MIGRAINE AND CEREBROVASCULAR DISEASES: AN OVERVIEW

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Abstract

Migraine and cerebrovascular diseases are among the most common neurological disorders. While migraine has traditionally been considered a benign condition, increasing evidence points to a strong association with stroke. The latter is strongest for migraine with aura, while migraine without aura doesn't increase the risk of stroke. Women, younger patients, patients with frequent attacks and new-onset migraineurs are mostly at risk of stroke. Smoking and oral contraceptive use further increase the risk. Migraine and cerebrovascular diseases are linked in four ways as migraine can: 1) be a symptom of stroke, 2) be the cause of stroke (i.e. migrainous infarction), 3) increase the risk of stroke and 4) can be a symptom of genetic syndromes predisposing to stroke. Cerebrovascular disease mimicking a migraine attack, while uncommon, can lead to important diagnostic and therapeutic dilemmas. Migrainous infarctions are rare and can only be diagnosed after extensive work-up but must be considered in young stroke patients. Multiple mechanisms have been proposed to explain the association between cerebrovascular disease and migraine, with cortical spreading depression, vascular reactivity and endothelial dysfunction being the most prevalent. The role of patent foramen ovale and microemboli is currently investigated. Unveiling the pathophysiology of migraine-related stroke can help prevent cerebrovascular disease, while recognizing the potential risk factors can help minimize stroke risk in migraineurs.

Key words: migraine, stroke, cerebrovascular diseases

Introduction

Migraine is the most common neurological disorder affecting almost 15% of the population in Europe [1]. In 30% of cases it is associated with transient neurological symptoms (aura) commonly manifesting as visual, sensory and language disturbances and rarely as brainstem-associated or motor deficits [2]. Traditionally, the pathophysiology of migraine has been associated with vascular changes in the brain, the so-called vascular theory. While the latter is not currently considered viable, the association of migraine with cerebral vascular disorders is undisputable.

Migraine is commonly thought of as a benign condition but is linked to cerebrovascular disease in four different ways: 1) headache at the onset, during or after acute cerebrovascular accidents can mimic migrainous headache; 2) migraine may be the cause of ischemic stroke (migrainous infarction); 3) migraine can be a risk factor for cerebrovascular disease (migraine-related strokes) and 4) migraine is a core symptom in genetic syndromes characterized by cerebral ischemia, such as CADASIL and MELAS.

Migrainous headache due to vascular disease (migraine-mimic)

Headache can in some cases accompany acute cerebrovascular diseases. In subarachnoid hemorrhage (SAH), headache occurs in the majority of patients, with almost all patients presenting with headache at the onset [3]. Cephalalgia preceding hemorrhage is also often reported by patients suffering from aneurysmal SAH and probably represents small sentinel bleeds or changes within the aneurysmal wall [4]. In intracranial hemorrhage (ICH) headache is also common, with most patients reporting headache in the hours following the onset of neurological symptoms. Irritation of pain sensitive intracranial structures by the expanding hematoma or increased intracranial pressure is probably responsible for the headache [3].

In ischemic stroke, headache is less often, probably underestimated and overshadowed by other symptoms. The frequency of headache depends on the study population and design and varies widely between different studies. In TIA or minor stroke headache has been reported in 16-65% of patients, whereas in complete or severe strokes 9-31% of patients report headache. Headache can accompany

the onset of ischemia, so-called onset headache, can precede (sentinel headache) or follow the ischemic event (late-onset headache) [5]. Sentinel headache, while common in impending SAH due to aneurysmal rupture, is present in only 10% of patients with stroke. Onset headache is present in 16-36% of patient with TIA and 8-34% of patients with stroke, while late-onset headache is less strictly defined and less common [3, 6].

Many theories have been proposed to explain headache in acute cerebral ischemia [7]. Dilation of collateral vessels during ischemia and stimulation of the trigeminovascular system, platelet aggregation and degranulation, distention of the vessels proximal to the site of occlusion and toxic effect of the thrombus and the vasoactive agents released are all attractive theories. However, none of these theories can completely explain the headache that accompanies cerebral ischemia. In a study where 38% of patients with acute stroke reported headache, intracranial and extracranial atherosclerosis were inversely associated with headache frequency [8] suggesting that healthy vessel walls are associated with more stroke-associated pain.

