Migraine and Vascular Disease

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Abstract

Migraine is a common disease that is considered to be a benign disorder. However, recently evidence was produced that migraineurs, especially those with aura, have an increased risk of stroke and cardiac disease. These patients have more cardiovascular risk factors, but migraine seems to bear a risk in itself. The pathophysiology is still unknown. Patients might have endothelial dysfunction, which is associated with an increased risk of stroke and cardiac events. Other potential mechanisms include coagulation abnormalities and platelet hyperaggregability. A patent foramen ovale (PFO) that might lead to cardiac embolism is more often observed in migraineurs than in people without migraine. It is not yet known whether the disorders are genetically linked or whether a PFO is a risk factor for migraine with aura. This review examines the occurrence of stroke and cardiac events in migraineurs and discusses potential mechanisms.

Keywords

Migraine, aura, stroke, endothelial dysfunction, patent foramen ovale, myocardial infarction

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Migraine is a common primary headache disorder with a lifetime prevalence of up to 33% in women and 13.3% in men.[1] Almost one-third of migraineurs experience transient neurological (visual, aphasic, sensory and motor) symptoms known as aura before onset of headache. Although migraine is known to be a benign disorder, migraine and stroke have been linked for many years.[2] Additionally, recent trials have demonstrated a higher occurrence of cardiovascular diseases in migraineurs.[3–6] People with migraine with aura seem to have an increased risk of cardiovascular events than migraineurs without aura, although the data are inconclusive and the underlying pathophysiology is not clear. This article summarises the recent literature connecting migraine to cerebrovascular and cardiovascular disorders.

Migraine and Stroke

People with migraine, especially those with migraine with aura, have a higher risk of stroke than adults without headache.[7–10] The increased risk is more evident in younger people[6,8,10,11] and in migraine with frequent attacks.[12] In a meta-analysis of observational studies published between 1966 and 2004, Etminan et al.[10] found an increased relative risk (RR) of ischaemic stroke of 2.16 (95% confidence interval [CI] 1.89–2.48) in migraineurs. The risk of stroke was further increased in women under 45 years of age (RR 2.76, 95% CI 2.17–3.52). In 2005, Kurth et al.[8] published a prospective cohort study using data from the Women's Health Study. In this trial, 39,754 healthy women 45 years of age or older were followed for an average of nine years. Women with migraine with aura who were between 45 and 55 years of age had an increased risk of stroke (RR 2.25, 95% CI 1.30–3.91). Women with migraine without aura were not at greater risk than people without headache. To assess the risk of stroke in men, Kurth analysed data from the Physicians' Health Study, which included 20,084 men.[6] In contrast to what was observed in women, migraineurs did not have an increased risk of stroke compared with men without headache. Another prospective trial included 12,750 men and women 55 years of age or older from the Atherosclerosis Risk in Communities Study.[9] Men and women with migraine with aura had an increased risk of stroke compared with people without headaches or migraineurs without aura (RR 2.91, 95% CI 1.39–6.11). Even after adjusting for risk factors, migraineurs had a higher risk of stroke. The Stroke Prevention in Young Women Study[12] included 386 women 15–49 years of age with a first ischaemic stroke. Participants with migraine with aura (visual symptoms) had an increased risk of ischaemic stroke compared with participants without headache (odds ratio [OR] 1.5, 95% CI 1.1–2.0). The risk further increased if attacks occurred at least once a month on average.

Migraine and Cardiac Disease

The assumption that migraine may imply a higher risk of stroke is more widely known than the possible association between migraine and myocardial disease.[13–15] In 1995, Sternfeld et al.[5] examined the relationship between migraine, chest pain and risk of myocardial infarction in a retrospective cohort of almost 80,000 people who were members of the Northern California Kaiser Permanente Medical Care Program. The authors found a co-morbidity between migraine and the occurrence of chest pain.

The risk of myocardial infarction in migraineurs was not increased. Similar findings were presented by Rose et al.,[4] who examined 12,409 participants from the Atherosclerosis Risk in Communities Study. Participants with headaches, particularly if accompanied by auras, had an increased risk of Rose angina. The authors concluded that the association of migraine with Rose angina is not related to coronary heart disease because the risk of cardiovascular disease was not increased.

Recently, Kurth et al. presented two large prospective cohort studies in women[3] and men[6] that evaluated the relationship between migraine and cardiovascular disease. In the Women's Health Study, 27,840 participants 45 years of age or older were followed for up to 10 years. Migraineurs with aura presented a higher risk of myocardial infarction (multivariable-adjusted hazard ratio [HR] 2.08, 95% CI 1.30–3.31), coronary revascularisation (HR 1.74, 95% CI 1.23–2.46) and angina (HR 1.71, 95% CI 1.16–2.53) compared with women without migraine. In the Physicians' Health Study,[16] 20,084 men were followed. Men with migraine had a statistically higher risk of myocardial infarction (HR 1.42, 95% CI 1.15–1.77) but not coronary revascularisation or angina compared with participants without migraine. As described earlier, the same population did not show an increased risk of stroke.

