Why Should Mild Hyperhomocysteinemia Be Responsible for CAD?

To the Editor:

Since June 1997, we have measured homocysteine (Hcy) in 42 patients with cervical artery dissection (CAD), and so far, the mean Hcy level has been 17.8±9.1 μmol/L. This finding confirms our previous ones demonstrating that mild hyperhomocysteinemia is associated with CAD.1 This result was confirmed by another group.2 It is still unknown whether hyperhomocysteinemia, responsible for endothelial damage, can cause secondary dissection. The role of hyperhomocysteinemia in inducing endothelial damage and early atherogenesis has been documented both in vitro and in vivo.3-5 On the other hand, Magyar et al6 reported that Hcy and inflammatory markers have a significant role in early-onset carotid atherosclerosis. Hcy should have another effect in CAD patients. Except for a few elderly CAD patients in whom atherosclerotic lesions are described together with CAD,1 no atherosclerotic lesions were found in younger CAD patients with mild hyperhomocysteinemia. So, it seems that Hcy produces an intimal tear with a secondary subintimal hematoma localized at a point of minor resistance without inducing wide damage. Thus, there could be a synergic effect coupled with a minor trauma, a pre-existing arterial wall defect, or both.

Another question is whether the increase recorded during CAD and stroke is in fact a temporary condition as believed. Since 2001, Hcy has been remeasured after a median follow-up time of 3.5 years (range, 1 to 7 years) in previously studied CAD patients and in additional consecutive CAD patients.

In 5 of the original 26 patients studied, remeasurement was not possible (2 patients died, 3 were lost to follow-up). Hcy was measured in another 16 consecutive CAD patients and was remeasured in 11 after 1 year. After follow-up, the mean Hcy value of all CAD patients was 15.1±6.3 μmol/L. Median age was 48.5 years (range, 16 to 69 years). Sixteen patients presented vertebral dissection; 17 presented carotid dissection. Mild hyperhomocysteinemia was still present after the acute event. During follow-up, no other vascular events were seen. The distribution of vascular factors was as follows: 8 (24%) had hypertension, 2 (6%) had diabetes, 6 (18%) had hyperlipidemia, and 1 (3%) had migraine with aura. None of the patients had a history of severe recent trauma; 4 patients reported minor trauma (sudden head movements during stretching, playing football, and vomiting); and 5 had severe coughing spells some days before CAD. CAD patients had no signs of early atherosclerosis evidenced by duplex examination and/or angiography. This indicates that, in these otherwise asymptomatic and apparently healthy subjects with hyperhomocysteinemia, there was a sole triggering event leading to CAD but not to a diffused atheropathy. Proposed triggering factors such as minor trauma and infection7 have been identified, but it is difficult to explain why these factors lead to only one event during a lifetime. At this point, follow-up should be lengthened to exclude the presence of other vascular events.

Electron microscopy studies of skin biopsies have detected connective tissue alterations.2 They could also be present in the perivascular connective tissue, which could lead hypermobility of the vessel and secondary microtrauma. This is particularly relevant in the extracranial segments of both vertebral and carotid arteries, which are mobile and highly traction sensitive. Microtraumas could lead to chronic degenerative vessel wall damage, including endothelium, because of the involvement of vasa vasorum. At this point, Hcy could precipitate endothelial damage, reducing elastin concentration and stimulating metalloproteinases and serine elastases.9,10 The type and direction of head movements probably dictate the side and type of vessel involved. After an acute event, the vessel can be recanalized, and there could be reinforcement of the vessel wall because of the evolution in scar tissue with an increase in connective tissue. This could explain why recurrent dissection on the same side is extremely rare. Obviously, if no recanalization occurs, a thrombus forms at the weakest point of the wall. In conclusion, hyperhomocysteinemia could also be responsible for dissection in other pre-existing arterial alterations such as arterial redundancies, intracranial aneurysms, aortic root dilatation, common carotid artery distensibility increase, and fibromuscular dysplasia because its end points and pathways are identical in all these pathologies.

In conclusion, mild hyperhomocysteinemia seems to be responsible for CAD without producing further detectable vessel wall damage. CAD patients are younger than other stroke patients, so the effects of long-term exposure to these mild Hcy levels have not been seen.

Valeria Caso, MD
Virgilio Gallai, MD
Department of Neuroscience
University of Perugia
Perugia, Italy

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