Hyperhomocysteinemia and Left Atrial Thrombus in a Stroke Patient With Sinus Rhythm

To the Editor:

We read with great interest the recent article by Ay et al concerning the relationship between high plasma homocysteine levels and risk for left atrial thrombus formation in patients with stroke caused by nonvalvular atrial fibrillation. Their finding supports the thrombogenic role of high homocysteine in conditions associated with blood stasis. We recently observed a cardioembolic ischemic stroke from a left atrial thrombus formation in a man with sinus rhythm and a previous history of coronary heart disease. Laboratory analysis revealed an hyperhomocysteinemia.

A 56-year-old man was admitted to our department presenting with an acute visual disturbance and a mild speech disorder. He was a previous smoker with a 5-year history of hypertension, currently treated with an ACE inhibitor. At age 51 he had had an anteroseptal myocardial infarction. Since that time he was under treatment with aspirin. Neurologic examination revealed right upper quadrantopia and anomic aphasia. A CT brain scan showed a hypodense, ischemic lesion in the left temporoparietal region. Brain MRI confirmed the temporoparietal ischemic lesion and disclosed an additional small ischemic lesion in the subcortical right hemisphere. EKG confirmed the signs of a previous anteroseptal myocardial infarction. Duplex ultrasonography of carotid and vertebral arteries did not show stenosis although it revealed an increased carotid artery intima-media thickness. MRI angiography was normal. Transthoracic echocardiography showed a slight left atrium enlargement and disclosed the presence of left atrial appendage thrombus, and spontaneous echo contrast. Laboratory analyses were performed and included blood chemistry, blood cell counts, erythrocyte sedimentation rate, and coagulation panel. He was started on anticoagulant treatment. Coagulopathy workup showed high fasting plasma homocysteine concentrations (23 μmol/L) and homozgyosity for the 677C→T substitution polymorphism in the methylene tetrahydrofolate reductase-encoding gene.

Left atrial thrombus is infrequently detected in the presence of sinus rhythm, although it has been described in selected patients with acute neurological events and, in these cases, is usually associated with additional cardiac pathologies. Patients in whom left atrial thrombus is detected in sinus rhythm are characterized by specific cardiac abnormalities (significant left ventricular dysfunction, valve disease, or previous episodes of AF). Significant left ventricular systolic and/or diastolic dysfunction predispose to LA thrombus formation via their secondary effect on LA hemodynamics. However, in the case reported here we observed a mild ventricular dysfunction. Transthoracic echocardiography also showed left atrial spontaneous echocardiographic contrast. This finding is unusual in patients with sinus rhythm. The presence of spontaneous echo contrast and the increased left atrial diameter are also strong markers of left atrial stasis. Transient paradoxysms of AF may result in atrial dysfunction during the arrhythmia and after conversion to sinus rhythm, thus predisposing to LA thrombus formation. However, in the case reported here previous episodes of AF were not documented, although they cannot be excluded.

Interestingly, a recent study provided evidence of a strong association between homocysteine levels and risk of ischemic stroke in patients with preexisting coronary heart disease (defined as history of myocardial infarction ≥6 months but ≤5 years before enrollment in the study, or history of angina pectoris confirmed by appropriate investigations). The authors concluded that serum total homocysteine concentration is a strong predictor for incident ischemic stroke among patients at increased risk because of chronic coronary heart disease. The graded association observed was independent of traditional risk factors or inflammatory markers and indicated the importance of serum homocysteine levels in patients with preexisting cardiovascular disease.

Homocysteine is postulated to cause ischemic stroke via various mechanisms. It may promote atherogenesis by damaging the vascular matrix, increasing oxidative injury to arterial endothelium, and enhancing proliferation of vascular smooth muscle. High levels of homocysteine have been associated with extracranial carotid disease. It may also be prothrombotic and impair vasomotor regulation. Homocysteine is thus a biologically plausible factor in the pathogenesis of ischemic stroke.

Few studies have evaluated the relationship between homocysteine and stroke subtype. Hyperhomocysteinemia was associated in particular with stroke due to large-artery disease and small-artery disease. These studies support the hypothesis that homocysteine is a causal risk factor for atherosclerotic cerebrovascular disease. On the other hand, the recent studies of Ay et al and Tanne et al outline the strong association also between hyperhomocysteinemia and cardioembolic stroke. Accordingly, the cardioembolic stroke reported here occurred in a patient with hyperhomocysteinemia and preexisting coronary heart disease. Prospective studies are needed to evaluate the possible benefit from interventions that lower total homocysteine concentrations in selected high-risk patients.

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