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Research Article

MIGRAINE HEADACHE ASSOCIATION WITH CARDIOVASCULAR AND CEREBROVASCULAR DISEASES

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ABSTRACT

Introduction: The migraine is one of the most common neurologic disorder, represented by recurring headache episodes associated with motor and somatosensory transitory disturbances. This pathology is more prevalent in the female population and is an important cause of incapacitation in the word. In this scenario, several studies propose the correlation between migraine, specially with aura, and cerebrovascular and cardiovascular diseases, due to pathophysiological aspects in common. However, the mechanisms of association between these diseases are not well enlightened, which difficults a better approach for the patients. **Objective:** The study aims to discuss and contribute for a better understanding of the association between migraine and cardiovascular and cerebrovascular diseases. **Methodology:** This article presents a narrative review of the literature based on the analysis of scientific articles published from 2012 to 2022, in PubMed and Science Direct, on migraine and its association with cardiovascular and cerebrovascular diseases. Two criterias were applied, titles that did not mention the thematic association between migraine and cardiovascular and cerebrovascular diseases and abstracts that did not address the theme migraine and cardiovascular and cerebrovascular diseases. After the application of the exclusion criterias, was obtained in total, 50 articles originally in English (including book chapters, guidelines and case reports) remained. **Discussion:** Migraine is a very frequent neurological disorder, being reported as one of the most disabling diseases in the world, affecting the quality of life, work and social functioning of the migraine patients. It is characterized by a pathological brain state that alters the patterns of neuronal activity, which may or may not be accompanied by the presence of aura, generating pain associated with several motor and somatosensory manifestations that appear both prior to the moment of headache and after the end of the pain crisis. In addition to these clinical associations, migraine can be related to an increased risk of developing cardiovascular and cerebrovascular diseases, due to its path physiology related to endothelial dysfunction, cortex spreading depression and increased coagulability markers and the inflammatory response, which can result in vasospasms and consequent hypoperfusion of some regions. **Conclusion:** This study discussed the relation between migraine, especially with aura, and cerebrovascular and cardiovascular pathologies. Overall, it was evidenced that there is an association of mechanisms between these disorders. In this context, there is an urgent need for more specific research and dissemination of data on the association of migraine and vascular heart and neurological diseases.

Keywords: migraine, cardiovascular, cerebrovascular

INTRODUCTION

The migraine is a very prevalent multidisciplinary and multi factorial neurologic disorder, represented by recurring headache episodes. This pathology is characterized by a headache associated with an infinity of motor and somatosensory transitory disturbances, being considered the second most incapacitating enfermity in the word, secondly to lumbar pain (1,2). Migraine affects, approximately, a billion people in the world, being more prevalent in females. The prevalence ratio between women and men varies from 1,5 to 1 in the age group of 12 to 17 years old, and from 3,25 to 1 for those between 18 and 29 years old (3,4,5), with general incidence of 8,1 per 1.000 people per year individuals initially without migraine (6). The clinical presentation is characterized by pain in half of the head, with intense palpitation, of throbbing nature, which worsens with effort or movement, with moderate to severe intensity that worsens with any physical effort and is frequently associated with nausea, vomit, photophobia or phonophobia (1). In about a third of the cases, the migraine is preceded or accompanied by transitory neurological disturbances named aura, which presents itself by fortification spectra, speech´s aphasic disturbances, brain stem´s symptoms (such as dysarthria and vertigo), motor weakness and retinal symptoms. Therefore, this pathology can be classified according to the presence or the absence of aura (7). When it is present, a typical migraine attack can develop in a cascade of events divided in four phases, initiating by the prodrome (affective or vegetative symptoms that appear 24 to 48 hours before the beginning of the headache), progressing to aura, and, lastly, the headache and the postdrome. In relation to the pathophysiology of this disturbance, it is known that the dysfunction of cerebral cells and arteries is the main component of this disorder (8). In the contemporary panorama, intense discussions have been happening about the relation between migraine and cerebrovascular and cardiovascular diseases. In this scenario, the migraine´s pathophysiology can be related to the endothelial activity, manifested by the elevation of coagulability markers, such as fibrinogen and Von Willebrand factor, and of CRP(C-reactive protein), being this association stronger in migraine with aura (9). Therefore, it is possible to associate the occurrence of migraine with the increase in cardiac vascular disturbances, such as acute myocardial infarction, and cerebral ones, such as cerebrovascular accident and dissection of the extra cranial cervical artery (10,11). In that regard, studies demonstrated that women with migraines have a higher incidence of

