What Kind of Stroke Is It?

The search for protein biomarkers in peripheral blood to aid in the diagnosis of stroke and the prediction of prognosis after stroke and risk of future stroke is an active area of investigation. Although some markers, such as S100b and neuron-specific enolase, have been shown to have prognostic value in ischemic stroke (1, 2), no biochemical markers have proven to be really useful in routine clinical practice. In this issue of Clinical Chemistry, Nybo and associates present similarly discouraging data for osteoprotegerin as a potential stroke biomarker (3). Why are we continuing to see lack of demonstrated clinical utility in studies for stroke biomarkers? Should the search for biomarkers for stroke be abandoned?

Some answers may lie in the deceptively simple question, what is a stroke?

Stroke is currently defined as a disruption of brain function due to a vascular insult, with symptoms lasting 24 h or more. This definition, now old, is in flux and in truth, our understanding of stroke has evolved tremendously with the evolution of new diagnostic technology. MRI has allowed us to show that ischemic stroke damage can occur with complete resolution of symptoms well before a 24-h time limit. Transient ischemic attack may be caused by microhemorrhage. And sophisticated imaging of the heart, great vessels, and extracranial and intracranial cerebral vessels has revealed that stroke can be caused by multiple underlying conditions. Thus, a modern definition might be that a stroke is a syndrome of brain dysfunction, temporary or permanent, with an underlying vascular cause.

Strokes can be categorized into 4 basic stroke types, ischemia (ischemic stroke and transient ischemic attack, 85% of all strokes), intracerebral hemorrhage (7%–8% of all strokes), subarachnoid hemorrhage (7%–8% of all strokes), and cerebral venous sinus thrombosis (≤1% of all strokes). In turn, each of these stroke types has multiple possible underlying causes. To be sure, common risk factors such as hypertension, diabetes mellitus, and cigarette smoking may underlie many strokes and more than one stroke type. The Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification system is typically used to categorize ischemic stroke into large artery disease, cardiogenic stroke, lacunar disease, and other, but even this division is crude (4).

Lacunar stroke may be embolic (5–7). Cardiogenic embolic stroke may include mural thrombus after myocardial infarction, atrial fibrillation, valvular heart disease, and aortic arch arteroembolism. Large artery disease may be the most homogeneous category, because it represents intrinsic atherosclerotic disease in the extracranial or intracranial arteries.

In the study reported in this issue, Nybo and co-workers used a careful case-control design within a large prospectively collected cohort from Scandinavia (3). Blood drawn at baseline was used to measure osteoprotegerin concentrations to predict future stroke. Cases of stroke were identified by using administrative data coding of stroke. The definition chosen was liberal and probably highly sensitive to patients admitted to a hospital with stroke of any type (8). However, many patients with transient ischemic attack or minor stroke either may not seek medical attention or they may be seen in a clinic or emergency ward and never be admitted to the hospital. Without an admission these patients will not ever be coded as a “stroke discharge.” Thus the possibility of misclassification bias, although small, remains.

The authors carefully classified ischemic stroke subtype according to the TOAST criteria. They performed this classification retrospectively by chart review. Without knowing the extent of the investigations completed, it is difficult to be certain that the classification is accurate. However, the quality of stroke unit care in Denmark is generally excellent, and so we can conclude that it is likely that this approach was accurate enough. The distribution of stroke types is similar to that seen in other cohort studies and in randomized trials of ischemic stroke patients. However, the TOAST categories illustrate that we are dealing with multiple underlying disease processes that cause ischemic stroke. Therefore, it may not be surprising that no relationship emerges with a single biomarker. Given the postulated biological mechanism for the inhibitory role of osteoprotegerin in vascular calcification, it would be of great interest to see if a relationship between ischemic stroke due to large artery disease and osteoprotegerin could be found.

Given that stroke is an episodic manifestation of its underlying cause or causes, why should we assume that a single measurement taken at one point in time would predict future stroke events? Perhaps, when the underlying cause (e.g., atrial fibrillation) is quiescent, the biomarker is quiescent. The timing of the protein measurement may be very relevant.

In summary, the search for biomarkers for stroke must go on, but it must be done according to specific stroke types. As our understanding of stroke progresses, we must also adjust our study methods. De-
etailed understanding of stroke mechanisms (in both ischemia and hemorrhage) is necessary to the identification of clinically relevant correlations of stroke with protein biomarkers and genetic characteristics. Lumping all types of stroke together is no longer a fruitful approach to such investigations.

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