Migraine patients should be cautiously followed for risk factors leading to cardiovascular disease

Pacientes com migrânea devem ser acompanhados com cuidado com relação aos fatores de risco para doenças cardiovasculares

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ABSTRACT

Migraine and ischemic strokes are two of the most prevalent diseases worldwide. Besides having a coincident symptomatology, for long researchers have been searching for a possible causal relation between these diseases. Current evidence based on data suggest that patients with aura migraine could have a doubled risk of developing an ischemic stroke, when compared to the rest of the population. At the same time, migraine sufferers apparently have higher incidences of risk factors for cardiovascular events. The aim of this review was not only to dissect some of the more compelling evidence based on data regarding this association, but also to discuss the possible clinical and therapeutic implications.

Key words: brain ischemia, cerebrovascular disorders, migraine, stroke.

RESUMO

Migrânea e acidentes vasculares cerebrais isquêmicos (AVCI) são duas das doenças de maior prevalência em todo o mundo. Além de apresentarem alguns sintomas em comum, há muito tempo pesquisadores procuram investigar uma relação causal entre as duas. As informações atuais baseadas em evidência sugerem que pacientes com migrânea com aura podem ter um risco duas vezes maior de desenvolver AVCI, quando comparados com o restante da população. Ao mesmo tempo, aqueles sofrem de migrânea possuem aparentemente maior incidência de fatores de risco para eventos cardiovasculares. O objetivo desta revisão foi não apenas avaliar grande parte das mais importantes e convincentes evidências científicas sobre esta associação, mas também discutir suas possíveis implicações clínicas e terapêuticas.

Palavras-Chave: isquemia encefálica, transtornos cerebrovasculares, migrânea, acidente vascular cerebral.

Migraine and ischemic strokes (IS) are two of the most prevalent diseases worldwide. Around 12 to 21% of women suffer migraine attacks and 2 in 1,000 per year people (older than 65 years-old) will have an acute ischemic stroke[1-3]. Therefore, frequently, neurologists and emergency medicine personnel face the challenge of dealing with symptoms that could be attributed to both pathologies, or even struggling to decide the best tests and therapy for the patient. Besides having some coincident symptomatology, for long researchers have been searching for a possible causal relation between these diseases, however the overlap of some risk factors makes the road even more tortuous. The aim of this review was not only to dissect some of the more compelling evidence based on data regarding this association, but also to discuss on how it would impact the clinical practice. We approached the subject in a problem-based fashion, discussing four of the most intriguing questions about the matter, always focusing on the clinical implications. In the end, we have introduced some diagnostic and therapeutic clinical pearls, presenting a stepped approach to difficult cases.

CAN MIGRAINE BE A VASCULAR RISK FACTOR?

The question about migraine being a risk factor for IS has been asked in several previous studies for the past half century. Two cohort studies[4,5] and three meta-analysis[6-8] consistently reported doubled risk for IS among migraine patients, with more robust evidence among young female patients with associated aura. This interesting observation would make us

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reflect about the influence of estrogen and progesterone as important actors, not only the well-known influence as a trigger and crisis modulator, but also their presumed protective cardiovascular and endothelial factors. Analyzing the cardiovascular literature, it would be expected to see an increased risk among postmenopausal patients or on hormone-replacement therapy, which suggests that young migraine sufferers would bear some other underlying risk factors or vascular predisposition. As will be further discussed, because patients with aura migraine (MA) are in higher risk of developing ischemic lesions than those with migraine without aura, cortical spreading depression and cerebral autoregulation could play a pivotal role in neuronal injury.

The greatest challenge when dealing with two very prevalent diseases is the overlap of risk factors and comorbidities among those patients. Some previous case-control studies highlighted the increased incidence of stroke within young MA patients, but usually they associated smoking habits with use of oral contraceptives[9-11], two well-known risk factors for cardiovascular disease. A great amount of those studies was subject to biases, such as different criteria for MA and imaging method. The more definite evidence came from the GEM study[12], which showed that MA patients were more prone to have hypertension, unfavorable lipid profile, and higher Framingham risk score for coronary artery disease. It is worth mentioning the genetic polymorphism of the methyltetrahydrofolate reductase (MTHFR) gene, which was described as associated with MA and cardiovascular disease[13].