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cardiovascular events. That being said, numerous mechanisms have been proposed to elucidate this relation, such as elevated vascular biomarkers, endothelial dysfunction, genetic predisposition and the use of analgesic drugs for migraine, among others (12). The association between migraine and aura with cardiovascular risk has been widely investigated nowadays. Therefore, it is suggested that pro thrombotic and vasoactive factors , along with the migraine´s pathophysiology, favor the risk of cardiovascular events, dyslipidemia and the blood pressure´s increase, that lead to a higher probability of hypertension and coronary disease (13). Another prevalent comorbidity prevalent in these patients is the patent foramen ovale, which, along with the increase of inflammatory biomarkers and with the use of non steroidal anti-inflammatory drugs (NSAIDs), increase the probability of acute myocardial infarction, venous thromboembolism and atrial fibrillation (2). The association between migraine and cerebrovascular accident is complicated due to the similarity between the symptoms secondary to a migraine attack and to cerebrovascular events (such as, ischemic and hemorrhagic cerebrovascular accident, subarachnoid hemorrhage and venous thrombosis) (3). The mechanisms that correlate migraine and vascular events are not totally enlightened, however, it was suggested that the cortical spreading depression, the hypercoagulation, the endothelial dysfunction and the shared genetic risk, can be associated with the pathophysiology (14,15). Another possible mechanism for these episodes of strokes in patients with this type of primary headache is the progressive hypoperfusion and the decrease in the brain's blood flow that occurs during the migraine (14). Therefore, it is possible to conclude that the migraine is a highly prevalent pathology, specially in the female population, besides being responsible for more incapacity than all the other neurologic disturbances combined (4,7). In this context, numerous studies correlated cardiovascular and cerebrovascular diseases, although the pathophysiology of this association is not well enlightened. Consequently, the necessity to investigate the mechanisms of this correlation is urgent, aiming to provide a better approach of the migraine patients. Overall, the present study aims to discuss and contribute for a better understanding of the association between migraine and cardiovascular and cerebrovascular diseases.

METHODOLOGY

This article presents a narrative review of the literature based on the analysis of scientific articles published from 2012 to 2022, in PubMed and Science Direct, about migraine and its association with cardiovascular and cerebrovascular diseases. In the application of the first set of criteria, titles that did not mention the theme ´association between migraine and cardiovascular and cerebrovascular diseases´, articles not included in the period of research 2012-2022 and articles that were not found in English were excluded. In the database of PubMed, 531 articles were found by the keywords “(migraine) AND (cardiovascular)” and 234 articles by the keywords "(migraine) AND (cerebrovascular)" from which 56 were selected. Following the same criteria, in the database of Science Direct, 259 articles were found using the keywords "(migraine) AND (cerebrovascular)" and 545 articles were found using "(migraine) AND (cardiovascular)", from which 24 were selected. The second set of criteria was applied, from which were excluded the abstracts that did not address the theme migraine and cardiovascular and cerebrovascular diseases, which led to 31 articles being excluded.

Of total, 49 articles originally in English (including book chapters, guidelines and case reports) remained.

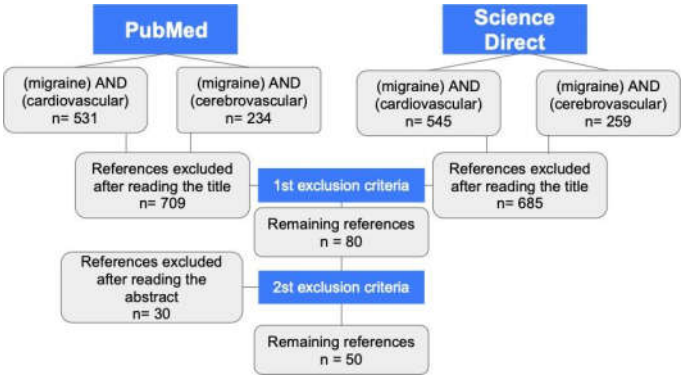

Figure 1. Flowchart of approach from the article selection with exclusion and inclusion criteria.

