Blood markers in TIA
Array of hope?

Clinicians who care for patients with TIA face two big problems. First, we are diagnostically deprived. Even among experts in cerebrovascular disease, agreement on the clinical diagnosis of TIA is remarkably poor.1 The cardiologist has EKG and troponin available to diagnose patients with acute chest pain at the bedside. As most patients with TIA present with normal neurologic examination results, the neurologist typically has only the patient’s history. As those in active clinical practice can attest, some patients are better at telling that history than others.

Second, we are prognostically deprived. The high short-term risk of stroke following TIA is often emphasized, but the ability to identify this subgroup is distinctly suboptimal. Clinical risk scores, such as the ABCD2 score, have been proposed as useful bedside tools for this purpose.2 However, the ABCD2 score may be more limited in this regard than initially thought.3,4 MR diffusion-weighted imaging (DWI) is a more powerful tool for risk stratification, as patients with negative DWI are at extremely low risk of stroke.5 However, MRI has limited physical availability in most EDs and in many hospitals, is often not staffed after normal business hours, and is extremely resource intensive.

Can blood biomarkers help? Markers of myocardial tissue necrosis, such as troponin, have become an integral part of the urgent evaluation of patients with suspected acute coronary syndromes (ACS), providing a rapid, cost-effective means of diagnosis and risk stratification. Similarly sensitive and specific blood markers for acute cerebral ischemia have been elusive. Identifying traditional protein markers of brain tissue necrosis with utility in early TIA evaluation is likely to be challenging given the small amount of tissue injury present and the prevention of entry of brain biomarkers into the peripheral circulation by the blood–brain barrier, particularly early in the course of ischemic injury. Conversely, a strategy aimed at identifying the upstream pathologic processes which precipitate or are associated with cerebral ischemia, or alternatively the downstream immune response to brain injury, might be more informative.

In this issue of Neurology®, Zhan et al.6 report a small study examining gene expression profiles in the blood of patients with acute TIA. Using microarray technology, they identified 449 genes that were differentially expressed in the blood of patients with TIA compared to controls. Functional analysis of these genes showed that they were associated with systemic inflammation and coagulation activation, supporting the biological plausibility of their association with TIA. Intriguingly, additional analysis showed 2 distinct, separate patterns of gene expression dividing the overall TIA cohort into 2 groups. The 3 patients with evidence of infarction on MR DWI and the single patient with a recurrent stroke were all clustered together into one of these groups, raising the possibility that this pattern of gene expression might signify a high-risk group of patients with TIA.

The identification of a unique signature for a specific disease based on gene expression profiles, and use of these profiles to provide insight into the genetic and molecular processes underlying a complex biological system, is intriguing. Of course, there are a number of limitations to this study which suggest caution. Most obvious is the small sample size. The case-control design is particularly problematic given the lack of a clear gold standard for the diagnosis of TIA. Another concern is the possibility that factors other than acute cerebral ischemia differed between the TIA and control subjects that could account for the identified variations in gene expression. The same research group has published work in patients with stroke showing differential gene expression profiles based on the underlying stroke mechanism, such as carotid stenosis or cardioembolism.7 It is unclear whether the patterns seen in this study might be accounted for by the cause of TIA, as opposed to TIA itself. Finally, it would be informative to analyze serial samples after TIA to understand how gene expression changes over time.
Analysis of gene expression using microarrays is complex and time-consuming, and cannot be performed quickly and cost-effectively in a manner that would allow clinical use. So, from a technical standpoint, how does this work move from “bench to bedside”? There are 2 potential pathways. First, the proteins coded for by the expressed genes may be identified and traditional antibody-based assays for these proteins developed. This strategy has been used by other groups in a systematic search for viable stroke biomarkers. Alternatively, quantitative RT-PCR might be used to identify the RNA of the expressed genes directly.

The search for useful blood biomarkers for determining diagnosis and prognosis in patients with acute cerebrovascular disease has so far been largely unsuccessful, and the challenges go beyond just identifying the right markers. Issues in study design, such as enrolling a patient population representative of that in which the test might be used and determining the additive value to clinical assessment, are also critically important. The results of Zhan et al. give reason for hope, but also suggest that the path forward will be long, complex, and challenging.

**AUTHOR CONTRIBUTIONS**

Dr. Cucchiara: drafting/revising the manuscript, acquisition of data. Dr. Nyquist: drafting/revising the manuscript.

**DISCLOSURE**

Dr. Cucchiara serves on a data safety monitoring board for Wyeth; has received travel and speaker honoraria from Boehringer Ingelheim and diaDexus, Inc.; has received publishing royalties from UpToDate, Inc.; serves as a consultant for Ferrer, diaDexus, Inc., and iNova Pharmaceuticals; and receives research support from the NIH and the American Heart Association/ American Stroke Association. Dr. Nyquist reports no disclosures.

**REFERENCES**