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The Association of Cardiovascular Disease and Migraine: Review

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Abstract

The relation between the migraine and cardiovascular system is an interesting and yet complex. The migraine headache, specifically with aura, has been suggested to be associated with certain cardiovascular disorders. The exact explanation of this association still mysterious, but it has been suggested that spreading depressions waves of the cortex may play a critical role in changing brain blood flow which may lead to ischemic changes. Patients with migraine headache associated with aura are more predisposed to genetic cardiovascular disease associated risk factors including hypertension, hyperlipidemia and diabetes. Moreover, the risks of arrhythmia and mitral valve prolapse have been found to be different from normal population. It is important for healthcare providers to be aware of those findings in their assessment of the cardiovascular disease risk in migrainueres. In this review article will discuss this association

Keywords: Migraine; Headache; Cardiovascular disease; Stroke; Complications; Migraine prevalence; MVP

Introduction

Migraine is a chronic disease which is characterized by recurrent attacks of headache which can be disabling disease. The general prevalence of migraine in the United States is about 13% per year and ranges between 10 to 20% globally. Women diagnosed with migraine 3 to 4 times higher than men. The prevalence is 18.2% in women and 6.5% in men [1-3]. The exact mechanism of migraine and associated symptoms is complex and still not full clear. Several theories have been postulated including but not limited to vascular theory, neurovascular theory and cortical spreading depolarization (CSD) which is a well-defined wave of neuronal activation in the cortical gray matter that spreads from the site of origin [4,5].

About 28% of patients with migraine experience an aura before or even during the headache episode and frequently involving the visual field. Migraine is one of the frequent cause of disability and has significant economic burden worldwide [6,7].

Several clinical data has suggested that brain ischemic changes do occur during the headache associated with the migraine, more over wider ischemic changes have been observed to involve other organs mainly the heart. The vascular, neurovascular and cortical spreading depression (CSD) theories are the most widely accepted theories proposed to explain the pathophysiology of migraine headache.

The vascular theory is based on the suggestion that vasoconstriction and vasodilation are responsible for the aura and headache associated with migraine, respectively. On the other hand, the neurovascular theory, suggests that a complex chain of major neurogenic and secondary vascular events produce migraine episode by altering the cerebral perfusion [8-10].

CSD theory has been proposed to explain the migraine with aura. CSD is a well-defined wave of excitation of the neurons of the cortical gray matter that propagate from the site of origin at speed of 2-6 mm/min. This depolarization will initiate the aura and will spread to activate the trigeminal nerve system and cause headache. The CSD will result in releasing potassium or amino acid glutamate from neurons which will result in depolarizing the adjacent tissue and will result in releasing more neurotransmitters and propagating the spreading depression. The latter will result in decreasing metabolism and moderate reduction of blood flow a state called Oligemia which is believed to be responsible for the aura. As CSD does propagate on the surface of the brain, H^+ and K^+ ions reach the pia mater and stimulate meningeal nociceptors, releasing a neurochemicals which induces sterile inflammatory process and cause plasma extravasation. Once the trigeminal system activation initiated it will lead to dilation of the cranial vessels which result in throbbing headache [11]. Moreover, CSD upregulates genes which produce the different inflammatory enzymes and proteins, such as cyclo-oxygenase 2 (COX-2), tumor necrosis factor alpha (TNF-alpha), interleukin-1beta, galanin, and metalloproteinases. The activation of metalloproteinases results in increased permeability of the blood-brain barrier, which allow potassium, nitric oxide, adenosine, and other neurochemicals released by CSD to access and sensitize the dural perivascular trigeminal afferent endings [12].

Magnesium deficiency has been postulated to play a role in the migraine headache by triggering a sequence of events which lead to platelet activation and aggregation; In addition it results in releasing glutamate and 5-hydroxytryptamine, which is a vasoconstrictor. Magnesium therapy has been suggested to be effective for acute treatment of migraine by some studies [13].

Endothelial dysfunction as a result of impaired cyclic guanosine monophosphate and abnormal response nitric oxide response has been suggested to participate in the activation of trigeminal neuron system [14]. The cardiovascular pathologies associated with migraine are an important cause of morbidity and possible mortality. The main objective of this review is to discuss the clinical association between the Migraine and the cardiovascular system. Including stroke, coronary arterial disease, valvular prolapse, and arrhythmia [15,16].