Stroke subtype and localization are associated with different prevalence of onset headache. Onset-headache is most common in patients suffering infarcts in the right anterior insular region, the somatosensory cortex of both hemispheres and the cerebellum [9]. Ischemic events in the posterior circulation, traditionally associated with headache, don't seem to have a higher frequency in recent studies [6]. The association of stroke subtype with onset headache is less defined [10]. Headache is less common in lacunar infarcts and cortical involvement is associated with a higher frequency of onset-headache during stroke [6]. Onset-headache frequency in cardioembolic strokes is probably comparable to strokes attributable to large vessel disease. As a consequence, the presence of headache cannot be used for the differential diagnosis between stroke subtypes.

Migrainous stroke

Migrainous stroke is considered a complication of migraine with aura. It is defined by ICHD-3 (International Classification of Headache Disorders, 3rd edition) as a migraine attack in a patient with migraine with aura, typical of previous attacks, persisting more than 60 minutes and presenting with typical neuroimaging abnormalities of ischemia in a relevant area. All other diagnoses must be excluded [2]. This definition does not allow the diagnosis of migrainous stroke in individuals suffering from migraine without aura, a point of controversy in several reports. Most studies show that migraine without aura does not increase the rate of stroke, while others disagree. In most cases of migrainous infarction the prognosis is favorable with good recovery [15].

Migrainous infarction is an uncommon diagnosis. It is mostly diagnosed in young women with cryptogenic stroke. Its incidence is estimated at 3,36/100.000/year accounting for 0.2%-0.8% of all ischemic strokes [11, 12]. Most cases present with ischemia located in the posterior circulation [13-15]. In the study by Kruit et al, 65% of migrainous infarction sufferers had lesions in the posterior circulation, with 85% of those located in the cerebellum. Most patients showed multiple round or ovoid lesions in multiple arterial or border zone territories [13].

The underlying mechanism of migrainous infarction is poorly understood. A multitude of theories have been proposed, mainly implicating a reversible decrease in cerebral blood flow that reaches critical ''ischemic'' levels during the aura. This theory is supported by the fact that aura symptoms frequently affect the visual system, which is supplied by the posterior circulation, where most lesions are located in migraineurs [13, 14]. Probable mechanisms include cortical spreading depression (CSD), increased vascular reactivity or endothelial changes.

CSD, the electrophysiological phenomenon that underlies migraine aura, could cause cerebral ischemia. During CSD a depolarizing wave travels the cortex at a rate of 3-5mm/min [16]. This depolarization causes metalloproteinase activation, blood-brain barrier disruption and changes in water and ion homeostasis [17]. This further leads to increased metabolic demands, coupled with raised cerebral blood flow at the onset and followed by cerebral oligemia due to decreased cerebral vascular responsiveness, as shown in a rat model [18]. Thus, CSD can lead to cerebral hypoperfusion and ischemic lesion formation or propagation [19]. Besides CSD, endothelial changes and vasoconstriction are also considered plausible mechanisms of stroke during migraine aura, but most studies show conflicting evidence. Endothelial activation and release of pro-inflammatory and pro-coagulatory cytokines has been shown during the aura phase [20], but further studies have failed to show consistent changes in vascular reactivity during the aura and a subsequent causal relationship with ischemia [21, 22]. A higher prevalence of patent foramen ovale (PFO) has been reported in migrainous individuals versus controls. The significance of this co-occurrence is still under investigation. [23]

Evidence that cerebral ischemia can manifest as a migraine aura further confounds the diagnosis of migrainous infarcts and their pathophysiology. Brain ischemia may cause prolonged neurological signs mimicking migraine aura and may trigger cortical spreading depression, producing aura symptoms [24]. Another link that connects brain ischemia and migraine is microemboli: a study documented CSD in

response to microemboli injected in the arterial circulation of rodents; the response was more pronounced in rodents showing ischemic brain changes [25]. The study linked the pathophysiological equivalent of migraine aura to arterial microemboli and provided a potential explanation for the increased prevalence of PFO in migraineurs.