DISCUSSION

Migraine: a brief overview

The migraine is a chronic paroxistic neurological disorder characterized by a pathological brain state in which alterations in the consistent patterns of brain activity are manifested, involving multiple regions and stereotyped associated behaviors, including changes in the activity of the cortex and of the brain stem during the pain episodes (16,17). This type of primary headache affects 15 to 18% of the general adult population, being 2 to 3 times more prevalent in women, who report more intense and long crises that have more risk factors of monthly relapse and need longer periods of time for a complete recovery (18,19). The incidence of migraine varies more in the age gap between 35 and 45 years old (20) and, after puberty, increases its effect on the functional capacity of the affected individuals, mainly in females, varying its degree from slight damage to the incapacity of enjoying social and work activities. Such depreciative action in the life quality of the carriers of this disorder is referenced in the Global Burden of Disease Study de 2015, which describes the migraine as the seventh main cause of lost life years by incapacity; and according to the World Health Organization, it is described as the second most incapacitating neurologic disorder in a comparison of global scenario (16,19, 21). In this context, the migraine can be classified, according to the Headache Classification Committee of the International Headache Society, in with or without aura (22). The presence of aura is the most present type in patients and is characterized by transitory focal neurological symptoms which begin before the pain crisis and can be extended until after the headache ceases. Manifestations of the sensorial, speech and visual alterations can be similar to the clinical presentations of ischemic events, which can create a challenge in the diagnostic differentiation, mainly in the groups that have vascular risk along with headache without aura (16, 23). This challenging scenario can lead to late diagnosis of both clinical situations mentioned and, consequently, cause side-effects and reduce the quality of life. Although it is complex, the migraine diagnosis is established by the clinical history, excluding the indication of imaging exams and biomarkers research or a better precision and conduction of the stories (20). However, it is well accepted that genetic factors play important parts in the definition of the susceptibility of an individual to migraine, as enlightened in association studies between the premature beginning and more severe pain scores related to a higher rate of family history, in comparison with the ones that develop manifestations only when adults and report pain scores of lower intensity (19, 24). Besides the influence of genetic factors in some cases of migraine, it presents some comorbidities which include neurological alterations (restless legs syndrome (RLS) and multiple sclerosis); medical alterations

(asthma, allergic rhinitis, angina) and psychiatric alterations (depression, anxiety, post-traumatic stress disorder) (25).

Overview Migraine Pathophysiology

The migraine crisis extends itself beyond the moment of pain that the patient goes though, being possibly divided physiologically in four phases based on its temporal relation with the headache, in order of biological events, they present themselves in premonitory phase, aura phase, headache phase and postdrome phase (26). Initially, the promontory phase is described as a period of symptoms experienced from a couple hours to days before the actual pain episode, characterizing itself by the absence of associated aura and by the manifestation of alterations in humor, concentration, visual pattern (blurred vision) and neck stiffness. This presentation can be based on the hypothalamic involvement, which acts playing a part in the amplification of pain during the headache attacks. Associated with this part, numerous hypothalamic neurotransmitters were included in the development of this pathology, such as orexigen, melatonin, cholecystokinin, somatostatin and dopamine. This one, during the premonitory phase, can be a pathway to abort the migraine attack that develops, through the antagonismo to its receptors. Such cerebral modifications can be revealed in imaging exams, for example, in the magnetic resonance, by a greater connectivity between this region and the brain areas involved in the pain transmission and in the autonomic functionality, besides an activation of the substantia nigra, region of the brainstem that contains dopaminergic neurons (27, 28). In temporal sequence, the aura phase is characterized by the depression of the slow development in the electroencephalography, named cortical spreading depolarization (CSD). This phenomenon occurs through a depolarization wave of slow propagation from cortical neurons and glial cells followed by a “silence” of the electric activity, which spreads in means of 4 mm/min and is triggered by toxic alterations in its ions transmembrane gradient. Such sequence of events results in a massive influx of Na, Ca and H2O and efflux of K, glutamate and ATP, besides neurotransmitters with vasoactive and inflammatory properties. In this context of electric events, the thalamus´ associating nuclei receive information from the sub cortical regions, such as the limbic system, the reticular formation and the other nuclei of the brain stem. These connections between the mentioned regions and the thalamus nuclei can explain the predominance of the pain symptoms in this moment of the crisis. Besides, the loss of excitatory activity in the reticular thalamic nuclei can lead to the increase of sensorial excitement and, therefore, explain the smell-oral sensorial characteristics in the migraine´s aura phase (26, 29, 30). By continuity, the patient in the migraine crisis with aura develops the headache phase. In this stage, the perception of pain is a multifactorial process that consists in a network of activation and modulation of peripheral afferences for the central structures of pain, making cortical, vascular and autonomic connections. Regarding the transmission of peripheral information to the central regions, it happens through C nociceptive unmyelinated fibers from the trigeminal ganglion and through Dural lightly myelinated Ad fibers that express the CGRP receptor, which is involved in the activation of the trigeminal, a process that is characterized by being key in the migraine´s headache processing. These nerves are responsible for the innervation of the cranial and meningeal vasculature, also contributing to the sensation of pain and its intensification (27, 20, 31). In the last stage of the migraine cycle, the postdrome phase is the period of time from the headache´s symptoms resolution until the return to baseline after a migraine attack. Such moment is characterized by cerebral activations similar to the ones that occur during the premonitory phases, besides the decrease in the cerebral blood flow, which contributes to the neuropsychiatric, sensorial and gastrointestinal symptomatology, that reflect in a state of general malaise in the patient (27, 32, 33).

