Cerebrovasc Dis 2010;30:41–42

DOI: [10.1159/000313610](https://doi.org/10.1159/000313610)

Dissecting the Relation between Migraine and Stroke: The Importance of New Phenotyping Strategies

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Over the last decades, migraine, especially migraine with aura (MA), has been consistently associated with increased risk of ischemic stroke, particularly among young women [1]. Despite the strong epidemiologic evidence, the mechanisms explaining this association are not fully understood.

In particular, only few rigorously conducted studies have explored the hypothesis that the magnitude of such an association may vary according to the pathogenic subtype of stroke. The study by Artto et al. [2] published in this issue of *Cerebrovascular Diseases* is therefore an important addition. The authors provide further support for previous observations suggesting that migraine might be linked to ischemic stroke through a mechanism of spontaneous dissection of the cervical arteries (cervical artery dissection, CAD). In a single-center, hospital-based, case-control study they found a higher prevalence of migraine among CAD patients as compared to a control group, as well as an increased frequency of MA (as opposed to migraine without aura, MO), prodromal neck symptoms and vomiting. Furthermore, CAD patients showed a change in migraine activity after the event, with a marked reduction in the frequency of migraine attacks.

What are the implications of this study in regard to the debated relation between migraine and cerebral ischemia? Although the study has several strengths compared with previous ones, including a larger sample and an assessment of migraine characteristics and symptoms by a validated questionnaire, it also has some limitations. A subgroup of patients whose mechanism of cerebral ischemia was unrelated to a CAD is lacking. This raises the question of whether the observed association is really CAD specific or, rather, whether it is only one aspect of the complex migraine-stroke pathway. The reported alleviation or even complete cessation of migraine symptoms after CAD is also an interesting finding with potential implications for elucidating how vascular injuries might influence migraine activity. However, little information

is provided on those variables which might modify the course of migraine after CAD (i.e. antithrombotic treatment, risk factor modification, change in life style) as well as on the duration of follow-up.

A striking finding of the present report is that, in contrast to what has been observed in previous studies, the association between migraine and CAD was stronger for MA than for MO. Obviously, because of its design, the study cannot provide explanations for such a discrepancy. As in most epidemiologic studies on migraine, Artto et al. [2] used the categories of the International Headache Society classification [3] as phenotypes (MO and MA). This might present an oversimplified picture of migraine phenotype, which in reality has a complex genetic and environmental background, and using this phenotype might result in too heterogeneous a set of patients for association analyses. As in other complex diseases, the use of single traits or other new phenotyping strategies for migraine might help in stratifying study samples into less heterogeneous groups. In this regard, latent class analysis of migraine symptoms indicated the existence of a continuum of severity, with MA being more severe but not etiologically distinct from MO, thus reinforcing the view that the two migraine subtypes are not separate entities [4, 5].

Given all these considerations, some open questions related to the epidemiologic link between migraine and ischemic stroke still remain. The report of Artto et al. [2] provides further useful arguments for the hypothesis that, within the broad category of brain ischemia, the predisposing effect of migraine might vary according to the pathogenic subtype of stroke. Like the few previous studies on this topic, it should, however, be viewed as a starting point rather than the culmination of epidemiologic analyses addressing the issue of a relationship between migraine and CAD. An important step forward in this regard will be done by the analysis of larger datasets such as that of the CADISP (Cervical Artery Dissection and Ischemic Stroke Patients) study (<http://www.cadisp.org>) [6]. Pending the availability of more data, what should be recommended for future epidemiologic research is the use of new phenotyping strategies for migraine and ischemic stroke in order to provide a more direct insight into the underlying biology of the two diseases and to address fundamental etiologic questions on their relationship.

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