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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

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Abstract

Background—Previous studies suggested that migraine is a risk factor for brain lesions, but methodological issues hampered drawing definite conclusions. Therefore, we initiated the MRI "CAMERA" study.

Procedures—We summarize our previously published results. A total of 295 migraineurs and 140 controls were randomly selected from a previously diagnosed population-based sample (n=6039), who underwent an interview, physical examination, and a brain MRI-scan.

Findings—Migraineurs, notably those with aura, had higher prevalence of subclinical infarcts in the posterior circulation (OR=13.7; 95%CI 1.7–112). Female migraineurs were at independent increased risk of white matter lesions (WML; OR=2.1; 95%CI 1.0–4.1), and migraineurs had a higher prevalence of brainstem hyperintense lesions (4.4% vs. 0.7%, p=0.04). We observed a higher lifetime prevalence of (frequent) syncope and orthostatic insufficiency in migraineurs; future research needs to clarify whether autonomic nervous system dysfunction could explain (part of) the increased risk of WMLs in female migraineurs. Finally, in migraineurs aged <50, compared to controls, we found evidence of increased iron concentration in putamen (p=0.02), globus pallidus (p=0.03) and red nucleus (p=0.03). Higher risks in those with higher attack frequency or longer disease duration were found consistent with a causal relationship between migraine and lesions.

Conclusion—This summary of our population-based data illustrates that migraine is associated with a significantly increased risk of brain lesions. Longitudinal studies are needed to assess whether these lesions are progressive and have relevant (long-term) functional correlates.

Introduction

Migraine has been considered for decades as an episodic disorder without long-term consequences to the brain. However, over the past 30 years several studies have been carried out looking at and delivering arguments for a possible association between migraine and brain changes. For this association, three lines of evidence can be recognized.

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First, several cases of 'migrainous infarction' or 'migraine-induced stroke' have been described, suggesting that migraine can act as an acute precipitant of ischemic stroke.[1–6] In such cases stroke is assumed to be directly and causally related to an acute migraine attack. Migrainous infarction has been estimated to occur with a low incidence (1.4-3.4/100.000)[1;7;8] and is probably an overdiagnosed condition,[9] accounting for <40% of clinical ischemic stroke in women with migraine under age 50.[10] Second, data from several hospital-based stroke case-control studies suggest that migraine is a risk factor for clinical ischemic stroke. A meta-analysis summarized the evidence and calculated a pooled relative risk of 2.2 for migraineurs.[11] It seems that higher risks apply for female patients with aura, with higher attack frequency, who smoke, who have hypertension, or who use oral contraceptives. Third, a number of clinic-based MRI studies found an increased prevalence of cerebral white matter hyperintense lesions (WMLs) in migraine patients; a meta-analysis calculated a pooled increased risk of 3.9 (95% CI 2.3–6.7).[12] Although most of these studies showed an apparent association between migraine and ischemic brain lesions, some results were discrepant: few did not find a statistically significant difference;[13–15] some found no difference in prevalence between MO and MA,[15–18] and two studies found a higher prevalence in MA;[13;19] only one study found an increased prevalence with increasing migraine attack frequency, however, the other studies did not assess the influence of attack frequency as an indicator of migraine severity.[19] In addition selection bias and various other methodological problems prohibited drawing definite conclusions from those results.[20] It remained uncertain whether migraineurs are at independent risk for permanent brain changes, and if so, there are still questions about whether there are specific subgroups of patients who are most at risk, and what etiologic mechanisms are involved.

However, in non-migraine patients, it has been shown that both clinical and subclinical brain lesions can lead to negative sequellae, affecting both physical and cognitive function.[21–24] If this also translates to lesions that develop as a consequence of migraine (as a condition with a high prevalence), migraine would be an important contributor to neurological deficits in the general population. Therefore, it is of primary importance to investigate whether migraine is an independent risk factor for (subclinical) white matter lesions and infarcts.

We planned and performed a cross-sectional MRI study in an already existing population-based sample of adults with migraine and controls with no a headache history: the Cerebral Abnormalities in Migraine, an Epidemiological Risk Analysis (CAMERA) study.[25;26] We assessed the presence of several types of structural brain changes, compared these between migraineurs and controls, and correlated presence and extension of these changes also to various demographic, medical and migraine characteristics. In addition, we collected data from neurologic physical examination and cognitive tests, to correlate these data with lesion load. The population-based sample allowed us to study a range of migraine presentation, different from clinic studies that are usually based on more severe cases.

