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STROKE (AB SINGHAL, SECTION EDITOR)

Migraine and the Risk for Stroke and Cardiovascular Disease

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Abstract Numerous data have pointed to an association between migraine and cardiovascular diseases. The majority of the available data have indicated that migraine with aura can be considered a risk factor for ischemic stroke, whereas migraine without aura cannot be reliably considered as such. High frequency of attacks and a recent onset of migraine have been related to an increased ischemic stroke risk. In addition, in young subjects with ischemic stroke migraine with aura represents an independent risk factor of overall recurrent vascular events and of recurrent ischemic stroke. Also the risk of transient ischemic attack seems to be increased in migraineurs, although this issue has not been extensively investigated. Several studies have also addressed the possible association between migraine and hemorrhagic stroke. Although the results of these individual studies were conflicting, their meta-analysis showed that migraine is associated with a 1.5-fold increase in the risk of hemorrhagic stroke (including intracerebral and subarachnoid hemorrhage). Some studies have identified migraine also as a possible risk factor for cardiac vascular events while others have yielded negative results. A meta-analysis did not show an increased risk of myocardial infarction in subjects with any migraine vs no migraine but subsequently, data has pointed to an association between any migraine with cardiac ischemic disease. Migraine has also been associated by some studies with vascular mortality and with vascular diseases in regions other than the brain and the heart. Several studies have also indicated that compared with nonmigraineurs, migraineurs have a higher burden of asymptomatic white matter brain lesions and, according to some studies, also infarct-like lesions at brain magnetic resonance. The mechanisms underlying the relationship between migraine and cardiovascular disease are still unclear. The possible explanation may rely on a peculiar vascular vulnerability of migraineurs that may contribute to the pathogenesis of migraine and, in the presence of some other unknown factors may also contribute, over time, to the development of cardiovascular disease. At the moment, there are no reliable features that may indicate which subjects, across the overall migraine population, will develop vascular events and so far, no drugs are recommended for the vascular prevention in migraineurs unless other clear indications are present. In general, the acute treatment and the secondary prevention measures of a patient with stroke who has a history of migraine do not differ from that of other stroke patients. There is currently no direct evidence to support that a migraine prophylactic treatment will reduce future stroke risk in secondary prevention.

Keywords Migraine · Migraine with aura · Stroke · Cardiac disease · Ischemic heart disease · Mortality · Cardiovascular disease

This article is part of the Topical Collection on *Stroke*

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Introduction

Migraine is one of the most common and disabling primary headache disorders that affects approximately about one-fifth of the general population, particularly women. In about one-third of patients, aura symptoms may precede the migraine attack. The lifetime prevalence of migraine reaches a peak in the late 30s and early 40s. Over the past decades numerous

data have pointed to an association between migraine and cardiovascular diseases (CVD).