Migraine as a risk factor (Migraine-related stroke)

It is generally acceptable that migraine, especially migraine with aura, is a risk factor for stroke. Importantly, the overall risk of vascular disease is also increased in migraineurs, as shown in a recent meta-analysis of 16 cohort studies by Mahmoud et al. [26]. In this analysis, the overall risk of major adverse cardiovascular and cerebrovascular events, including ischemic and hemorrhagic stroke, myocardial infarction and all-cause mortality, was moderately increased in individuals with migraine, reaching a Hazard Ratio (HR) of 1.42. A cohort study in the Danish population also showed a positive association between the risk of myocardial infarction, atrial fibrillation or flutter, peripheral arterial disease, venous thromboembolism and migraine [27]. Furthermore, a population-based study and a prospective cohort study in women established increased cardiovascular risk in patients with migraine [29, 30]. While the overall cardiovascular risk is increased in individuals with migraine, the coronary and carotid arteries of most migraineurs show less atherosclerotic changes than individuals without migraine [31]. These findings support the theory that migraine-related vascular events are not mediated by atherosclerosis and classic risk factors. The pathophysiology of migraine-related vascular events remains to be elucidated.

Numerous studies showed increased risk of stroke in individuals with migraine. Five meta-analyses have been published in the last 15 years, all of them showing an increased risk of stroke in migraineurs [26-35]. The estimated relative risk of stroke in individuals with migraine is double compared to migraine-free individuals. This association is stronger for migraine with aura and remains uncertain for migraine without aura. Furthermore, this association is strongest for women, but not men, probably due to confounding factors, such as the overall greater prevalence of migraine in women [32]. Migraine is more prevalent during the fertile period of a woman's life and oral contraceptive (OCP) use is common during this period. An increased risk of thrombotic events in women using OCP's is well-established. A further risk of stroke in migraineurs on the pill is also probable, as shown by a number of studies [38]. This effect seems to be dose-dependent and low estrogen concentrations are associated with a much lower risk, thus making the use of modern contraceptives safer in migraineurs [39].

Young patients have the highest risk of migraine-related stroke, while this risk seems to drop in older individuals [36]. Furthermore, in older patients, migraine is not a risk factor for stroke, unless the headaches started in later life. Another factor conveying increased stroke risk in migraineurs is the number of attacks suffered. Active migraine is associated with increased stroke risk, as shown in a study by Kurth et al, in which patients with weekly migraine attacks had an adjusted HR of 1.93 [37]. Besides frequency, attack severity is not associated with the risk of stroke.

Smoking increases exponentially the risk of stroke in migraineurs. In the meta-analysis by Schurks et al. it was shown that smokers suffering from migraine with aura had an adjusted HR of1.5 [32]. In this meta-analysis, concurrent use of OCPs further increased the risk of stroke, with an adjusted HR of 10. Other lifestyle changes in migraineurs can also have an impact on stroke risk. Migraine is associated with obesity and reduced physical activity, with an unfavorable lipidemic profile and with depression [40-43]. All these factors undoubtedly contribute to the increased stroke risk in migraineurs.

Another mechanism that could be potentially implicated in the increased risk of stroke in migraineurs is their exposure to drugs used to prevent and treat migraine. Both triptans and ergot alkaloids, commonly used in the acute phase of migraine, have vasoconstrictive properties. These drugs are contraindicated in patients with previous stroke or myocardial infarction and in toxic concentrations can lead to ischemic events. Nevertheless, most studies have not found a link between these drugs and stroke in migraineurs [44]. Furthermore, significant vasoconstriction was not shown in the intracranial arteries of migraineurs taking triptans during an attack, whereas vasoconstriction was present in the extracranial arteries [45]. Thus, acute migraine treatments are considered safe and do not increase the risk of stroke in migraine with aura.

Migraine is frequently encountered in the history in young stroke patients. In younger patients, cryptogenic ischemic stroke is increasingly prevalent, with 35-50% of strokes considered cryptogenic after extensive workup. A strong association of migraine with aura with cryptogenic stroke, especially in women, has been shown [46]. This association has in many cases been attributed to the higher prevalence of PFO in patients with migraine with aura [23]. A recent study by Martinez-Majander et al. shows that risk of stroke in patients with migraine is not dependent on PFO status [46]. In this study, the magnitude of right to left shunt, a marker of PFO severity, was associated with the prevalence of migraine with aura,

thus supporting the theory of common pathogenesis of PFO and migraine with aura.

Besides ischemic stroke, several studies evaluated the risk of intracranial hemorrhage in patients with migraine, most of them showing an increased risk. A recent meta-analysis of 16 cohort studies by Mahmoud et al, reported an adjusted HR of 1.43 relative to non-migrainous controls, while a second cohort study in the Danish population showed a HR of 1.94 [26, 27]. Contrary to ischemic stroke, the presence or not of aura doesn't seem to play a significant role in this association. Young women have higher risk both for intracranial hemorrhage and brain ischemia [28].