Migraine and stroke

Several studies had included patients from different settings including registries and general population and found significant association between the migraine and cerebral ischemic events [16-27]. A meta-analysis of 14 observational studies performed by Etminan et al. [11] case control studies and three associate studies between 1966 and 2004) has found that the migraine could be a risk factor of developing ischemic stroke. They found that, the stroke risk was enhanced significantly in patients with migraine, and was consistent in both patients with (MA) or without aura (MO) (relative risk [RR], 2.16; 95% confidence interval [CI], 1.9–2.5). However, the risk of stroke was higher in MA patient group (RR, 2.27; 95% CI, 1.61–3.19) versus MO (RR, 1.83; 95% CI, 1.06–3.15) [10]. Likewise, in a stroke prevention study in young females, which is population-based, case-control study it was found that the odds of stroke of undetermined origin was increased in women who had new onset migraine with visual aura. Women with MA had 1.5 more chance of ischemic stroke, in comparison to people without migraine (95% CI, 1.1–2.0) [19].

The mechanisms that connect migraine headache and ischemic cerebral event stay not exactly determined and defined. Cortical spreading depression (CSD) and neurogenic inflammation have been suggested to play a major role in the development of migraine headache. CSD is a self-spreading waves of mass neuronal and glial depolarization that change ion homeostasis and blood flow. It is considered a physiologic substrate of aura [20,21]. Moreover, it has been implicated in disorders of neurovascular regulation such as stroke, head trauma, and migraine [22]. As a result of the mass cortical depolarization associated with CDS, a progression of cellular as well as molecular occasions, bringing about transitory failure of membrane ionic gradients, and also gigantic surges of extracellular potassium, neurotransmitters, and intracellular calcium. Moreover, CSD might to some degree by changing the porousness of the blood brain barrier by means of initiation of matrix metalloproteinases (MMPs), a group of neutral metalloproteases. The latter also was found to increase in level in patient with cerebral ischemia [21,22].

During CSD, nitric oxide, oxygen free radicals and proteases that have been involved in MMP initiation are significantly expanded. The CSD related MMP initiation might bring about changes in CNS vascular permeability, consequently, enhance the production of migraine indications [23]. In addition, structural changes have been found in the somatosensory cortex of the patients with migraine headaches by neuroimaging. This brain area supposed to act as foundation in distribution of changes included in visual aura [24].

Migraine and coronary heart disease

Because of the relationship between migraine headaches, in particular MA, has been suggested to be associated to cerebral ischemia, and because of the vascular characteristics of migraine, it's important to review if migraine is likewise connected to coronary artery disease (CAD).

Several reports and studies have found that the chest pain is more frequently found in migaineures than non migranuers, however the data regarding the increased risk of myocardial infarction is conflicting and inconsistent [25-27]. Migraine headache was connected to ischemic electrocardiographic changes and increased risk of angina. In the Atherosclerosis Risk in Communities study, patients with migraine were generally twice chance of having angina episode at the past when contrasted with controls, with the risk most raised in the migraine with aura [28]. In the Women's Health Study, MA but not MO increased the relative risk of major cardiovascular diseases including ischemic stroke, angina, myocardial infarction, coronary revascularization, and mortality associated with ischemic cardiovascular events [29,30]. These relationships stayed vital after regulating some cardiovascular risk factors. In Physician's Health Study, a prospective study in which total of 1449 men with migraine headache (with or without aura) were followed up for a mean of 15.7 years, for the occurrence of a first major CVD event (nonfatal ischemic stroke, nonfatal myocardial infarction, or death from ischemic CVD). It was found that apparently healthy men with migraine who were above age of 40 years had increased risk of CVD (HR 1.24; 95% CI, 1.06–1.46), which was mainly driven by a 42% increase in risk of myocardial infarction [30,31].

Small studies had suggested a possible link of migraine with vasospastic disorders such as variant angina and Raynaud's phenomenon. A metanalysis by Garner et al. showed that the Migraine and primary Raynaud's phenomenon had a positive significant association with a pooled OR of 4.02 (95% CI 2.62 to 6.17) in six studies [32]. Moreover patient with migraine are frequently treated by drugs that may increase the risk of coronary spasm including the triptans and compound having ergotamine. Triptan targets vascular-smooth muscle 5-hydroxytryptamine (5-HT1) serotonin receptor. Although 5-HT1 receptors mainly found in the cerebral vessel, there have been studies showing coronary vasoconstriction associated with the injectable form of these medications. There have been few reports of patients having myocardial ischemia or infarction with the oral form of sumatriptan [33].

Moreover, the anxiety of associated with headache attacks has been suggested that it could unmask coronary artery disease or could lead to progression of atherosclerosis through the span of different migraine assaults. However, if the later is true this relationship also should be found with patient without aura, not only MA [33].