Pathophysiology

Pathophysiological Mechanisms Underlying Cardio- and Cerebrovascular Events

Several studies found an unfavourable cardiovascular risk profile in patients with migraine. Participants in the Genetic Epidemiology of Migraine study with migraine with aura presented more often with an unfavourable cholesterol profile, arterial hypertension and a history of smoking.[17] Their Framingham risk score for coronary heart disease was more likely to be increased. Kurth et al.[11] found an elevated predicted 10-year risk of coronary heart disease (according to the Framingham risk score) in participants with migraine (with and without aura). The risk of stroke or cardiac events in migraineurs is higher if participants use oral contraceptives, smoke,[12,18] have a high blood pressure[6,19] or have elevated cholesterol levels.[6]

However, migraine itself bears the risk of cardiovascular events. Most trials report an increased risk of cardiovascular events even after correcting for cardiovascular risk factors.[3,6,7,9,10,18] Accordingly, the risk of cardiovascular events is more increased in migraineurs with a low cardiovascular risk profile[3,9] and in younger participants[3,6,10] compared with controls. Additionally, migraine-specific drugs might produce a higher morbidity due to vascular events. Migraineurs frequently use triptans or ergots to medicate their headache. Patients using ergots have a higher risk of white matter lesions (WMLs)[20] and ischaemic events.[21] However, an increased risk of cardio- and cerebrovascular events could not be shown for triptans.[20–22]

Several biological mechanisms are discussed through which migraine might lead to cardiovascular events. Migraine might be a systemic disorder that affects the vasculature. Endothelial dysfunction is a potential mechanism. During a migraine attack, levels of von Willebrand factor, a serum marker of endothelial dysfunction, increase.[23,24] People with migraine with aura might have a vulnerability to oxidative stress,[25] which promotes endothelial dysfunction. Endothelial dysfunction is associated with an increased rate of cerebro- and cardiovascular ischaemic events.[26] Further evidence of vascular dysfunction comes from Vanmolkot et al.,[27] who found that young migraineurs (under 35 years of age) have a decreased diameter and compliance of peripheral arteries.

In addition to vascular dysfunction, coagulation abnormalities[28,29] and platelet hyperaggregability[16] have been observed in migraineurs, which might lead to a higher incidence of thrombotic events. A recently published population-based study showed that migraineurs had a higher lifetime history of venous thromboembolism than non-migraineurs.[30]

Finally, migraine and ischaemic events might be linked genetically. Migraine is a symptom in genetic diseases such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)[31] and mitochondrial myopathy, encephalopathy, lactacidosis and stroke (MELAS).[32] Genetic factors that might add to the risk of cardiovascular disease have also been linked to migraine.[33,34] The angiotensin-converting enzyme gene deletion polymorphism (ACE-DD) seems to be associated with an increased frequency of migraine attacks,[33] and the methylene-tetrahydrofolate reductase (MTHFR) C677-TT polymorphism is associated with an increased risk of migraine with aura.[34]

Characteristics of the Pathophysiology Leading to Stroke

While cardiovascular risk factors and biological mechanisms lead to a higher incidence of ischaemic events in the brain and the heart, other findings in migraineurs explain only the increased risk of cerebral events. Clinically silent brain infarcts and WMLs are observed more frequently in migraineurs than in people without headache.[35–38] The risk of WMLs is higher in patients with migraine with aura than in those without aura, and increases in line with the frequency of attacks.[20] Most often, ischaemic lesions are localised in the posterior circulation territory.[20]

Other studies indicate an association between migraine, particularly migraine with aura, and patent foramen ovale (PFO).[39–41] Migraine-triggering vasoactive components, which are removed during passage through the lungs, could reach the cerebral circulation via a PFO. As observed in migraineurs, ischaemic infarctions due to paradoxical emboli tend to occur in the posterior circulation.[42] The cortical spreading depression might be triggered through focal ischemia. It was observed that a PFO closure improved the frequency and severity of migraine attacks.[43,44]

Against this background, the Migraine Intervention with STARflex® Technology (MIST) trial was conducted.[45] Participants with migraine with aura who were refractory to at least two prophylactic medications and had frequent attacks were randomised to PFO closure or a sham procedure. This trial could not support earlier findings. Only when removing two outliers was the frequency of migraine attacks reduced after PFO closure compared with a sham procedure.

In summary, the possible explanations for why migraine and PFO frequently occur together are insufficient. The disposition for both disorders could be inherited simultaneously and may not have a causal link.

Conclusion

Recently, it was shown that people with migraine – a usually benign disorder – tend to suffer more often from cerebral and cardiac ischaemic events than people without headaches. Especially in migraine with aura, the risk of stroke and cardiovascular events is at least two-fold higher than in people without migraine. While the data concerning migraine with aura are consistent, the association between migraine without aura and cerebro- or cardiovascular diseases is less clear. However, the underlying pathology seems to be comparable in migraine with or without aura. In both groups, an increased vascular risk profile and biological mechanisms such as vascular dysfunction and coagulation abnormalities have been observed. However, the definite cause that leads to the increased risk remains unclear. In order to clarify these mechanisms and provide a reasonable background to identify migraineurs at risk of stroke or cardiovascular events, further research is required. ■

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