Migraine and Cardiovascular Disease

The mechanisms that lead to the increase in the risk of cardiovascular events are multifactorial, such as cortical spreading depression, hypercoagulation, endothelial dysfunction, shared genetic risk, vasospasm or greater prevalence of cardiovascular events in migraine patients (16, 21). The cardiovascular risk factors associated with this disturbance are blood pressure (BP), total cholesterol and low density seric lipoprotein (LDL), smoking, the use of oral contraceptives and coronary disease familiar background (13, 34). These elements were reported, mainly, in young females, and have been associated, specially, with migraine with aura (35, 36). Regarding that, data from Nurses' Health Study II demonstrated that in women with age between 25 and 43 years old, the migraine was associated with myocardial infarction, angina/ coronary revascularization and cardiovascular mortality (37). Besides, according to the Women's Health Study, the increase in the risk of cardiovascular diseases was present only in women that reported migraine with aura (38). Furthermore, the migraine, specially with aura, is a systemic disease associated with generalized endothelial dysfunction and the stimulation of inflammatory responses, due to the increase in the release of prothrombotic and vasoactive factors (21,39). Amongst the released endothelial biomarkers it is fitting to highlight: endothelial vascular growth factor, t-PA (tissue-type plasminogen activator), Von Willebrand factor, C-reactive protein and decreased levels of nitrate. These inflammatory cytokines released in the aura phase activate the endothelium, leading to a procoagulatory and prothrombotic state (40). Therefore, consequently to those pathophysiological mechanisms, there is a strong association between migraine with aura and the increase in the risk of cardiovascular disease, myocardial infarction, ischemic cerebrovascular accident and death by ischemic cardiovascular disease, coronary revascularization and angina (13). Besides, migraine with aura also have been associated with other risk factors, such as hypertension, lipid levels and body composition (12). In that regard, components of metabolic syndrome, such as obesity, arterial hypertension, dyslipidemia, insulin resistance and increased inflammation are considerably prevalent in patients with migraine, contributing to the increase of cardiovascular risk. In this scenario, a diet rich in fats heightens the LDL plasmatic cholesterol, which increases the state of platelet aggregation (41). It is worth mentioning that numerous studies showed that obesity increased the risk of having migraines and the risk goes up with the IMC growth. Besides, according to data from Atherosclerosis Risk in Communities Study, the patients with headache have approximately a doubled chance of having an angina history than the control groups and the migraine with aura group has the highest risk score (42). In a joint analysis of 21 studies, it was demonstrated that the patent foramen ovale (PFO) has an increase of 3,4 times higher and prevalence of about 50% of the patients that have migraine with aura (21, 43). This pathology can act as a channel to the passage of blood clots or platelet plugs, and its presence is associated with the occurrence of transitory ischemic attacks and cerebrovascular accident, through a mechanism of paradoxical embolism and transitory hipoxemia (40, 44). The migraine is a disease with multiple associated genetic factors; recent studies of genome-wide association identified 44 variants in 38 genetic loci that affect the risk of developing migraine (45). In this scenario, there are numerous studies that address the genetic associations between migraine with aura and cardiovascular events; for example, a genetic analysis showed that the risk of cardiovascular disease was duplicated in the people that have migraine with aura and express the deletion/deletion (DD) genotype of the angiotensin

converting enzyme (ACE) (43). Under this perspective, numerous studies of genre about migraine with aura suggest that sexual hormones are the main contributors for the high incidence in females, mainly estrogens, which increase the thrombotic risk (43). Furthermore, the use of oral contraceptive pills, hormonal reposition therapy and the use of nonsteroidal anti-inflammatory drugs (NSAIDs) are associated with the increase of cardiovascular events (46). In this scenario, the use of NSAIDs is associated with increased risks of myocardial infarction, venous thromboembolism, atrial fibrillation or atrial flutter (37).