Migraine and arrhythmia

Cardiac arrhythmias have been reported in migraine patients [34-36]. Coronary artery spanning has been recognized to lead to ischemia and MI, ventricular tachycardia, and unexpected death; though, these are very occasional sequelae [37]. A case study reported that congenital coronary artery abnormalities have been associated to rapid cardiac death, however, hardly ever cause death in individuals younger than 31 years. Migraine and the autopsy outcomes described, have been linked with cardiac arrhythmias and unexpected death [36]. Migraine headache may cause temporary changes in the brainstem function, resulting in destruction of action of medullar autonomic nuclei. Transient cardiac arrhythmias in migraine patients suggested that the abnormalities in the cardiac rhythm might be detected by cardiographic monitoring in some basilar migraine cases [36]. Patients with the basilar migraine or severe persistent attacks of migraine headache may need electrocardiographic monitoring through the attack for the recognition and treatment of cardiac arrhythmias [38].

Migraine and mitral valve prolapse

Increased prevalence of Mitral valve prolapse (MVP) has been observed in patients with migraine headache. It has been found that about 27% of patients with MVP had migraine headache, and about quarter of the patients with migraine has MVP [39,40]. Echocardiographically the MVP was found to be higher in the MA group patients in comparison to the control group patients. The odds

ratio of having MVP in the presence of migraine with aura was 2.7 (95% CI 1.17 to 6.29) [41].

The relationship between MVP and migraine is uncertain. Interestingly there is increased risk of transient ischemic attack in migrainers with MVP. It has been suggested that the TIA episodes stopped after few days from starting antiplatelet therapy [42]. These experiences raised many questions about the acknowledged associations amongst migraine headache and platelet abnormalities, as well as amongst migraine and stroke, particularly in light of the enlarged occurrence of MVP in patients with stroke and other symptoms (Table 1). A few studies had reported that the platelet activity is increased in patients with migraine not only through the acute episode of the migraine headache but also during the headache free time [43-45]. According to those findings, various patients who has a MVP and migraine association might be at larger risk of CVDs because they express both constant platelet activation as well as regions of myxomatous deterioration of prolapsing mitral valve leaflets, that may be the position of platelet aggregation and consequent thrombi development [43,46].

Migraine and patent foramen ovale

Interestingly, Migraine in general and MA in particular are happening more frequently in patients with PFO and vice versa [47]. However, this finding is uncertain whether it is a causal-relationship or just a co-existence. It is estimated that a quarter of the overall population, has PF, however it is found in 40-60% of migrainures with aura [48,49]. According to ameta-analysis by Schwedt et al. the patient with MA are 4 times more likely to have a PFO [OR 4.45] than the normal population [50].

Autosomal-dominant pattern of inheritance has been suggested to play a major role in PFO pathogenesis [51]. It is hypothesized that PFO and migraine could be co-inherited because of conjoint development of endothelium, platelets and endocardium. Interestingly, PFO may play a major part in the mechanism of the headache associated with migraine have a direct cause relationship associated to migraine headache. It can be postulated that shunting the blood into the left atrium and bypassing the filtering effect of the lung plays an important role in migraine headache. The shunting of blood allows small emboli to cross to the left system and/or greater concentrations of nitric oxide, serotonin, kinins or other migraine precipitating vasoactive chemicals to reach the brain and initiate migraine headache attacks [51-52]. Further supportive a causal-relationship, a noteworthy increase in migraine aura attacks and progress of de novo attacks has been acknowledged in patients ensuing PFO closure. The incidence of such attacks, possible due to thrombus development on the closure device or platelet degranulation, is decreased after the administration of aspirin and clopidogrel [52].

Conclusion

The interesting association of Migraine and cardiovascular system is important in clinical cardiovascular risk stratification. The MA found to have association with increased ischemic stroke risk, the risk of Angina, cardiac arrhythmia, PFO, ASD, and MVP. Based on these results, healthcare providers taking care of patients with MA should have heightened vigilance for modifiable cardiovascular risk-factors. Women that have MA and taking oral contraceptives should be advised to avoid smoking and they may need to have alternative contraceptive methods. More studies are needed to evaluate if MA itself a modifiable risk factor for CVD and to explore if preventing migraine attacks or antiplatelet therapy to patients with migraine will less the risk of CV events in in this patient population.

Mechanisms of association	Supposed mechanisms
The Causal association (e.g. migraine causes vascular ischemic events)	Repetitive occurrences of cortical spreading depression may prompt ischemia, blood perfusion imbalance and activates chronic inflammatory process.
Common predisposition (environmental or biological factors predispose to both migraine and ischemic vascular disease)	Migraineurs with aura are more likely to have uncontrolled cholesterol, higher Framingham risk-score for CHD, hypertension, and history of ischemic cardiac event.
Other co-morbidities	-Obesity and metabolic-syndrome patients may have increased frequency of headache attack and increase the stress level, and the incidence of attacks is linked with number of deep brain-lesions. ;
	- Patent-foramen-ovale and other congenital heart complications are commonly found in MA.

Table 1: Mechanisms of association and supposed mechanisms.

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