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Commentary

Stroke, Migraine and Triptans: From Bedside to Bench

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Migraine is a neuro-vascular disease characterized by recurrent attacks of moderate to severe headache, lasting 4–72 h and associated with nausea/vomiting and sensitivity to light and noise. Its remarkable prevalence together with the high likelihood of overtreatment carries significant clinical and economic implications. Although plenty of studies have investigated the possible association of migraine and cardiovascular diseases, especially stroke, the nature of this complex, bi-directional link is still obscure (Schurks et al., 2009).

From a clinical standpoint, it is important to differentiate migraine-induced stroke (i.e., a rare and distinct occurrence of stroke following typical attack of migraine with aura, also known as "migrainous infarction"), from migraine-related stroke. In fact, the latter occurs remotely from a migraine attack and probably implies different mechanisms. The contribution of drugs in the occurrence of migraine is a matter of current debate; the documented vascular effect of migraine-specific medications, namely triptans and ergot derivatives, has received increasing attention because of their complex vasoconstricting properties (Chan et al., 2011), which might increase the risk of serious cardiovascular events (Roberto et al., 2014, 2015).

In this scenario, the cohort study by Albieri and colleagues addressed the relationship between stroke and migraine in the Danish population using triptans, and characterized the risk in terms of age, gender, stroke severity and subtypes (Albieri et al., 2016). The study has the merit of analyzing a 9-year period (2003 − 2011) through a record-linkage strategy of the Danish Prescription and Stroke registries. Data quality is remarkable, as important clinical covariates were considered in the statistical models: education, income, stroke severity (by a validated Scandinavian scale), type of stroke (ischemic vs hemorrhagic, by information from computed tomography or magnetic resonance scanning), alcohol consumption, smoking status and other cardiovascular risk factors (e.g., diabetes and atrial fibrillation). The authors found a borderline increased risk of ischemic stroke in patients with migraine, selected by triptan utilization; stratifying by gender and type of stroke, only the risk for hemorrhagic stroke in women clearly emerged (RR = 1.41; 95% CI = 1.11–1.80). Notably, the estimated risk was closely associated with age: highest among women aged 25–45 (RR: ~1.7), decreasing rapidly thereafter with no association with triptan use after 55 years of age. As regards severity, severe strokes (as measured by the Scandinavian Stroke Scale) were significantly less prevalent among migraineurs (RR = 0.77; 95% CI = 0.65–0.91).

Defining the actual role of triptans in precipitating stroke is challenging for a number of methodological issues. In the study by Albieri et al., triptans were used as a proxy of migraine (or, better, of severe migraine): thus, no information on the difference between people exposed to triptans and other migraineurs is available. In addition, patients with migraine have multiple treatment options (analgesics for advanced symptoms, prophylactic therapy for more severe cases, ergot derivatives as an alternative to triptans), but the variety of pattern of use (both in frequency and combinations) and the multiple indications of most options do not allow to stratify migraineurs for therapy nor to attribute stroke occurrence to a specific therapy rather than a combination of them or only to the migraine status. Another general limitation of observational studies aiming to evaluate antimigraine therapies, especially symptomatic treatment, is represented by the time distance between prescription and actual use: since migraineurs are very careful to have medication available when needed to control attacks quickly, temporal correlations between triptan intake and stroke occurrence cannot be easily studied.

The data by Albieri and coworkers are in line with recent literature, including various meta-analyses, documenting both increased risk of ischemic and hemorrhagic stroke in women (Spector et al., 2010; Sacco et al., 2013). Surprisingly, they noticed a lower prevalence of cardiovascular risk factors among patients with stroke that were also triptan users; the risk was unrelated to the number of dispensed prescriptions (lack of a dose-response effect). Taken together, these findings strengthen the notion that, on one hand, the underlying disease per se contributes largely to the observed risk and suggest a migraine-specific etiology of stroke (which might be different from that of

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atherosclerotic thromboembolism) and, on the other hand, suggests that in Denmark triptans are likely to be prescribed taking into account known cardiovascular contraindications. This study underlines, once more, the importance of a careful risk/benefit assessment before prescribing triptans for migraine. In particular, both ischemic and hemorrhagic risks should be considered depending on individual patient characteristics: middle-aged women without cardiovascular risk factors are at increased risk of hemorrhagic stroke and should be screened for additional bleeding risk factors that may increase the risk of hemorrhagic stroke such as concomitant hypercoagulability states. In men, attention should be paid to undetected subclinical cardiovascular diseases that may precipitate ischemic stroke, such as patent foramen ovale (PFO).

From a research standpoint, important unanswered questions regard (a) the explanation for increased risk of hemorrhagic stroke in migraine and (b) whether a role of triptans *per se* exists. The former (i.e., underlying mechanisms subtending the hemorrhagic risk) is still hypothetical: activated platelet aggregation and serotonin release caused by subclinical artery dissection, hypercoagulability as a consequence of endothelial dysfunction or arterial microemboli due to PFO have been hypothesized (Mawet et al., 2015). In this context, the potential role of additional concomitant drugs interfering with platelet or endothelial functions (e.g., antithrombotics and nonsteroidal antiinflammatory drugs, statins) deserves further investigation. The latter (i.e., the pharmacological basis of vasoconstriction induced by triptans and ergot derivatives and real definition of the drug-related component in stroke occurrence) has been largely investigated, but still incompletely appreciated; in fact the ergots were originally developed as sympatholytics, but it was later suggested that their antimigraine effect was probably mediated by vasoconstriction of cranial blood vessels, through a variety of receptors including serotonin, dopamine and noradrenaline receptors (Chan et al., 2011).

In conclusion, basic scientists have a topic for future studies addressing the mechanistic basis of migraine-specific etiology: clarifying the pathophysiological mechanisms underlying migraine may help both clinical practice and the identification of additional pharmacological targets, which may vary depending on the type of migraine (i.e., with or without aura). As a matter of fact, mouse models and genetics (genome-wide association studies) are becoming an attractive source of clinical information to identify novel indicators of susceptibility (e.g., polymorphism in methylene tetrahydrofolate reductase) and selective therapeutic agents (e.g., monoclonal antibodies targeting calcitonin gene-related peptide), which may potentially target not only migraine but also underlying comorbidities such as epilepsy and depression (Ferrari et al., 2015). In the era of precision medicine, the identification and validation of biomarkers will represent the next research challenge.

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