Correlation Between Carotid Intraplaque Hemorrhage and Clinical Symptoms

To the Editor:

In the systematic review by Gao et al about the correlation between intraplaque hemorrhage (IPH) and neurological symptoms in patients with carotid disease, the authors analyzed findings from 31 observational studies in order to determine the role of IPH as a predictor of cerebral ischemic events, and demonstrated that the incidence of IPH in symptomatic patients was significantly higher than in the asymptomatic group. However, Gao et al emphasize that their analysis is undermined by substantial heterogeneity between studies, suspicious publication bias, comparisons between groups with different degrees of stenosis, and methodologically less-rigorous earlier studies. One aspect that must be recognized is that all the studies incorporated in Gao et al’s well-conducted systematic review involved patients that had undergone endarterectomy procedures. This may represent the most important limitation in the investigation of the alleged association between carotid IPH and ipsilateral symptoms of cerebral ischemia. To precisely estimate the underlying correlation, we cannot ignore the fact that patients undergoing surgical procedures are, by definition, highly selected and nonrepresentative of the different stages of the atherothrombotic processes taking place in the cerebrovascular arterial system. It is reasonable to speculate, for instance, that IPH may be a common phenomenon in symptomatic patients that simply do not fulfill accepted luminal stenosis criteria for endarterectomy. On the other hand, plaque bleeding may also be common in the asymptomatic population with carotid atherosclerosis, but who are merely not being screened.

This vital dilemma will not be unraveled until we have safe, reliable and reproducible in vivo noninvasive characterization of the carotid atherosclerotic plaque. Recent investigations have tried to identify in vivo morphological characteristics of the vulnerable carotid atheroma, and its potential correlation with symptoms. The validation of these techniques is based on several correlation studies between different imaging techniques, histological analyses and clinical data, using strict study design and methodological recommendations. Most of these studies were not incorporated in the systematic review by Gao et al. Moreover, after Gao et al’s publication, we have demonstrated that IPH is reliably identified by high-resolution MRI (κ coefficient of 0.91) and correlates with neurologically unstable patients, regardless of the degree of carotid stenosis. Unfortunately, the patients enrolled in our study were also submitted to surgical procedures. Another critical aspect that deserves careful consideration is the proper clinically based patient classification. The physiopathological events that substantiate the alleged association of IPH and cerebral ischemic symptoms are related to the concept of plaque vulnerability. In this scenario, carotid plaque vulnerability is not directly influenced by the obstructive nature of the plaque but is mainly associated with specific structural, molecular, and biochemical disarrangements of the atheroma. With this perspective in mind, the rationale of clinical characterization must take into account the instability of symptoms, rather than the absolute presence or absence of clinical neurological ischemia. Patients with remote vascular events should not be grouped with those with recent symptoms, because the pathogenesis might be substantially different. In our analysis, 98% of neurologically unstable patients (defined as those with ipsilateral hemispheric symptoms in patients in whom plaques were removed within 90 days of the event) had signs of IPH on high-resolution MRI. This temporal cutoff seems particularly reasonable because there is recent large-scale evidence suggesting that patients who remove carotid plaques sooner than 60 to 90 days after the most recent event or symptom are those with histological features of instability.

Finally, we congratulate Gao et al for the initiative to investigate such an important aspect of the pathogenesis of atherosclerotic cerebrovascular disease, and their effort to summarize the available data on the impact of IPH as a predictor of subsequent symptoms. Unfortunately, findings from their study did not shed light on this unresolved issue. One may argue that the immense methodological discrepancies between studies could even preclude the attempt to perform a summation analysis. Furthermore, the clinical significance of IPH in patients not eligible for endarterectomy is essentially unknown, but certainly represents the majority of patients with carotid atherosclerotic disease. The association between plaque bleeding and symptoms will remain an open issue until well-conducted prospective studies using simple, inexpensive and reliable noninvasive tools to identify IPH are conducted.

Disclosures

None.

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