar M, Muhlhauser F, Daffertshofer M, et al. Leakage of brain-originated proteins in peripheral blood: temporal profile and diagnostic value in early ischemic stroke. *J Neurol Sci* 1997;148:101-5.
4. Buttner T, Weyers S, Postert T, Sprengelmeyer R, Kuhn W. S-100 protein: serum marker of focal brain damage after ischemic territorial MCA infarction. *Stroke* 1997;28:1961-5.
5. Abraha HD, Butterworth RJ, Bath PMW, Wassif WS, Garthwaite J, Sherwood RA. Serum S-100 protein, relationship to clinical outcome in acute stroke. *Ann Clin Biochem* 1997;34(pt 5):546-50.
6. Aurell A, Rosengren LE, Karlsson B, Olsson JE, Zbornikova V, Haglid KG. Determination of S-100 and glial fibrillary acidic protein concentrations in cerebrospinal fluid after brain infarction. *Stroke* 1991;22:1254-8.
7. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med* 1995;333:1581-7.

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