Besides acute symptomatic stroke, migraine is associated with neuroimaging abnormalities. These include white matter abnormalities (WMA), silent infarct-like lesions and grey or white matter changes. WMA are detected in 4-59% of patients with migraine [47]. A more robust association with migraine with aura exists, while their presence in migraine without aura is disputed [48]. They are not specific for migraine and their etiology or clinical significance remain uncertain. In a study no association was found between WMA and cognitive decline, while another study found higher stroke risk in patients with increased WMA burden [49, 50]. Silent infarct-like lesions are described in migraineurs as small, discrete, round or ovoid lesions in the posterior circulation and especially the cerebellum [51]. Some studies have also identified silent infarct-like lesions in the deep white matter and the basal ganglia [48]. They are not associated with cognitive decline, while their presence signifies increased cardiovascular and cerebrovascular risk [48-52].

Primary prevention of stroke in individuals with migraine with aura is based on risk factor modification. Control of hypertension, treatment of diabetes and hyperlipidemia are essential steps for stroke prevention. Smoking cessation especially in young women using oral contraceptives is imperative. Use of oral contraceptives should be carefully discussed in each case and stopped in women with increased thrombotic risk [53]. While aspirin seems to reduce the frequency of migraine aura and warfarin may reduce the frequency of migraine attacks, the use of antithrombotics is not recommended for primary prevention in migrainous patients [54, 55].

Secondary prevention and treatment after stroke includes use of antiplatelets and modification of risk factors. Some antiplatelets, such as cilostazol and dipyridamole, seem to worsen migraine, by triggering migraine attacks in migraineurs [56, 57]. Beta-adrenergic blockers and calcium-channel blockers have a favorable profile in migraineurs, reducing attack frequency and are preferable for the treatment of hypertension [58]. Statins, besides their effect on lipids, may also influence migraine attacks [59].

Arteriopathies associated with stroke and migraine

Hereditary disorders may be associated with migraine and cerebral ischemia. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) and mitochondrial encephalomyopathy with lactic acidosis and stroke like episodes (MELAS) have been extensively studied. Beyond these two disorders, other syndromes that commonly present with both ischemic stroke and migraine include retinal vasculopathy with cerebral leukodystrophy (RVCL) and hereditary infantile hemiparesis with retinal arteriolar tortuosity and leukoencephalopathy (HIHRATL). [60]

CADASIL is an autosomal dominant angiopathy, caused by mutations in the NOTCH3 gene on chromosome 19. The mutation of the NOTCH3 protein leads to vasculopathic changes predominantly involving small penetrating arteries, arterioles, and brain capillaries. Almost half of affected individuals report migraine with aura, in most being the initial manifestation starting at early 30s. In most cases aura symptoms are typical, but about 50% of the patients experience atypical manifestations, such as hemiplegia, confusion, or long-lasting neurologic symptoms. Ischemic and less frequently hemorrhagic stroke and TIAs affect 85% of these patients, usually at a median age of 50 years [61]. Multiple strokes, cognitive decline, psychiatric symptoms and dementia follow. [62, 63]

MELAS is a maternally inherited mitochondrial disorder characterized by encephalopathy, myopathy, stroke-like episodes and migraine-like headaches. In patients with MELAS stroke-like episodes lead to hemiparesis, hemianopia, or other neurologic symptoms, with atypical imaging characteristics. Headaches are common and can either mimic migraine or be the presenting symptom of stroke-like episodes, leading to diagnosis of migrainous stroke. [64]

RVCL is a much rarer disorder that presents with retinal vasculopathy, migraine without aura, cognitive changes and stroke-like episodes with focal neurologic symptoms. Besides the central nervous system and the retina, vasculopathy is also present in other systems, such as the liver, the gastrointestinal system and the kidneys. In late stages, imaging of the central nervous system may show enhancing mass lesions, potentially confounding this diagnosis. [65]

Understanding the complex genetic and pathophysiologic mechanisms underlying these disorders can unveil the vascular changes involved in migraine, leading to better understanding of the relation between migraine and the acquired vasculopathies.