Epidemiologic Evidence

The pioneering study of the Collaborative Group indicated an association between stroke, both of ischemic and hemorrhagic etiology, and migraine in women using oral contraceptives [1]. Subsequent studies pointed to an association between migraine and ischemic stroke that was also independent of oral contraceptive use [2–12]. Nevertheless, studies confirmed that use of oral contraceptives in migraineurs was associated with a further increase in the risk of stroke [5, 12]. The majority of the available studies have indicated that migraine with aura (MA) can be considered a risk factor for ischemic stroke, while migraine without aura (MO) cannot be reliably considered as such [4, 5, 8, 9, 12, 13]. The data referring to the association between migraine and ischemic stroke were pooled in 3 meta-analyses, which showed that MA is associated with a 2-fold increase in the risk of ischemic stroke [14–16]. Only in the earliest of the 3 meta-analyses, MO was associated with ischemic stroke [14]. After the publication of those meta-analyses, the American Migraine Prevalence and Prevention study (AMPP), confirmed the association between any migraine and ischemic stroke and between MA and ischemic stroke and supported the lack of an association between MO and ischemic stroke [2]. Referring to migraine characteristics, while the increased severity of the migraine attack has not been associated with an increased risk of ischemic stroke, a high frequency of attacks and a recent onset of migraine have been related to an increased risk [6, 10, 17]. As migraine is more common in women and most studies mainly included women there exists a huge body of evidence linking ischemic stroke with migraine in women [4, 11, 12]; data on migraine in men are scarce and lacking in details, mostly referring to migraine type [3, 18]. Since no direct estimates of the risk in men vs women are available, it is impossible to establish whether it is higher in one gender. With the exception of smoking most studies suggest that the association between migraine and stroke is only apparent among individuals without cardiovascular risk factors such as arterial hypertension and diabetes [5, 8, 10, 12]. In addition, there is consistent evidence that smoking substantially increases the risk of ischemic stroke among young women with migraine in particular if they additionally use oral contraceptives [5, 10, 15]. Moreover, data from the Women's Health Study (WHS) indicated that the association between MA and ischemic stroke was proved only among women in the lowest Framingham risk score group [19]. With regard to the individual components of the Framingham risk score, this pattern of association was driven by a particularly increased risk of ischemic stroke among women with MA who were young (aged 45–49 years) and who had low total cholesterol levels. Because of the low number of events in many of the reported case subjects, little information is available on the frequency of the different types of ischemic stroke in migraineurs. Studies have indicated that MA was associated with stroke of undetermined origin and showed a trend toward an association with lacunar stroke while no associations were found with atherothrombotic or cardioembolic stroke [10, 20]. With regard to functional outcome after ischemic stroke, the analysis of data from the WHS cohort showed that MA is only linked with ischemic strokes of good functional outcome [20]. More recently, it has been shown that in young subjects with ischemic stroke, MA represents an independent risk factor of overall recurrent vascular events and of recurrent ischemic stroke [21•]. In this study, none of other considered risk factors (arterial hypertension, cigarette smoking, diabetes mellitus, hypercholesterolemia, factor V Leiden, prothrombin mutation, patent foramen ovale, atrial fibrillation, and alcohol consumption) with the exception of antiphospholipids antibodies, emerged as an independent marker of risk of recurrent vascular events together with MA indicating the striking importance of this condition in young subjects with ischemic stroke.

Also the risk of transient ischemic attack (TIA) seems to be increased in migraineurs, although this issue has not been extensively investigated. Misdiagnosis of migrainous aura as TIA may represent a limitation in the proper study of this association. In a case-control study women with MO vs nonmigrainous women had a 2-fold increase in the risk of TIA [4]; at variance, an analysis of data from the WHS reported an increased risk of TIA in subjects with MA but not in subjects with MO [20].

Several studies have also addressed the possible association between migraine and hemorrhagic stroke [1, 3, 5, 7, 22–25]. Although the results of these individual studies were conflicting, their meta-analysis [26••] showed that migraine is associated with a 1.5-fold increase in the risk of hemorrhagic stroke (including intracerebral and subarachnoid hemorrhage). The risk of hemorrhagic stroke was also increased when female migraineurs of any age and female migraineurs aged less than 45 years were compared with control subjects. However, solid conclusions could not be made for the different migraine types because of insufficient data as only 3 studies [5, 24, 25] collected data on the risk of hemorrhagic stroke according to migraine type. Two of them [5, 25] showed an association between MA and hemorrhagic stroke, whereas only 1 of them showed an association between MO and hemorrhagic stroke [24]. Regarding hemorrhagic stroke type, available data suggest that the association between migraine and hemorrhagic stroke is driven by an increase of intracerebral but not subarachnoid events [22, 25].

Some studies have identified migraine also as a possible risk factor for cardiac vascular events [18, 27, 28] whereas

others have yielded negative results [7, 29, 30]. A meta-analysis did not show an increased risk of myocardial infarction in subjects with any migraine vs no migraine [15] but subsequently, data has pointed to an association between any migraine with cardiac ischemic disease [31] and between MA and MO with myocardial infarction [2]. A recent meta-analysis showed that the presence of any migraine did not alter the risk of coronary artery disease mortality [32] whereas according to the more recent Reykjavik population-based cohort study only MA increased the risk of coronary artery disease mortality [33]. In addition some data are reported also about the association of migraine with angina. In the large cohort of the Atherosclerosis Risk in Communities (ARIC) study, migraine (particularly MA) was associated with Rose angina that, in the absence of a corresponding association with coronary artery disease, suggested that the association between migraine and angina was not mediated by coronary artery disease [34]. Data from the WHS showed that the association with myocardial infarction was evident only among women in the highest Framingham risk score group and this pattern of association was driven by a particularly increased risk of myocardial infarction in women with MA who had high total cholesterol levels [19].