Table 1. Relationship between migraine and cardiovascular disease

Mechanisms of association	Putative mechanisms	Comments
Causal association: migraine causes cardiovascular disease	Cortical spreading depression, hypercoagulation, endothelial dysfunction and shared genetic risk are mechanisms that link migraine to cardiovascular disease.	Justifies migraine with aura as a risk factor.
Associated predisposition: factors that predispose migraine and cardiovascular disease	Smoking, hypertension, obesity and high LDL levels are associated with both migraine with aura and cardiovascular disease.	Migraine with aura and cardiovascular disease shared similar risk factors. Some studies show that migraineurs with aura are more likely to have risk factors for cardiovascular disease.
Comorbidities	Studies metabolic show that syndrome has a high frequency in migraines. Patent foramen ovale has a high prevalence in migraineurs with aura.	The relationship between migraine with aura and cardiovascular disease can be magnified by the presence of common comorbidities.

Migraine and Cerebrovascular Disease

The relation between migraine and cerebrovascular accident (CVA) was consistently reported by recent meta-analysis, being even more concrete for ischemic CVA and migraine with aura. Furthermore, factors such as women using oral contraceptives or smoking aggravate the risk of these disturbances (47), situations that result in an increased long life risk of latent cerebral infarcts for these patients, getting to two times higher than in the non affected population. It was proposed that the hypoperfusion dissemination associated with the neuronal depression would be the most probable cause for this scenario (23). This happens due to the possible main pathogenetic mechanism for aura in migraine, which is cortical spreading depression (CSD), a wave of potent depolarization, self-propagating and of short duration that moves through the cortex with a rate of 3-5 mm/min, can favor ischemic events in the brain, and the cerebral hypoperfusion that starts in the aura phase and is followed by hypoperfusion in a migraine attack (47,48). Besides, the CSD was associated with the increase of integrin expression, causing more helper T cells to adhere, with the plasmatic increase of platelets and with the growth of oxidative stress, mechanisms that promote endothelial activation, as represented in Figure 1 (49). Another suggested mechanism was the role of endothelial dysfunction, caused mainly by oxidative stress and inflammation. Furthermore, it was observed that patients with episodic and chronic migraine have higher erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) correlated with the thickness of the minimum carotid-intima, characterizing an inflammatory state that corroborates with the increase in the risk of cerebrovascular diseases (50). Endothelial disturbances are characterized by decreased vasodilating activities, increase of vasoconstrictors that are derivative of the endothelium and consequent compromising of the vascular reactivity. This presentation can lead to a proinflammatory, procoagulant and proliferative state, which predisposes atherosclerosis (50). The cytokines from IL-1 family constitute one of the main inflammatory mediators that contribute to a broad variety of vascular, metabolic and neurological diseases, being the proinflammatory forms of IL-1α and IL-1β the ones that are involved in central and systemic inflammatory mechanisms. In studies with animal models, the blockage of IL-1´s actions had protecting results against cerebral lesions. The polymorphisms of IL-1β and/or NLRP3 and the alterations in the genetic expression are associated with depression, migraine and ischemic stroke in patients (48). Other associated genetic factors are polymorphisms of Methylenetetrahydrofolate Reductase (MTHFR) C677T, the polymorphism of the angiotensin converting enzyme (ACE)-DD, and, the most known of them is CADASIL, which was the first genetic locus known for strokes, with pathogenic mutations (47). It is worth mentioning, the association between the patent foramen ovale, a congenital malformation, and the increased risk of CVA, due to the predisposition of thrombi formation, conditions that share common genetic characteristics with the migraine (42).

