Serum S-100 Protein in Acute Stroke

To the Editor:

We read with interest the work of Missler et al and Büttner and colleagues, and agree with both sets of researchers on the need for reliable, noninvasive markers of neuronal damage following acute stroke. Such markers may allow prognostication of future clinical outcome and may be useful in acute therapy trials as surrogate markers of efficacy.

However, neither study cited our publication on serum S-100 protein levels in acute stroke,1,2 a study that examined 81 patients (68 with ischemic stroke and 13 with hemorrhagic stroke) within 48 hours of stroke ictus and compared them with 51 age-, race-, and gender-matched control subjects. As with both recent papers in Stroke, we found significantly higher serum S-100 protein levels in the stroke population than in the control group. Furthermore, the highest S-100 protein levels were seen in the hemorrhagic stroke group, and differentiation between the two stroke populations almost reached statistical significance. We also performed a temporal study (24, 48, 72, and 96 hours after ictus) in 13 patients and, unlike the recent Stroke studies, did not find differences between these time points. Convalescent samples were also analyzed in 57 of the 74 patients still alive at 3 months after stroke; S-100 protein levels had significantly fallen (2 P<.0001) at this time but were still above the level seen in the control population, suggesting partial restoration of glial cell integrity.

We have previously shown3 that neuron-specific enolase level and carnosinase activity are individually associated with clinical outcome, determined with use of the Rankin Scale score and Barthel Index, although their ratio has the strongest association. We also found that S-100 levels were associated with clinical outcome.3 The results of our S-100, neuron-specific enolase, and carnosinase activity work and the recent S-100 protein studies show that serum biochemical markers can be readily measured using commercially available assays and appear to provide useful prognostic information. We believe the combination of the results of two (or more) markers, as used in our neuron-specific enolase/human serum carnosinase article,4 may improve their usefulness and reliability. We are currently assessing whether early drug therapy can modulate these serum markers in patients with acute stroke, thereby supporting their use as surrogate markers of efficacy.

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References

Response

We thank Butterworth et al for their additional remarks concerning our work on S-100 protein in cerebral infarction.

The mechanisms leading to delivery of S-100 protein into blood are not yet understood in detail. It has been widely accepted that S-100 protein leaks from structurally damaged central nervous system cells into the cerebrospinal fluid and secondarily into the blood. Thus, elevated levels of S-100 in cerebrospinal fluid as well as in blood have been found to be a sensitive, although nonspecific, indicator of nervous system damage in patients with various neurological disorders. On the other hand, the group of S-100 proteins is involved in a variety of physiological functions.1 There is evidence that S-100 not only leaks from damaged cells, but may also be actively secreted by central nervous system cells and may be a mediator of glial reformation.2,3 In addition, the ratio between S-100 concentrations in cerebrospinal fluid and blood may be altered by impairment of the blood-brain barrier. It is not known how these factors influence S-100 measurements in cerebral infarction.

The significance of these pathophysiological mechanisms may differ in hemorrhagic and nonhemorrhagic stroke. To obtain a homogeneous patient population, we included in our study only patients suffering from nonhemorrhagic cerebral stroke. Thus, we could perform CT volumetry of the infarction and establish a quantitative correlation between S-100 level and infarct volume.

Since measurement of S-100 protein in blood is not specific for the type of damage to the central nervous system, we do not believe it is a suitable parameter to differentiate between hemorrhagic and nonhemorrhagic stroke. Butterworth et al found that the S-100 levels differed almost significantly between hemorrhagic and nonhemorrhagic stroke. This can be caused by differences between the two patient groups with respect to severity of neurological damage. In addition, the time course of S-100 concentrations may be different in hemorrhagic and nonhemorrhagic stroke due to different mechanisms of the release of S-100 into the blood.

Butterworth et al reported only partial restoration of the S-100 level 3 months after cerebral infarction. With respect to a possible role of S-100 in glial reformation, this is a very interesting finding. Unfortunately, they did not comment on whether S-100 levels in patients 3 months after infarction differed significantly from those in healthy control subjects. In our study, S-100 levels of the majority of patients had returned to normal 10 days after infarction. In contrast to the findings of Butterworth et al, we could demonstrate significant changes of S-100 levels during the first 8 days after cerebral infarction (n=8). We observed the highest concentration of S-100 on day 3, and S-100 levels on days 2 and 3 did not differ significantly. However, the S-100 concentration on day 3 differed significantly from those on days 1 and 4. Our data are supported by the findings of Büttner et al.5

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Stroke. 1998;29:730
doi: 10.1161/01.STR.29.3.730

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