In the paragraphs below, we summarize the published, primary results from the CAMERA-study. We conclude with remarks on the relevance of the findings presented, and describe the necessity of future research initiatives.

Migraine as a risk factor for subclinical brain lesions: the CAMERA study

The CAMERA studyis a population-based case-control MRI study in an unbiased sample of 295 migraine cases (n=161 migraine with aura [MA]; n=134 migraine without aura [MO]) and 140 age-and sex-matched non-migraine controls.[26] The participants were randomly-selected from a previously diagnosed sample (n=6039) from the Dutch general population.[25] This epidemiologic approach minimized the role of potential selection bias, and a proper, multistep method to establish the migraine diagnosis minimized the possibility of diagnostic

misclassification and recall bias. Sensitive imaging and lesion rating methods, including full brain covering thin (3mm) T2 and FLAIR slices, blinded expert reading, and semi-quantitative lesion volume quantification, minimized the possibility of lesion misclassification. The complete description of the cohort, with several baseline measurements available from the GEM-study, allowed to statistically control for relevant confounders. This is important as many brain lesions in population based samples result from cardio-vascular risk factors. These measures resulted in a study population that was well characterized using standardized measures. The cohort includes migraine sufferers with general migraine symptomatology and average migraine severity.

From the analyses of the MRI images in conjunction with socio-economic data, cardiovascular risk factors, neurologic exam, and migraine characteristics, it appeared that silent brain infarction in the posterior circulation territory occurred far more frequently in migraine cases than expected.[26] Findings were most pronounced in cases with migraine with aura: 8% had subclinical cerebellar infarcts (OR 13.7; 95% CI 1.7–112; compared to controls, controlling for cardiovascular risk factors). Female migraine cases were at increased risk of high-DWML-load (top 20th percentile of the distribution of DWML-load), independent of migraine subtype and independent of the effects of cardiovascular risk factors (OR 2.0; 95% CI 1.0–4.2). This risk was higher in those with higher attack frequency (in those with ≥1 attack/month: OR=2.6; 95% CI 1.2–6.0), suggestive of a causal relationship. We also confirmed that concurrent smoking, hypertension and long oral contraceptive use increased the risk further.

These population-based findings suggest strongly that migraineurs with and without aura are at independently increased risk for sub-clinical brain lesions. We concluded that – given the high prevalence of migraine - these findings are of potential public-health importance and may have implications for management guidelines for migraine; further study into the possible etiologic mechanisms, but also into the potential functional consequences of brain lesions in migraine patients is required.

Posterior circulation territory infarcts

Based on our finding of an increased prevalence of posterior circulation infarct-like lesions in migraineurs, we further focused on these lesions.[27] Of all 60 identified subclinical brain infarcts, 39 (65%) were in the posterior circulation territory, and a majority of these (85%) were located in the cerebellum. Lesions were often multiple, and round or oval shaped, with a mean diameter of 7 mm. The majority (88%) of infratentorial infarct-like lesions had a vascular border zone location in the cerebellum. Prevalence of these border zone lesions differed between controls (0.7%), cases with migraine without aura (2.2%) and cases with migraine with aura (7.5%). Besides higher age, cardiovascular risk factors were not more prevalent in migraineurs with posterior circulation infarct-like lesions compared to those without lesions. The combination of vascular distribution, deep border zone location, shape, size and imaging characteristics on MRI makes it likely that the lesions have an ischaemic origin.

The most likely etiologic mechanism seems to be hypoperfusion and/or embolism, rather than atherosclerosis or small vessel disease. During and after migraine attacks, sluggish low cerebral flow below an ischemic threshold has been described.[28–32] A decrease in brain perfusion pressure (*e.g.* during migraine) theoretically affects the clearance and destination of embolic particles; narrowing of the arterial lumen and endothelial abnormalities stimulate formation of thrombi; occlusive thrombi further reduce blood flow and brain perfusion.[33] Because the deep cerebellar territories have a pattern of progressively tapering arteries with

only few anastomoses present, they are likely to be particularly vulnerable to hypoperfusion related border zone infarct mechanisms.[34;35]

No previous study specifically reported on cerebellar lesions in migraine. But interestingly, subclinical cerebellar dysfunction has been reported in migraineurs,[36;37] which raises the question whether more advanced functional tests would have identified cerebellar dysfunction in our cases.

