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Editorial

Cerebrovascular reactivity in subjects with migraine: Age paradox?

Migraine, and especially migraine with aura, is a recognized risk factor for stroke [1]; however, the mechanisms underlying the association between migraine and stroke are unclear. Notably, previous studies found that the contribution of migraine to the risk of stroke is more significant in younger women compared with the older ones [2,3] and in women with active migraine compared with those with past history of migraine [4], suggesting the presence of a migraine-specific factor increasing the risk of stroke. Altered cerebrovascular reactivity (CVR) has been proposed as a possible link between migraine and the risk of stroke; however, no study, to date, assessed the effect of age on the CVR of subjects with migraine.

The case-control study published in the present issue of the *Journal of Neurological Sciences* found decreased CVR in all cerebral arteries in migraineurs compared with control subjects [5]. In that same study, the path analysis showed that CVR of the posterior cerebral artery decreased with decreasing age at migraine onset and with increasing migraine duration, suggesting a possible role of the burden of migraine in the association between migraine and impaired CVR; notably, sex, migraine frequency, and aura status did not interact with CVR according to the Authors' data [5].

The most interesting hypothesis emerging from the study presented in this issue of the *Journal of Neurological Sciences* is that migraine duration might progressively decrease CVR in subjects with migraine. In that context, an increased migraine frequency might also have a negative impact on CVR; however, and rather surprisingly, the Authors found no correlation between migraine frequency and CVR in their study.

Peripheral arterial function might explain the increased risk of vascular disease among patients with migraine [6]; however, several aspects of the relationship between arterial function and migraine are still unclear, including the relationship between CVR and endothelial dysfunction; indeed, the Authors of the present case-control study focused on CVR as a surrogate marker of cerebral endothelial function, while evidence suggests that CVR is not related to systemic endothelial function [7]. Therefore, the Authors' findings should be confirmed and put in a wider context by further research.

The interesting finding of an impaired CVR in young subjects with migraine is worth testing in those with vascular risk factors. The Authors of the present case-control study duly excluded subjects with vascular risk factors, including hypertension, diabetes, dyslipidemia, cardiac disease, stroke, and smoking, to control for possible confounders of the relationship between CVR and migraine. According to the results of the present study, more attention should be paid to the vascular risk of subjects with young age at migraine onset, which might be exposed to higher vascular risk as compared with those with older age at migraine onset. It would be interesting to know whether the subjects with younger age at migraine onset also develop vascular risk factors, due to impaired vascular function, at a young age. Indeed, the available literature data suggest that conventional risk factors, including arterial hypertension and smoking, are more prevalent among subjects with migraine compared with the general population [8]. The study results also suggest paying attention to the vascular risk of young age at migraine onset, as their CVR might be severely impaired; further research is needed to assess whether drugs acting on both migraine and vascular risk, including those acting on the renin-angiotensin system [9], might be more effective in young migraineurs compared with the older ones.

It should be kept in mind that migraine is not entirely a vascular disorder; according to the neurovascular theory of migraine pathogenesis, the different CVR of subjects with migraine compared with non-migraineurs might be the result not only of endothelial dysfunction, but also of an impaired brainstem control of perivascular nerves [10]. In that context, a younger age at migraine onset might be the result of a greater impairment of brainstem control mechanisms, leading to a greater impairment of CVR. However, further research is needed to prove that hypothesis.

In conclusion, the case-control study presented in this issue of the *Journal of Neurological Sciences* stresses the importance of age and of the burden of migraine in determining vascular risk. The paradoxical finding of a decreased CVR in younger migraineurs is in line with the paradoxical association between migraine and vascular events in the young, reaffirming the role of the still unknown migraine-specific mechanisms of vascular risk.

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