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LETTER TO THE EDITOR

Endothelium-dependent and -independent functions in migraineurs

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Dear Editor,

We read the article published by Fujioka et al. [1] with great interest. In their case–control study, they evaluated endothelium-dependent and -independent functions in 12 migraineurs without aura and non-migraineurs by means of flow-mediated dilatation (FMD). Briefly, they found comparable values of FMD between migraineurs and non-migraineurs, but higher values of nitrate-mediated dilatation (NMD) in migraineurs than in non-migraineurs. They speculated that patients with migraine without aura in the interictal period had selective sensitivity in dilator response to nitroglycerin, possibly indicating systemic nitric oxide (NO) sensitivity [1]. Additionally, they demonstrated that von Willebrand factor, a biological marker of endothelial function, was comparable between migraineurs and non-migraineurs. Therefore, they commented that endothelial dysfunction may not underlie the pathogenesis of increased migraine, as previously reported [2, 3], and that the sensitive dilator response to nitroglycerin (NTG) was due to a vascular smooth muscle cell abnormality in migraineurs without aura [1].

FMD measures endothelium-dependent vasodilatation by means of hyperemic flow and endothelium-independent vasodilatation by means of nitrate administration. In this regard, Fujioka et al. [1] also mentioned that migraineurs did not have endothelial dysfunction but also had an over-responsive dilation response to NTG. Although controversial results exist, increased dilator responses to NTG have been reported in those with proven endothelial dysfunction [4, 5]. It might be challenging to distinguish between endothelial-dependent and -independent vasodilatation. Likewise, Adams et al. reported that the vasodilator response to exogenous NO was impaired in asymptomatic subjects with reduced endothelium-dependent dilatation, consistent with smooth muscle dysfunction in adults at risk for atherosclerosis [6]. So, this does not mean that endothelium and the underlying smooth muscle cells do not function separately or independently. Additionally, headache response to nitrate may show variation depending on the underlying clinical circumstances such as heart failure and coronary artery disease [7]. Indeed, the contribution of endothelial function to the pathophysiology of migraine is not yet well documented.

In addition to studies indicating endothelial dysfunction or increased NMD in the pathophysiology of migraine, indirect evidence also supports the possible role of vascular dysfunction in the migraine pathophysiology. Migraine has been shown to be linked with atherosclerosis, in which endothelial dysfunction is the key phenomenon [8]. Kurth et al. showed that male migraineurs had significantly increased risk of myocardial infarction [9]. Increased cardiovascular risk in migraineurs is likely to be independent of other risk factors [9]. Statins have been supposed to play a role in reducing the number of migraine attacks via their anti-hyperlipidemic and pleiotropic effects [10–13]. The eventual beneficial effects of statins might be due to the improvement in endothelial function, arterial stiffness, and vascular tone. Buettner et al. demonstrated that simvastatin plus vitamin D therapy was effective for the prevention of headache in adults with episodic migraine, which might be explained by the ability of statins to repair endothelial dysfunction [12].

In conclusion, we agree with the authors that migraineurs have an oversensitive response to NTG, but we do not agree with the authors that migraineurs have a normal endothelium-dependent vasodilator response. Further studies including a large number of migraineurs with/without aura are warranted to understand the vascular pathophysiology and to alleviate the pain of migraine.

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