The discussion became even more intriguing when the subgroup analysis of two large population-based studies, the Women's Health and the Atherosclerosis Risk in Communities studies[2,14], primarily designed to study cardiovascular risk factors, disclosing that those patients had not only an increased risk of stroke, but also cardiovascular events, such as acute myocardial infarctions and cardiac-related death. Recently, a large population-based cohort study in Finland added more evidence to this polemic issue and showed that MA patients were at increased risk of mortality from coronary heart disease and stroke (hazard ratios of 1.28 and 1.40, respectively)[15]. Also, another subgroup analysis of the Women's Health study revealed that the association between migraine and cardiovascular disease varies by migraine frequency, as patients with higher frequency of MA attacks (more than once a week) were more prone to develop IS[16].

Although the current evidence points to a possible association or overlap of comorbidities, the absolute number of stroke cases is small among MA patients, even more when you consider the male cohort. For the clinical practice, our approach is to pay attention to risk factors, even in young patients, making sure that comorbidities, such as hyperlipidemia and arterial hypertension, are adequately treated by the neurologist or primary care physician. Moreover, we strongly encourage the patients to stop smoking and avoid at all costs the dangerous combination of tobacco and oral contraceptives.

COULD MIGRAINE ATTACKS CAUSE ISCHEMIA?

Previous neuroimaging studies, using magnetic resonance imaging (MRI) and computed tomography (CT) scans, revealed an interesting occurrence of clinically silent white-matter abnormalities among migraine patients, when compared to the Control Groups[17-20], including a meta-analysis[21] of seven studies. Most of those studies showed predominance of posterior circulation infarcts. Those findings somewhat enlighten the discussion that migraine is commonly a phenomenon of the posterior circulation, as clinically seen in patients with visual auras and in the extremely rare cases of basilar migraine, as well as the fact that the cerebral autoregulation is more tightly controlled in the anterior circulation. Nonetheless, a recent population-based French study[22] with individuals aged 65 years and older disclosed an interesting association between MA and infarct lesions located mainly outside the cerebellum and the brainstem, hypothesizing that migraine could be a progressive disease.

The mechanisms of migraine attacks are still unknown, but their possible causal effects can lead to cerebral ischemia. Some previous hypothesis have been studied and suggested, the most debated being vasomotor phenomena, cortical spreading depression, trigeminal activation, role of calcitonin gene-related peptide (CGRP), and increased prevalence of patent foramen ovale (PFO) among patients with migraine, mainly MA.

There is not much clinical and laboratorial evidence explaining on how migraine could directly cause ischemic lesions, formally defined as migrainous infarct by the International Headache Society (IHS). Some previous large series estimated that migrainous infarcts do not account for more than 1.5% of all IS, however they could represent 10 to 14% among young patients[23,24].

As noticed by such brain imaging studies, the lesions mainly happen in the posterior circulation territory, which is believed to be the same place where spreading depression is started[25-27]. This would be an astonishing explanation, but previous studies using cerebral blood flow (CBF) measurement techniques observed truly oligoemia during spreading depression, with a threshold far from causing ischemic lesions[28,29]. It is also of clinical interest to mention that spreading depression was observed in patients with aneurysmatic subarachnoid hemorrhage and delayed neurological deficits, without evident radiographic vasospasm[30,31]. Could spreading depression severely disturb the cerebral autoregulation and cause infarcts, or could itself cause irreversible brain damage?

Some of the drugs that we commonly use to abort migraine attacks act by eliciting vasoconstriction of the cerebral vessels, and some of them are known causes of reversible cerebral vasoconstriction syndrome (RCVS), however large studies reported the safety of those treatments[32,33], although with a slight increase of cardiovascular events in patients with previous cardiac history. Retrospectively, we could imply that some rare cases of migrainous infarct could be subtle ones of medication-related RCVS.

Coagulation disorders can play a role as causal factors, as mentioned regarding the MTHFR gene mutation. There is also some evidence that MA patients have increased platelet adhesion and activity[34], and inconsistent data regarding pro-thrombotic markers as V Leiden mutation[35], anti-phospholipid antibody[36], and von Willebrand factors[37]. Aspirin is very effective as the first treatment for migraine attacks[38], mainly due to its analgesic properties, but also possibly as an anti-platelet drug. In our understanding, a trial of prophylactic aspirin to evaluate migraine attacks frequency reduction, but also of long-term cardiovascular protection, would be highly desirable.