Infratentorial hyperintense lesions

We also evaluated the prevalence, frequency and distribution of infratentorial hyperintense lesions (IHLs). Lesions were identified in 13/295 (4.4%) migraineurs and in 1/140 (0.7%) controls (P=.04).[38] Twelve cases had IHLs, mostly bilaterally, in the dorsal basis pontis, seeming to notably affect the transverse fibers on this location. The increased prevalence of IHL in migraineurs extends the knowledge about vulnerable brain regions and type of lesions in migraine brains.

Although the brainstem is involved in migraine pathophysiology, and activation of the dorsal rostral pons and periaqueductal gray matter has been described during attacks, these regions seemed not to be affected by hyperintense signal changes. IHL are likely due to small-vessel disease (arteriosclerosis) and/or repetitive perfusion deficits, similar to the proposed mechanism(s) for the occurrence of similar lesions in non-migraine subjects with pronounced cardiovascular risk profile[39] or cases with CADASIL.[40] The precise etiology of these lesions in migraine and the reason why migraineurs seem to be more susceptible for this kind of vasculo-ischemic brain changes remains still unknown.

Etiologic considerations

There is now strong evidence that migraine is indeed an independent risk factor for DWMLs, silent posterior circulation territory infarcts and IHL. The earlier medical opinion that only female migraine patients below age 45 with MA are at increased clinical stroke risk,[10;41–44] likely underestimates the real extent of brain injury in migraine patients in the general population.

Several features of migraine could contribute to the pathogenesis of both hyperintense lesions and infarcts in migraine, but a combination with other factors may be necessary to finally result in focal lesions. An increased coagulatory propensity, vasoconstriction,[45–48] local excessive neuronal activation, neurogenic inflammation, neuropeptide and cytokine release[49] or excitotoxity,[50] and cardiac abnormalities (like a patent foramen ovale, PFO) have been suggested to act as potential contributing or causal factors. Reversible MRI abnormalities during migraine aura, including regions of cerebral vasogenic edema[51] and evidence of vasogenic blood-brain barrier (BBB) leakage in prolonged aura have been reported.[52;53] These abnormalities were linked to (temporary) impairment of the BBB integrity and enhanced permeability of meningeal microvessels.[53;54] It has been suggested that cortical spreading depression (CSD) causes disruption of the BBB through a matrix metalloproteinase-9 dependent cascade mechanism., that may result in local tissue damage.[55] Penetration of any toxic agent through a temporarilyreduced BBB, might be an explanation for the development of (focal) WML or (silent) infarcts. From studies in experimental and human cerebral ischaemia it is known that peri-infarct CSD-like depolarization potentiates infarct growth.[56]

With the established relationship between migraine and brain lesions, we now need to plan studies assessing etiology and relevance of brain lesions in migraine.

Iron deposits in migraine

In two small MRI studies, higher brain iron levels were found in the periaqueductal grey matter (PAG) and red nucleus of patients attending an headache clinic for migraine or chronic daily headache.[57] As the PAG is activated during migraine attacks, the increased local iron load was suggested to reflect an impairment of brainstem structures involved in the central anti-nociceptive neuronal network in patients with severe migraine. We examined iron concentration in deep brain nuclei with MRI in participants from the CAMERA study.[58] T2 values derived from dual-echo MR images (1.5 T) were measured in seven deep brain nuclei in migraine cases (n=138) and controls (n=75); this allows a quantitative assessment of differences in iron concentration *in vivo*. We separately analyzed subjects under (n=112) and above age 50 (n=101), because measurements in older subjects are increasingly influenced by non-iron-related factors. In migraineurs aged <50, compared to controls, T2-values were lower in the putamen (P=.02), globus pallidus (P=.03) and red nucleus (P=.03). Controlling for age, those with longer migraine-history had higher concentrations in the putamen (P=.01), caudate (P=.04) and red nucleus (P=.001). We found no differences between MA and MO.

The findings suggest that repeated migraine attacks are associated with increased iron concentration in multiple deep brain nuclei that are known to be involved in central pain processing and migraine pathophysiology, and not only in the periaqueductal grey matter. It remains unclear whether the increased iron concentration is just a physiological response induced by repeated activation of nuclei involved in central pain processing, or whether the increased iron concentration could also damage these structures secondarily, *e.g.* due to formation of free radicals in oxidative stress. Theoretically, damage to these pain-processing nuclei might explain the occurrence of chronification of the disease in a minority of migraine patients. Recent observations from other MRI studies also point at disturbances in the pain-processing-network, and support the concept that changes in a chain of brain locations occur in migraineurs.[59;60] Further study into pain mechanisms in migraine should not be limited to the brainstem areas, but should cover a broader scope, and consider the whole involved pain network.