Migraine has also been associated by some studies with vascular mortality [32, 3] and with vascular disease in other regions such as in the lower limbs [35, 36] and the eye [37]. In addition, also Raynaud's disorder, Sjögren's syndrome, and livedo reticularis have been associated with migraine [38–40]. Furthermore, in patients with systemic lupus erythematosus, a history of migraine is reported to be associated with vascular damage [41]. Furthermore, a large registry of pregnancy-related hospitalizations, found that migraineurs women had an increased risk of several pregnancy-related vascular diseases such as stroke, myocardial infarction, embolus, venous thromboembolism, hypertension, and preeclampsia, gestational hypertension, smoking and diabetes [42]. A further study also indicated that preeclampsia is more common in migraineurs than in nonmigraineurs [43].

Several studies have also indicated that compared with nonmigraineurs, migraineurs have a higher burden of asymptomatic white matter brain lesions and, according to some studies, also infarct-like lesions at brain magnetic resonance [44–47]. White matter abnormalities in migraineurs have an uncertain clinical significance and may correspond to gliosis, demyelination, and loss of axons; this set of findings has been attributed to microvascular damage. Prevalence of white matter abnormalities in migraineurs ranges from 4 % to 59 % [44]. According to the CAMERA study migraine was associated with deep white matter abnormalities in women; this association was independent of the presence or absence of aura and the risk increased with attack frequency [48]. At variance, this same study showed that in men, deep white matter abnormalities were not influenced by the presence, subtype, or frequency of migraine. The EVA study confirmed the association of migraine with white matter abnormalities [46]. The association with deep white matter abnormalities was stronger for MA than MO but extended also to nonmigraine headaches, especially tension-type headaches. A meta-analysis of available studies showed an association between white matter abnormalities and MA and no association with MO [44]. Two studies addressing the impact of migraine on white matter hyperintensities progression over-time provided conflicting results. One of them showed that migraine was associated with significantly greater white matter abnormalities progression among women [49], whereas the other showed the lack of any association [45]. The available studies do not support the hypothesis that migraineurs with white matter abnormalities are at risk of cognitive impairment [46, 49, 50]. Infarct-like lesions appear as small infarcts on brain magnetic resonance imaging mostly in the absence of a clinical history of stroke. Their exact nature still remains elusive, as some of them may represent enlarged perivascular spaces or alternatively might be of a different nature rather than ischemic. Even in this case data point toward a clear association with MA, whereas data referring to any migraine or MO are controversial [46, 48, 51, 52]. Available evidence mostly suggests that infarct-like lesions are particularly common in the posterior circulation, and in small cerebellar border zones [53–56]. At variance, the results of the EVA study indicated that most of the infarcts were located outside of the cerebellum or the brain stem [46]. Migraine was not associated with the progression of infarct-like lesions over-time [49].

Mechanisms Linking Migraine to Cardiovascular Diseases

The mechanisms underlying the relationship between migraine and CVD are still unclear and several hypotheses have been raised and extensively revised and discussed [57–60]. Current hypothesis mostly try to prompt vascular events in migraineurs to those mechanisms that usually cause the same vascular events in nonmigraineurs subjects. Hypothesized mechanisms include the role of confounders such as pharmacologic agents used to treat migraine (nonsteroidal anti-inflammatory drugs, triptans, and ergotamine) or anxiety and depression; prothrombotic factors, including prothrombin factor, factor V of Leiden, elevations in von Willebrand factor antigen and activity, decreased platelet hemostasis time, clotting time and collagen-induced thrombus formation time; MTHFR, and ACE D/I polymorphisms; cervical arterial dissection; and patent foramen ovale. However, since none of those factors can entirely explain the CVD risk of migraineurs we should also consider that a peculiar migraine-specific mechanism may be responsible of the increased risk. Migraine has long been considered a vascular headache and cerebral