References

[1] Stovner LJ, Andree C. Prevalence of head-

ache in Europe: a review for the Eurolight project. J Headache Pain. 2010/05/16. 2010 Aug;11(4):289-99.
[2] The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia. 2013 Jul;33(9):629-808.
[3] Gorelick PB, Hier DB, Caplan LR, et al. Headache in acute cerebrovascular disease. Neurology. 1986 Nov;36(11):1445-50.
[4] Polmear A. Sentinel headaches in aneurysmal subarachnoid haemorrhage: what is the true incidence? A systematic review. Cephalalgia. 2003 Dec;23(10):935-41.
[5] Mitsias P, Ramadan NM. Headache in ischemic cerebrovascular disease. Part I: Clinical features. Cephalalgia. 1992 Oct;12(5):269-74.
[6] Evans RW, Mitsias PD. Headache at onset of acute cerebral ischemia. Headache. 2009 Jun;49(6):902-8.
[7] Mitsias P, Ramadan NM. Headache in ischemic cerebrovascular disease. Part II: Mechanisms and predictive value. Cephalalgia. 1992 Dec;12(6):341-4.
[8] van Os HJA, Mulder IA, van der Schaaf IC, et al. Role of atherosclerosis, clot extent, and penumbra volume in headache during ischemic stroke. Neurology. 2016 Sep;87(11):1124-30.
[9] Seifert CL, Schönbach EM, Magon S, et al. Headache in acute ischaemic stroke: a lesion mapping study. Brain. 2016 Jan;139(Pt 1):217-26.
[10] Tentschert S, Wimmer R, Greisenegger S, et al. Headache at stroke onset in 2196 patients with ischemic stroke or transient ischemic attack. Stroke. 2005 Feb;36(2):e1-3.
[11] Arboix A, Massons J, García-Eroles L, et al. Migrainous cerebral infarction in the Sagrat Cor Hospital of Barcelona stroke registry. Cephalalgia. 2003 Jun;23(5):389-94.
[12] Henrich JB, Sandercock PA, Warlow CP, et al. Stroke and migraine in the Oxfordshire Community Stroke Project. J Neurol. 1986 Oct;233(5):257-62.
[13] Kruit MC, van Buchem MA, Launer LJ, et al. Migraine is associated with an increased risk of deep white matter lesions, subclinical posterior circulation infarcts and brain iron accumulation: the population-based MRI CAMERA study. Cephalalgia. 2010 Feb;30(2):129-36.
[14] Wolf ME, Szabo K, Griebe M, et al. Clinical and MRI characteristics of acute migrainous infarction. Neurology. 2011 May;76(22):1911-7.
[15] Laurell K, Artto V, Bendtsen L, et al. Migrainous infarction: a Nordic multicenter study. Eur J Neurol. 2011 Oct;18(10):1220-6.
[16] Tietjen EG. Migraine and ischaemic heart disease and stroke: potential mechanisms and treatment implications. Cephalalgia. 2007 Aug;27(8):981-7.
[17] Gursoy-Ozdemir Y, Qiu J, Matsuoka N, et al. Cortical spreading depression activates and upregulates MMP-9. J Clin Invest. 2004 May;113(10):1447-55.
[18] Seitz I, Dirnagl U, Lindauer U. Impaired vascular reactivity of isolated rat middle cerebral artery after cortical spreading depression in vivo. J Cereb blood flow Metab Off J Int Soc Cereb Blood Flow Metab. 2004 May;24(5):526-30.
[19] Dreier JP. The role of spreading depression, spreading depolarization and spreading ischemia in neurological disease. Nat Med. 2011 Apr;17(4):439-47.
[20] Tietjen GE. Circulating microparticles in migraine with aura: Cause or consequence, a link to stroke. Cephalalgia. 2015 Feb 8;35(2):85-7.
[21] Vernieri F, Tibuzzi F, Pasqualetti P, et al. Increased cerebral vasomotor reactivity in migraine with aura: an autoregulation disorder? A transcranial Doppler and near-infrared spectroscopy study. Cephalalgia. 2008 Jul;28(7):689-95.
[22] Rajan R, Khurana D, Lal V. Interictal cerebral and systemic endothelial dysfunction in patients with migraine: a case-control study. J Neurol Neurosurg Psychiatry. 2015 Nov;86(11):1253-7.
[23] Carod-Artal FJ, da Silveira Ribeiro L, Braga H, et al. Prevalence of patent foramen ovale in migraine patients with and without aura compared with stroke patients. A transcranial Doppler study. Cephalalgia. 2006 Aug;26(8):934-9.
[24] Dohmen C, Sakowitz OW, Fabricius M, et al. Spreading depolarizations occur in human ischemic stroke with high incidence. Ann Neurol. 2008 Jun;63(6):720-8.
[25] Nozari A, Dilekoz E, Sukhotinsky I, et al. Microemboli may link spreading depression, migraine aura, and patent foramen ovale. Ann Neurol. 2010 Feb;67(2):221-9.
[26] Mahmoud AN, Mentias A, Elgendy AY, et al. Migraine and the risk of cardiovascular and cerebrovascular events: a meta-analysis of 16 cohort studies including 1 152 407 subjects. BMJ Open. 2018 Mar 27;8(3):e020498.
[27] Adelborg K, Szépligeti SK, Holland-Bill L, Ehrenstein V, Horváth-Puhó E, Henderson VW, et al. Migraine and risk of cardiovascular diseases: Danish population based matched cohort study. BMJ [Internet]. 2018 Jan 31;360:k96. Available from: https://www.bmj.com/lookup/doi/10.1136/bmj.k96
[28] Sacco S, Ornello R, Ripa P, et al. Migraine and Hemorrhagic Stroke. Stroke [Internet]. 2013 Nov 1;44(11):3032-8. Available from: https://doi.org/10.1161/STROKEAHA.113.002465
[29] Bigal ME, Kurth T, Santanello N, et al. Migraine

