INVITED COMMENTARY

A Step Closer to Finding Mr. Right

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Finally, there is a study that tests a potential biomarker solely in asymptomatic patients with carotid artery stenosis. Once a protein has (repeatedly) proved to be elevated in symptomatic patients compared with asymptomatic patients, both in serum and in plaques, the next step is to focus on asymptomatic patients, in whom the biomarker can indeed eventually prove useful. Unfortunately, too many promising biomarkers seem to get lost in this transition to the asymptomatic population.[1]

The paper by Eilenberg et al.[2] focuses on a burning issue with direct clinical application. The 2017 ESVS clinical practice guidelines state that "carotid endarterectomy should be considered in average surgical risk patients with an asymptomatic 60—99% stenosis in the presence of one or more imaging characteristics that may be associated with an increased risk of late ipsilateral stroke".[3] These characteristics (silent infarction on CT, stenosis progression, plaque echolucency, intraplaque haemorrhage on MRI, etc.) are still tentative and await further research. A validated circulating biomarker could definitely add to the list, and impact future guidelines for the management and follow up of these patients.

The finding of similar sensitivity of serum neutrophil gelatinase associated lipocalin (NGAL) to ultrasound plaque echolucency in identifying histologically vulnerable plaques is no small feat. If confirmed and validated, it could open the door to serological follow up in primary care facilities, without the need for repeated specialised ultrasound assessment, thus impacting cost effectiveness. The fact that no differences were found for NGAL concentrations with age, gender, and degree of carotid stenosis renders easier eventual clinical application.

The study has some important limitations. The series comprises only patients treated by carotid endarterectomy. The number managed conservatively in the same period is unknown. If significant, there could be some selection bias. The study is also cross sectional and the real deal is proving the prognostic value of the biomarker. This is the third prerequisite that a biomarker should fulfil, after biological plausibility and correlation with disease progression; this is the criterion that no promising biomarker has reached yet. Plaque histology in asymptomatic patients is considered a surrogate marker for risk of cerebrovascular events, but not all vulnerable plaques will inevitably generate symptoms and not all symptoms reflect a vulnerable plaque. Of note, extracranial carotid artery disease is directly responsible for only 10—15% of strokes.[3] Additional possible aetiologies of the silent cerebral infarctions found on CT/MRI could partially explain the borderline association with elevated NGAL serum levels that the authors found.

So, the next necessary step is to quantify NGAL levels in an adequately powered cohort of consecutive asymptomatic patients with significant carotid stenosis managed conservatively, with the incidence of ipsilateral cerebrovascular symptoms as the primary outcome. That is the paper I am eager to read.

REFERENCES

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