Diagnostic Test for Acute Cerebral Ischemia
To the Editor:

We read with interest the article recently published by Lynch JR et al.1 The authors report that the knowledge of 1 marker of glial activation (S100B), 2 markers of inflammation (matrix metalloproteinase [MMP]-9 and vascular adhesion molecule [VCAM]) and 1 marker of thrombosis (von Willebrand factor [vWF]) in the first 6 hours can help identify patients with acute cerebral ischemia who could benefit from thrombolytic treatment. Thrombolysis is an effective therapy for ischemic stroke whether administered intravenously within 3 hours or intraarterially within 3 to 6 hours.2 Many stroke patients arrive in emergency rooms too late to receive thrombolysis.3 It is possible to shorten admission delay by using systems for fast identification and transport of acute ischemic stroke patients. The development of a panel of blood-borne biochemical markers may be beneficial for the quick diagnosis of ischemic stroke, as used today in cases of myocardial infarction. These biomarkers should in only minutes differentiate patients with TIA or other conditions causing acute focal neurological deficits from patients with ischemic stroke candidates to thrombolytic therapy. However, an increased expression of VCAM, MMP-9, and vWF is expected in inflammatory disorders, autoimmune diseases, or in patients with atherosclerosis,4 and S100B is increased in patients with brain injury of different causes.5 In addition, levels of these markers after cerebral ischemia probably vary significantly between patients depending on stroke severity, lesion location, spontaneous reperfusion, and interval between stroke onset and blood sampling. We have recently studied plasma levels of several inflammatory parameters, including VCAM, in a selected population of 115 patients with ischemic stroke admitted within 12 hours of stroke onset (excluding those with fever at admission, inflammatory diseases, or malignancies). We did not observe differences in VCAM plasma levels between patients within 12 hours of stroke onset and 30 age- and sex-matched controls. In our study, as well as that of other investigators6 VCAM levels showed a considerable overlap with levels in normal individuals. Therefore, biochemical markers analyzed in the study of Lynch et al1 are upregulated in ischemic stroke but interindividual variability is large.

Criticism about the extensive use of thrombolyis is based on the lack of diagnostic procedures demonstrating the presence of an arterial occlusion and potentially salvageable ischemic tissue. Neuroimaging techniques can provide information about the presence of penumbra tissue and vessel occlusion in hyperacute phases of stroke,2 but biochemical markers cannot.

It therefore appears that biochemical markers are time-consuming and are not helpful for the rational selection of patients as candidates for thrombolysis for several reasons. First, given the variability of serum levels of the different biochemical markers among patients, this method cannot absolutely confirm or reject ischemic stroke diagnosis. Also, given the lack of information obtained with these markers about the presence of penumbra tissue or vascular occlusion, their utility in the emergent evaluation of ischemic stroke is very limited. Obviously, as Lynch et al1 point out, further studies will be necessary to validate the use of these markers in clinical practice. Since time is critical in acute stroke management, patients with suspicion of ischemic stroke should be urgently taken to a hospital with expert stroke care.

Panel of Serum Markers for Rapid Diagnosis of Acute Stroke
Response:

We appreciate the thoughtful comments of Drs Irimia and Martinez-Villa, who raise concerns regarding the utility of a panel of blood-borne biochemical markers as a diagnostic adjunct for stroke. Of particular concern was the potential lack of specificity of these markers in patients without stroke but with comorbid illnesses including “inflammatory disorders, autoimmune diseases, or in patients with atherosclerosis.” We agree that the lack of specificity of individual markers in acute cerebral ischemia is a problem that limits the use of any single marker as a stand-alone diagnostic test. That is why a panel of markers was developed so that complementary information regarding discrete components of the ischemic and inflammatory cascade could be used in combination to provide greater accuracy in diagnosing stroke than would be possible using individual markers alone. In fact, using this approach we were able to demonstrate 90% specificity at a sensitivity of 90%. However, it is important to point out the limitations of this pilot study, as many of the control population were age-matched patients without neurological symptoms. We are currently evaluating the robustness of this technique to discriminate stroke patients from patients presenting to the emergency room with acute neurological deficits that are not ultimately diagnosed as stroke.
The authors also correctly point out that serum markers will vary with size and location of the stroke as well as with reperfusion. We agree that, although the sensitivity of a biochemical test will depend largely on the volume of injured tissue, the ultimate severity and nature of neurological symptoms will also vary as a function of location. Finally, Drs Irimia and Martinez-Villa states that “biological markers are time consuming.” In fact, this panel of markers is designed as a point-of-care platform that yields results in minutes, and could ultimately be available as a point-of-care test in the prehospital setting to help triage patients for rapid transport for thrombolytic therapy. It is the potential widespread availability, speed, and ease of use that makes this technology so promising. Obviously, as acknowledged in our original paper, further studies will be necessary to validate the utility of these markers in clinical practice.

John R. Lynch, MD
Neuroscience Critical Care Unit
Associate in Medicine (Neurology)
Duke University Medical Center
Durham, North Carolina

Daniel T. Laskowitz, MD
Neuroscience Critical Care Unit
Associate Professor of Medicine (Neurology)
Anesthesiology and Neurobiology
Duke University Medical Center
Durham, North Carolina
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Pablo Irimia and Eduardo Martínez-Vila

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