and cardiovascular disease: a population-based study. Neurology. 2010 Feb;74(8):628-35.
[30] Kurth T, Winter AC, Eliassen AH, et al. Migraine and risk of cardiovascular disease in women: prospective cohort study. BMJ [Internet]. 2016 May 31;353:i2610. Available from: https://www.bmj.com/lookup/doi/10.1136/bmj.i2610
[31] van Os HJA, Mulder IA, Broersen A, et al. Migraine and Cerebrovascular Atherosclerosis in Patients With Ischemic Stroke. Stroke [Internet]. 2017 Jul 1;48(7):1973-5. Available from: https://doi.org/10.1161/STROKEAHA.116.016133
[32] Schürks M, Rist PM, Bigal ME, et al. Migraine and cardiovascular disease: systematic review and meta-analysis. BMJ. 2009 Oct;339:b3914.
[33] Etminan M, Takkouche B, Isorna FC, et al. Risk of ischaemic stroke in people with migraine: systematic review and meta-analysis of observational studies. BMJ. 2005 Jan;330(7482):63.
[34] Spector JT, Kahn SR, Jones MR, et al. Migraine headache and ischemic stroke risk: an updated meta-analysis. Am J Med. 2010 Jul;123(7):612-24.
[35] Hu X, Zhou Y, Zhao H, et al. Migraine and the risk of stroke: an updated meta-analysis of prospective cohort studies. Neurol Sci Off J Ital Neurol Soc Ital Soc Clin Neurophysiol. 2017 Jan;38(1):33-40.
[36] Mosek A, Marom R, Korczyn AD, et al. A history of migraine is not a risk factor to develop an ischemic stroke in the elderly. Headache. 2001 Apr;41(4):399-401.
[37] Kurth T, Schürks M, Logroscino G, et al. Migraine frequency and risk of cardiovascular disease in women. Neurology. 2009/06/24. 2009 Aug 25;73(8):581-8.
[38] Sheikh HU, Pavlovic J, Loder E,et al. Risk of Stroke Associated With Use of Estrogen Containing Contraceptives in Women With Migraine: A Systematic Review. Headache J Head Face Pain. 2018 Jan;58(1):5-21.
39] Calhoun AH, Batur P. Combined hormonal contraceptives and migraine: An update on the evidence. Cleve Clin J Med. 2017 Aug;84(8):631-8.
[40] Vo M, Ainalem A, Qiu C, et al. Body mass index and adult weight gain among reproductive age women with migraine. Headache. 2011 Apr;51(4):559-69.
[41] Le H, Tfelt-Hansen P, Skytthe A, et al. Association between migraine, lifestyle and socioeconomic factors: a population-based cross-sectional study. J Headache Pain. 2011 Apr;12(2):157-72.
[42] Scher AI, Terwindt GM, Picavet HSJ, et al. Cardiovascular risk factors and migraine: the GEM population-based study. Neurology. 2005 Feb;64(4):614-20.
[43] Rist PM, Schürks M, Buring JE, et al. Migraine, headache, and the risk of depression: Prospective cohort study. Cephalalgia. 2013 Sep;33(12):1017-25.
[44] Hall GC, Brown MM, Mo J, et al. Triptans in migraine: the risks of stroke, cardiovascular disease, and death in practice. Neurology. 2004 Feb;62(4):563-8.
[45] Amin FM, Asghar MS, Hougaard A, et al. Magnetic resonance angiography of intracranial and extracranial arteries in patients with spontaneous migraine without aura: a cross-sectional study. Lancet Neurol. 2013 May;12(5):454-61.
[46] Martinez-Majander N, Artto V, et al. Association between Migraine and Cryptogenic Ischemic Stroke in Young Adults. Ann Neurol. 2021 Feb;89(2):242-53.
[47] Bashir A, Lipton RB, Ashina S, et al. Migraine and structural changes in the brain: a systematic review and meta-analysis. Neurology. 2013/08/28. 2013 Oct 1;81(14):1260-8.
[48] Kurth T, Mohamed S, Maillard P, et al. Headache, migraine, and structural brain lesions and function: population based Epidemiology of Vascular Ageing-MRI study. BMJ [Internet]. 2011 Jan 18;342:c7357.
[49] Rist PM, Dufouil C, Glymour MM, et al. Migraine and cognitive decline in the population-based EVA study. Cephalalgia. 2011 Sep;31(12):1291-300.
[50] Buyck J-F, Dufouil C, Mazoyer B, et al. Cerebral white matter lesions are associated with the risk of stroke but not with other vascular events: the 3-City Dijon Study. Stroke. 2009 Jul;40(7):2327-31.
[51] Kruit MC, Launer LJ, Ferrari MD, et al. Infarcts in the posterior circulation territory in migraine. The population-based MRI CAMERA study. Brain. 2005 Sep;128(Pt 9):2068-77.
[52] Palm-Meinders IH, Koppen H, Terwindt GM, et al. Structural brain changes in migraine. JAMA. 2012 Nov;308(18):1889-97.
[53] Øie LR, Kurth T, Gulati S, Dodick DW. Migraine and risk of stroke. J Neurol Neurosurg & Psychiatry. 2020 Jun 1;91(6):593-604.
[54] 1. Turk WE, Uiterwijk A, Pasmans R, et al. Aspirin Prophylaxis for Migraine with Aura: An Observational Case Series. Eur Neurol. 2017;78(5-6):287-9.
[55] Maggioni F, Bruno M, Mainardi F, et al. Migraine responsive to warfarin: an update on anticoagulant possible role in migraine prophylaxis. Neurol Sci. 2012 Dec 6;33(6):1447-9.
[56] Kruuse C, Lassen LH, Iversen HK, et al. Dipyridamole may induce migraine in patients with migraine without aura. Cephalalgia. 2006 Aug;26(8):925-33.