Syncope, migraine and brain lesions

Many earlier studies evaluated the function of the autonomic nervous system (ANS) in migraineurs. Studies were mostly performed interictally in clinic-based samples,[61–69] However findings are inconsistent with reports of either increased or decreased sympathetic or parasympathetic function. Because of these discrepancies, and because previous studies did not address clinical symptoms of ANS failure, including syncope, orthostatic insufficiency (OI) and postural tachycardia syndrome (POTS), we assessed the prevalence of these entities in migraine using a population-based design.[70]

Migraineurs (n=323) and control subjects (n=153) from the CAMERA study answered a systematic questionnaire and underwent cardiovascular measurements during rest, while standing and after venipuncture, together addressing the prevalence of syncope, OI, orthostatic hypotension (OH) and POTS. The data showed that migraineurs had a higher lifetime prevalence of syncope (46% vs. 31%, P=.001), frequent syncope (≥5 attacks; 13% vs. 5%, P=.02) and OI (32% vs. 12%, P<.001). There was no association between ANS symptoms and the severity of migraine or migraine subtype. Cardiovascular measurements and the prevalence of POTS and OH did not differ significantly between migraineurs and controls. This first population-based study assessing clinical presentations of ANS dysfunction as well as BP and HR reflexes in migraine, showed an increased prevalence of syncope-related ANS symptoms in migraineurs. Our next step is to assess whether those

with symptoms of ANS dysfunction are at increased risk for (subclinical) brain lesions and to assess whether it explains part of the increased risk of WMLs in female migraineurs.

Significance of brain lesions in migraine

The data from the population-based CAMERA study support and extend the results from earlier studies, and indicate that migraine is associated with a significantly increased risk of subclinical and clinical ischemic brain lesions.[26] The robustness of the methods and the validity of the findings have been acknowledged.[71;72]

Our cross-sectional findings suggest migraine attacks may lead to brain lesions and iron depositions. Our conclusions regarding the temporality of the associations are supported by the finding of a higher risk of lesions in those with higher attack frequencies or longer migraine history. To show ongoing migraine attacks lead to progression of lesions, we need follow-up data showing that there is a higher rate of developing new lesions, and more lesion progression over time in migraine cases, compared to (*e.g.* age related) progression of lesions in controls. In addition, identification of a linear relationship between migraine severity (*e.g.* attack rate) and volume of lesions (progression), will increase the likelihood of a causal relationship.

Numerous studies in non-migraine elderly subjects demonstrated that silent brain infarcts and WML are associated with increased risk of stroke, dementia, and cognitive decline.[21–24] Findings in several studies also suggest that impairment of cortical brain function occurs more often in clinic-based migraine patients than in controls,[73] and some authors described significant cognitive changes during and between migraine episodes,[74–78] but others failed to confirm these findings.[79–82] Cerebellar dysfunction in migraineurs has also been suggested in a few studies,[36;83] and is a known entity in familial hemiplegic migraine (a rare type of inherited migraine).[84;85] However, with respect to migraine patients, it is still unknown whether brain lesions do have any negative (long-term) functional consequences. For these reasons together, it is now essential to measure cerebral or cerebellar function in migraineurs, and correlate the results with eventual presence and progression of brain lesions.

Confirmation that recurrence of migraine attacks is indeed associated with an increasing risk of brain lesions and/or brain dysfunction, will change migraine from an episodic disorder to a chronic-episodic or chronic progressive disorder.[71] Such a shift in conceptualization of the disease also will change goals of treatments, and prevention of migraine may then potentially need to become an important target for secondary prevention in the general population.

Identification of specific factors that increase the risk of brain lesions in migraine patients, such as migraine type, migraine severity, sympathetic nervous system dysfunction, cardiovascular risk factors and PFO, may allow identification of specific subgroups to be treated. For instance, demonstration of an association between MRI lesions and the presence of a PFO would promote the (renewed) initiation of prospective randomized clinical trials on the effect of closure of PFO on migraine severity and associated brain lesions.