PATENT FORAMEN OVALE: SHOULD WE CLOSE THE QUESTION?

PFO is recognized as a possible risk factor for IS, mainly among young patients, even more when associated with inter-atrial septum aneurysm[39]. It is also worth saying that MA patients have higher prevalence of PFO than the rest of the population[40,41]. Our group also found an increased incidence of PFO in patients with trigeminal autonomic cephalalgias and hemicrania continua[42].

Therefore, could PFO not only play a role as a trigger for MA attacks, but also could it possibly be a causative factor for infarcts? Some hypotheses have been suggested to trying to clarify the question: PFO could allow some substances that would normally be filtered by the lungs to reach the cerebral circulation and trigger spreading depression; micro-emboli could cause ischemia, leading to spreading depression; and migraine attacks could be triggered by hypoxia caused by right-to-left shunt. Small PFO closure studies showed a modest benefit as a preventive approach to migraine attacks[43-45], all of which had several biases, including aspirin use, nonblinding, and time for follow-up.

The Migraine Intervention with STARFlex Technology (MIST) trial[46] was a large, prospective, multicenter, double-blinded, sham-controlled trial to evaluate the effectiveness of PFO closure with STARFlex septal repair implant in order to resolve refractory migraine headache. It enrolled 147 patients and had as a primary endpoint the migraine headache cessation. No significant difference was observed in the primary endpoint of migraine headache cessation between implant and sham groups. This trial, at least temporarily, decreased the interest of using interventional measures to treat and prevent migraine attacks. Nevertheless, two randomized prospective trials (PREMIUM and PRIMA) are still under process, using a different implant through a different technique. At the same time, the CLOSURE[47] trial, which was developed to analyze if PFO closure could reduce the recurrence of stroke in young patients with cryptogenic strokes, failed to show superiority against the best medical therapy.

In conclusion, even if the PREMIUM and PRIMA trials present any positive benefit, the fact that the MIST trial was negative and that cryptogenic strokes cannot be prevented with PFO closure, makes this a non-cost-effective treatment. It is worth reminding that those trials with invasive procedures are difficult to be blinded, and most patients could be influenced by the fact that 'the procedure will close a hole in my heart', being that a powerful placebo effect.

MIMICS OR SECONDARY MIGRAINE?

Commonly, the clinician will face patients presenting complaints that resemble migraine, but with underlying severe vascular disease.

In clinical practice, a varying percentage of patients with hemorrhagic strokes have headache as their first symptom, however most of times without previous episodes of documented migraine. Usually, even patients with migraine history describe the new headache as different in quality and characteristics to their actual migraine attacks. To the moment, there is conflicting evidence about migraine being a risk factor for hemorrhagic strokes[48], but newer evidence suggests that MA slightly increases the chance of having an intra-cerebral hemorrhage[49]. It is still unclear if this is also a reflection that migraine suffers tend to have more arterial hypertension. Of note, a small percentage of patients with IS can present acutely with migraine-like headache, mainly those with cervical artery dissection[50] and with posterior circulation ischemia. In our experience, patients rarely presented with thunderclap headache as the main opening symptom of an acute IS[51]. None of them had intracranial or extracranial vascular pathologies.

Some rare vascular diseases can also present as migraine-like attacks. Arteriovenous malformations (AVM) are sometimes related to MA attacks[52], mainly if the aura is contralateral and the headache is ipsilateral to the malformation. Some anecdotal reports also described patients with migraine and Sturge-Weber syndrome[53] and cerebral venous thrombosis[54]. RCVS is known to present sometimes as a thunderclap or migraine-like headache. Newman et al. analyzed 139 documented cases of RCVS, and found that prior migraine was documented in 40% of the patients, and vasoconstrictive drug exposure in 42%[55].

The syndrome of cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL) is a genetic disease (Notch-3 gene) affecting the vascular and smooth-muscle cells of cerebral vessels, leading to subcortical dementia, leukoencephalopathy, and small deep infarcts[56]. Almost one third of CADASIL patients present MA attacks, accordingly to the HIS criteria, but can also have other forms of headache. MA is usually the first symptom, sometimes preceding the ischemic lesions for years[57].

Finally, another disease presenting stroke and migraine is the syndrome of mitochondrial myopathy, encephalopathy, lactic acidosis and stroke (MELAS), a genetic disease with mutations in the mitochondrial DNA, leading to dysfunction of the organelle. These patients usually present MA attacks[58], with long lasting auras, suggesting that migraine could be related to an energy dysfunction, however the genetic mutations of MELAS are not present within migraine patients[59].