[57] Guo S, Olesen J, Ashina M. Phosphodiesterase 3 inhibitor cilostazol induces migraine-like attacks via cyclic AMP increase. Brain. 2014 Nov;137(Pt 11):2951-9.
[58] Evers S, Afra J, Frese A, et al. EFNS guideline on the drug treatment of migraine--revised report of an EFNS task force. Eur J Neurol. 2009 Sep;16(9):968-81.
[59] Liberopoulos EN, Mikhailidis DP. Could Statins Be Useful in the Treatment of Patients With Migraine? Headache J Head Face Pain. 2006 Apr 1;46(4):672-5.
[60] Stam AH, Haan J, van den Maagdenberg AMJM, et al. Migraine and genetic and acquired vasculopathies. Cephalalgia. 2009 Sep;29(9):1006-17.
[61] Koutroulou I, Karapanayiotides Th, Grigoriadis N, Karacostas D. CADASIL presenting with spontaneous intracerebral hemorrhage: report of a case and description of the first family in Northern Greece. Hippokratia. 2016;20(1): 76-79.
[62] Dichgans M, Mayer M, Uttner I, et al. The phenotypic spectrum of CADASIL: clinical findings in 102 cases. Ann Neurol. 1998 Nov;44(5):731-9.
[63] Lesnik Oberstein SAJ, van den Boom R, et al. Incipient CADASIL. Arch Neurol. 2003 May;60(5):707-12.
[64] Ohno K, Isotani E, Hirakawa K. MELAS presenting as migraine complicated by stroke: case report. Neuroradiology. 1997 Nov;39(11):781-4.
[65] Stam AH, Kothari PH, Shaikh A, et al. Retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations. Brain. 2016 Nov;139(11):2909-22.