Future perspectives

Whether progression of migraine is related to progression of brain lesion can only be demonstrated in a longitudinal design. We therefore started in 2008 to rescan and re-evaluate the entire CAMERA population to measure the change in brain lesion load in migraineurs vs. controls after 8 years. Because of the high prevalence of PFO in MA, we included a cardiac right-to-left shunt-screening with transcranial Doppler, to assess the

contribution of PFO in the risk of migraine-related brain lesions. Another aim is to study the functional consequences of the brain lesions. Another approach to assess whether migraine attacks change the brain is to perform MRI scans during migraine attacks. Several types of MRI data are of interest, including structural information, (regional) brain perfusion values, permeability of BBB, brain activation measures and patterns, and concentration values of several metabolites.

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Reference List

1. Henrich JB, Sandercock PA, Warlow CP, Jones LN. Stroke and migraine in the Oxfordshire Community Stroke Project. Journal of Neurology. 1986; 233(5):257–62. [PubMed: 3772405]
2. Bogousslavsky J, Regli F, Van Melle G, Payot M, Uske A. Migraine stroke. Neurology. 1988; 38(2):223–7. [PubMed: 3340283]
3. Rothrock JF, Walicke P, Swenson MR, Lyden PD, Logan WR. Migrainous stroke. Arch Neurol. 1988; 45(1):63–7. [PubMed: 3337678]
4. Sacquegna T, Andreoli A, Baldrati A, Lamieri C, Guttmann S, de Carolis P, et al. Ischemic stroke in young adults: the relevance of migrainous infarction. Cephalalgia. 1989; 9(4):255–8. [PubMed: 2611882]
5. Rothrock J, North J, Madden K, Lyden P, Fleck P, Dittrich H. Migraine and migrainous stroke: risk factors and prognosis. Neurology. 1993; 43(12):2473–6. [PubMed: 8255442]
6. Sochurkova D, Moreau T, Lemesle M, Menassa M, Giroud M, Dumas R. Migraine history and migraine-induced stroke in the Dijon stroke registry. Neuroepidemiology. 1999; 18(2):85–91. [PubMed: 10023131]
7. Welch KM. Relationship of stroke and migraine. Neurology. 1994; 44(suppl 7 10):S33–6. [PubMed: 7969944]
8. Broderick JP, Swanson JW. Migraine-related strokes. Clinical profile and prognosis in 20 patients. Arch Neurol. 1987; 44(8):868–71. [PubMed: 3632398]
9. Bousser MG. Estrogens, migraine, and stroke. Stroke. 2004; 35(11 Suppl 1):2652–6. [PubMed: 15459439]
10. Chang CL, Donaghy M, Poulter N. Migraine and stroke in young women: case-control study. The World Health Organisation Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Bmj. 1999; 318(7175):13–8. [PubMed: 9872876]
11. Etminan M, Takkouche B, Isorna FC, Samii A. Risk of ischaemic stroke in people with migraine: systematic review and meta-analysis of observational studies. Bmj. 2005; 330(7482):63. [PubMed: 15596418]
12. Swartz RH, Kern RZ. Migraine is associated with magnetic resonance imaging white matter abnormalities: a meta-analysis. Arch Neurol. 2004; 61(9):1366–8. [PubMed: 15364681]
13. Ferbert A, Busse D, Thron A. Microinfarction in classic migraine? A study with magnetic resonance imaging findings. Stroke. 1991; 22(8):1010–4. [PubMed: 1866746]
14. Ziegler DK, Batnitzky S, Barter R, McMillan JH. Magnetic resonance image abnormality in migraine with aura. Cephalalgia. 1991; 11(3):147–50. [PubMed: 1889071]
15. Fazekas F, Koch M, Schmidt R, Offenbacher H, Payer F, Freidl W, et al. The prevalence of cerebral damage varies with migraine type: a MRI study. Headache. 1992; 32(6):287–91. [PubMed: 1399549]