vasoconstrictive phenomena associated with migraine had been considered the cause of cerebrovascular ischemic events in migraineurs. However, more specific mechanisms are only now being discovered. Migraine headache depends on the activation and sensitization of the trigeminovascular pain pathway, whereas cortical spreading depression (CSD) is considered the neurophysiologic correlate of migrainous aura [61]. CSD may activate the trigeminal nucleus caudalis and is, thus, capable to generate the pain in migraine. CSD may predispose to brain lesions by hypoperfusion (spreading oligemia), by activating a cascade of inflammatory events, and by a failure of neurovascular coupling to provide a sufficient increase in blood flow for the raised energy use in CSD [57, 58, 62, 63]. The origin of the CSD in human migraineurs remains unclear, but in animal models, CSD has been triggered by ischemic phenomena, such as through infusions of endothelin-1, a powerful vasoconstrictor [64]. Other authors have similarly shown that CSD can be elicited in mice through microembolization in the carotid circulation using tiny plastic spheres, cholesterol crystals, and microbubbles, following large reduction of local blood flow [65]. However, in migraineurs the risk of cardiovascular events is increased even outside the brain and it is difficult to implicate CSD in systemic cardiovascular events (ie, ischemic heart disease) and in hemorrhagic stroke. Even if it cannot be excluded that other mechanisms may be of importance in those events, this possibility is unlikely and consequently the search for a cause for the association between migraine and CVD should look at a general level. An alternative hypothesis may rely on a peculiar vascular vulnerability of migraineurs that may contribute to the pathogenesis of migraine and, in the presence of some other unknown factors may also contribute, over time, to the development of CVD. Numerous data suggest that in migraineurs the vascular system is impaired at a systemic level since migraineurs with respect to nonmigraineurs showed an alteration of arterial function (greater stiffness or impaired compliance of the arterial system) and according to some studies also of the endothelial function (altered flow-mediated dilation, reduced number of endothelial progenitor cells) [66]. The suggestion that a common alteration may cause both migraine and CVD is further supported by the existence of genetically determined conditions that include among their clinical manifestations attacks of migraine as cerebrovascular events. The best known among those diseases is cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) caused by Notch3 mutations on chromosome 19, though other conditions have also been recognized. These conditions might serve as models to study migraine-VD mechanisms [67–69]. Mice that express human mutations in Notch3 (Arg90Cys) have abnormal myogenic responses, including constriction and dilation of cerebral and systemic vessels [70], and have significantly larger brain infarcts after middle cerebral artery occlusion compared with mice without these mutations [71], suggesting a deficit in compensator mechanisms such as collateral blood flow. In addition, an experimental study suggested that glutamatergic hyperexcitability associated with migraine mutations renders the brain more susceptible to ischemic depolarization [72]. As a result, the minimum critical level of blood flow required for tissue survival is elevated and infarction occurs, even in mildly ischemic tissues. Those may represent paradigm shifts in the search for a mechanism for increased stroke risk in migraineurs and differs from those previously postulated on the basis of clinical data alone.

Implications for Clinicians

Although the evidence that links migraine to CVD is robust the overall increase in absolute risk of CVD in migraineurs is rather small. Unfortunately at the moment there are no reliable features that may indicate which subjects, across the overall migraine population, are at the highest risk of vascular events even if a high frequency of migraine attacks may point to an increased stroke risk. The role that comorbid conventional vascular risk factors have on the risk of cardiovascular events in migraineurs is controversial. Although according to some studies the risk of ischemic stroke in migraineurs is magnified in the presence of some acknowledged vascular risk factors, according to other studies the risk is higher in those subjects not having comorbid vascular risk factors [1, 5, 10, 12, 19, 73]. However, it can be accepted, that in migraineurs women, in the presence of cigarette smoking the risk of ischemic stroke is increased 3- to 9-fold and 4- to 8-fold in the presence of oral contraceptive use [5, 11, 12, 14–16]. The combination of smoking and oral contraceptive use in women is associated with a 10-fold increase in the risk with respect to the presence of migraine only [5]. According to those data, subjects with MA should be strongly advised to quit smoking and prescription of combined oral contraceptives deserves special caution [74]. Since MO is not a definite risk factor for stroke, no specific restrictions are warranted in women with this condition, especially in the absence of comorbidities. Oral contraceptives use should be carefully discussed in women with MA since they may contribute to an unacceptable increased vascular risk in particular if women smoke. Their prescription should be contraindicated in women with MA and other comorbid vascular risk factors or congenital or acquired thrombophilia [74].