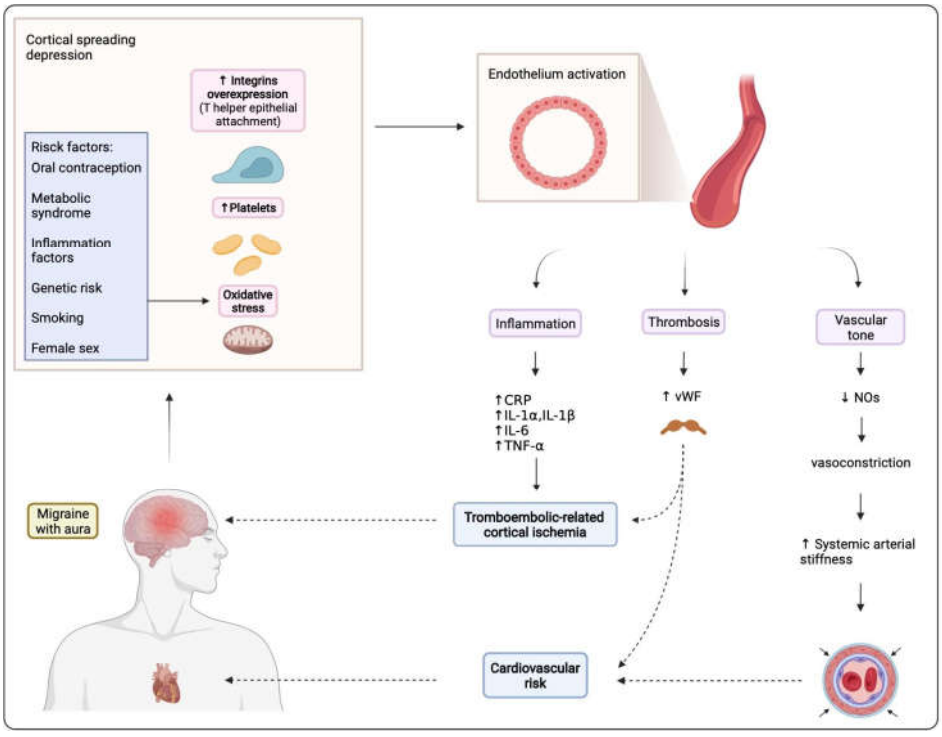

Figure 1. Migraine with aura pathophysiological mechanisms include cortical spreading depression, which is associated with integrin over expression, increase serum levels of platelets and increase oxidative stress. These common characteristics lead to endothelium activation resulting in inflammation, thrombosis and increase in vascular tone, leading to a common path between thromboembolic cortical ischemia and cardiovascular risk. Figure created by the authors using BioRender.

Table 2. Relationship between migraine and cerebrovascular disease

Mechanisms of association	Putative mechanisms	Comments
Causal association: migraine causes cerebrovascular disease	• Cortical spreading depression • Hyper coagulation • Endothelial dysfunction • Genetic risk	Because of these mechanisms, migraine with aura is justified as a risk factor for cerebrovascular disease.
Associated predisposition: factors that predispose migraine and cerebrovascular disease	Smoking, combined oral contraceptives and atherosclerosis are associated with migraine with aura and cerebrovascular disease.	Somes studies show that migraineurs with aura are more likely to have risk factors for stroke
Comorbidities	Patent foramen ovale (PFO) has a high prevalence in migraineurs with aura.	PFO act as a conduit for the passage of blood clots or platelet plugs to cause stroke or myocardial infarction in patients who have migraine with aura.

CONCLUSION

The present article discussed the association of migraine with cardiovascular and cerebrovascular diseases. On account of the existing knowledge, it was evidenced that a broad relation of mechanisms exist between these disorders, highlighting the cortical spreading depression, hypercoagulation, endothelial dysfunction and shared genetic risks as the main ones. Therefore, these factors are responsible for the increase in the risk of cardiovascular diseases, myocardial infarction and ischemic cerebrovascular accidents. Overall, the migraine presents a great prevalence and incapacitating potential, generating high costs in the health services. In this context, it is of extreme importance the adequate prevention of this neurological disorder, besides the knowledge and development of new treatment approaches. On that account, the necessity of more specific research and propagation of data regarding the relationship between migraine, specially with aura, and cerebrovascular and cardiovascular pathologies, by the health planners and formulators of policies.

Conflict of interest

The authors declare that they have no conflicts of interest. All authors read and approved the final manuscript.

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