As we will discuss bellow in the clinical pearls section, normally MA sufferers do not have an underlying vascular disease, but cases with atypical presentations should be thoroughly investigated. Again, several diseases with vascular pathology can mimic migraine attacks, reinforcing even more that vascular and endothelial factors are deeply involved in the pathophysiology.

CLINICAL PEARLS: WHEN SHOULD MORE TESTS AND THERAPEUTICS BE CONSIDERED?

First of all, it is important to reinforce that time is brain, and if the clinician is facing a case that could be an IS or transient ischemic attack, it should be treated as an acute ischemia, even if a complex migraine aura or migrainous infarct is among the differential diagnosis. IS are far more common, disabling and fatal, and a large body of evidence shows that intravenous thrombolytic therapy is safe, even in patients with stroke mimics[60]. The neurologist should always bear in mind that migrainous infarcts are extremely rare.

Migraine attacks should be an exclusion diagnosis, mainly in elderly patients. It is very rare to start a migraine disorder later in life, so in our experience, we always consider patients older than 50 years to be experiencing a transient ischemic attack (TIA) until proven otherwise. It is recommended that an extensive stroke workup should always be performed, including brain vessel imaging and cardiac ancillary tests, including search for underlying intermittent arrhythmias. The preferred method of brain imaging would always be a MRI to search for small ischemic lesions.

Another pearl, albeit truly anecdotic, is to cautiously use tryptans and ergotamine in patients with symptomatology that could even remotely be a TIA or in those without a documented history of migraine with aura headaches, as it could potentially exacerbate vasoconstriction and worsen an evolving brain infarct. In addition, it is advised to refrain from using vasoconstrictors to treat migraine attacks in patients with history of IS or TIA. For them, a beta-blocker would be considered for prophylaxis of migraine attacks, as it would also contribute to decrease the occurrence of cardiovascular events[61] and control arterial hypertension.

The clinician should encourage their MA patients to treat risk factors for stroke, such as diabetes mellitus, arterial hypertension, and hyperlipidemia. Smoking cessation should be aggressively attempted, and the combination of tobacco use and oral contraceptives always avoided. Until further data clarify the true association between strokes and MA, those patients should be treated as having a considerable risk for cardiovascular events. Aspirin should be an adequate option in patients with MA and multiple risk factors for cardiovascular events, as it could relieve the migraine attacks and prevent future vascular complications. However, until this moment, the only data about stroke prevention and aspirin in this group of patients is a post-hoc subgroup analysis of the Women's Health study, which showed that first stroke could be fairly prevented with small doses of aspirin, but the effect was independent of the migraine presence[62].

In patients with disproportionate amount of white matter disease to their age bracket, the clinician should consider pursuing more detailed brain and vessel imagings, including a cerebral digital angiogram, as the patient could have an underlying vessel pathology, such as CADASIL, cerebral AVM moyamoya or antiphospholipid syndrome. Genetic testing should also be considered for possible CADASIL or MELAS cases. Also, patients with atypical attacks, late onset of MA, recent increase of attack frequency, or attacks with constantly unilateral aura and contralateral headaches should undergo thorough brain and vascular imagings to investigate secondary migraine[63].

Finally, suspicion should be raised in patients with history of migraine, but with a new onset of a headache different from usual crisis pattern. Brain imaging, preferably MRI, should be ordered to rule out ischemic or hemorrhagic strokes. Always consider possible meningitis or brain neoplasm as a differential diagnosis.

FINAL REMARKS

The available literature supports that MA could be an independent risk factor for ischemic strokes, even higher within young patients using oral contraceptives and with smoking habits. Recent studies suggest that MA could also

be a systemic disease, with increased risk for cardiovascular events. Some hypotheses have been formulated, but the real pathophysiology is still obscure.

Recent evidence suggest that MA patients should be followed with caution for risk factors leading to cardiovascular disease. Investigation regarding anti-platelet prevention for those patients should be further developed. The available evidence also do not support closure of PFO as a therapy for migraine or stroke prevention.

Migraine might be seen in the future as a progressive systemic disorder, under the influence of numerous genetic, environmental, inflammatory, and metabolic factors.

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