So far, no drugs are currently recommended for the vascular prevention in migraineurs. Patients with migraine should not be prescribed aspirin or other antithrombotics for cardiovascular prevention unless other (ie, nonmigraine) clear indications are present. The same should be applied to migraineurs showing at brain magnetic resonance evidence of white matter hyperintensities or infarct-like lesions. Since

patent foramen ovale has not been reliably associated with migraine nor to ischemic stroke in migraineurs or the presence of those lesions at brain magnetic resonance [75], no specific strategies should be adopted in the presence of patent foramen ovale even in association with white matter hyperintensities and infarct-like lesions unless in some isolated cases showing proven additional markers of high vascular risk (eg, thrombophilia). In general, the acute treatment and the secondary prevention measures of a patient with stroke who has a history of migraine do not differ from that of other stroke patients [76]. There is currently no direct evidence to support that a migraine prophylactic treatment will reduce future stroke risk [77]. Angiotensin converting enzyme inhibitors and angiotensin receptor blockers that in some preliminary studies have shown some efficacy in migraine prevention [78–81] have been also associated with reduction of cardiovascular risk independently form their blood pressure lowering effect [82, 83]. However, further evidence is needed to support their role as migraine preventive treatment in the absence of high blood pressure values and to demonstrate any possible benefit on the CVD risk of migraineurs. On the contrary, β-blockers (propranolol, metoprolol, atenolol, bisoprolol) that are commonly used as migraine prophylactic agents have not been reliably associated with vascular preventive effects independently of blood pressure lowering. In addition, ergot alkaloids and triptans, 2 effective migraine acute treatments, may raise concerns regarding CVD safety because of their vasoconstrictive effect. However, available data suggest that those drugs when used at the suggested doses do no lead to increased CVD risk [7, 84]. In addition, the fact that the migraine-stroke association is limited to MA argues against a strong influence of migraine treatment in stroke occurrence as patients with MA and MO are similarly treated. However, in patients with documented history of CVD, use of ergot derivatives as of triptans for acute migraine attacks is contraindicated as also in patients with uncontrolled high blood pressure.

Future Directions

Future research is needed to clarify several aspects of the association between migraine and CVD. Further and more detailed epidemiologic evidence is needed to link migraine with CVD other than stroke with details on migraine type. Regarding the association between migraine and stroke future studies should better detail the type of stroke (location, etiology, severity, and prognosis) in migraineurs with respect to nonmigraineurs and identify the subgroup of migraineurs at a higher risk for CVD. In addition future studies should clarify the span of time from migraine onset to the development of cardiovascular events as well as if only active MA is associated with increased risk or if the risk also exists in subjects with past history of MA. Mechanism to explain the mechanism underlying the association between migraine and CVD need to be studied with particularly regard to the role of genetic predisposing factors and environmental or comorbid triggers. This is the starting point to try to develop any reliable strategy to identify migraineurs who are at risk of CVD and to try to establish whether any specific treatment could modify the risk.

Conclusions

Migraine, particularly MA, is an established risk factor for ischemic stroke and possibly for CVD more in general. The mechanisms underlying this association are still unclear but their comprehension is mandatory to fulfill the need of tools to identify migraineurs at risk as to provide them any treatment. At the moment, only a heightened vigilance toward comorbid vascular risk factors that further increase the CVD risk of migraineurs is possible, whereas no specific treatments to target the CVD risk of migraineurs should be applied.

Compliance with Ethics Guidelines

Conflict of Interest Simona Sacco and Tobias Kurth declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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