16. Pavese N, Canapicchi R, Nuti A, Bibbiani F, Lucetti C, Collavoli P, et al. White matter MRI hyperintensities in a hundred and twenty-nine consecutive migraine patients. Cephalalgia. 1994; 14(5):342–5. [PubMed: 7828192]
17. Cooney BS, Grossman RI, Farber RE, Goin JE, Galetta SL. Frequency of magnetic resonance imaging abnormalities in patients with migraine. Headache. 1996; 36(10):616–21. [PubMed: 8990603]
18. Igarashi H, Sakai F, Kan S, Okada J, Tazaki Y. Magnetic resonance imaging of the brain in patients with migraine. Cephalalgia. 1991; 11(2):69–74. [PubMed: 1860133]
19. Gozke E, Ore O, Dortcan N, Unal Z, Cetinkaya M. Cranial magnetic resonance imaging findings in patients with migraine. Headache. 2004; 44(2):166–9. [PubMed: 14756856]
20. Kruit MC, Launer LJ, van Buchem MA, Terwindt GM, Ferrari MD. Migraine as a Risk Factor for White Matter Lesions, Silent Infarctions, and Ischemic Stroke: The Evidence for a Link. Headache Currents. 2005; 2(3):62–70.
21. Longstreth WT Jr, Manolio TA, Arnold A, Burke GL, Bryan N, Jungreis CA, et al. Clinical correlates of white matter findings on cranial magnetic resonance imaging of 3301 elderly people. The Cardiovascular Health Study. Stroke. 1996; 27(8):1274–82. [PubMed: 8711786]
22. Vermeer SE, Prins ND, den Heijer T, Hofman A, Koudstaal PJ, Breteler MM. Silent brain infarcts and the risk of dementia and cognitive decline. NEnglJ Med. 2003; 348(13):1215–22.
23. Bernick C, Kuller L, Dulberg C, Longstreth WT Jr, Manolio T, Beauchamp N, et al. Silent MRI infarcts and the risk of future stroke: the cardiovascular health study. Neurology. 2001; 57(7): 1222–9. [PubMed: 11591840]
24. Vermeer SE, Hollander M, van Dijk EJ, Hofman A, Koudstaal PJ, Breteler MM. Silent brain infarcts and white matter lesions increase stroke risk in the general population: the Rotterdam Scan Study. Stroke. 2003; 34(5):1126–9. [PubMed: 12690219]
25. Launer LJ, Terwindt GM, Ferrari MD. The prevalence and characteristics of migraine in a population-based cohort: the GEM study. Neurology. 1999; 53(3):537–42. [PubMed: 10449117]
26. Kruit MC, van Buchem MA, Hofman PA, Bakkers JT, Terwindt GM, Ferrari MD, et al. Migraine as a risk factor for subclinical brain lesions. Jama. 2004; 291(4):427–34. [PubMed: 14747499]
27. Kruit MC, Launer LJ, Ferrari MD, van Buchem MA. Infarcts in the posterior circulation territory in migraine. The population-based MRI CAMERA study. Brain. 2005; 128(Pt 9):2068–77. [PubMed: 16006538]
28. Woods RP, Iacoboni M, Mazziotta JC. Brief report: bilateral spreading cerebral hypoperfusion during spontaneous migraine headache. N Engl J Med. 1994; 331(25):1689–92. [PubMed: 7969360]
29. Olesen J, Friberg L, Olsen TS, Iversen HK, Lassen NA, Andersen AR, et al. Timing and topography of cerebral blood flow, aura, and headache during migraine attacks. Ann Neurol. 1990; 28(6):791–8. [PubMed: 2285266]
30. Bednarczyk EM, Remler B, Weikart C, Nelson AD, Reed RC. Global cerebral blood flow, blood volume, and oxygen metabolism in patients with migraine headache. Neurology. 1998; 50(6): 1736–40. [PubMed: 9633719]
31. Cutrer FM, Sorensen AG, Weisskoff RM, Ostergaard L, Sanchez dR, Lee EJ, et al. Perfusion-weighted imaging defects during spontaneous migrainous aura. Ann Neurol. 1998; 43(1):25–31. [PubMed: 9450765]
32. Sanchez del Rio M, Bakker D, Wu O, Agosti R, Mitsikostas DD, Ostergaard L, et al. Perfusion weighted imaging during migraine: spontaneous visual aura and headache. Cephalalgia. 1999; 19(8):701–7. [PubMed: 10570723]
33. Caplan LR, Hennerici M. Impaired clearance of emboli (washout) is an important link between hypoperfusion, embolism, and ischemic stroke. Arch Neurol. 1998; 55(11):1475–82. [PubMed: 9823834]
34. Duvernoy H, Delon S, Vannson JL. The vascularization of the human cerebellar cortex. Brain Res Bull. 1983; 11(4):419–80. [PubMed: 6652521]
35. Fessatidis IT, Thomas VL, Shore DF, Hunt RH, Weller RO, Goodland F, et al. Assessment of neurological injury due to circulatory arrest during profound hypothermia. An experimental study in vertebrates. Eur J Cardiothorac Surg. 1993; 7(9):465–72. [PubMed: 8217225]

36. Sandor PS, Mascia A, Seidel L, De PV, Schoenen J. Subclinical cerebellar impairment in the common types of migraine: a three-dimensional analysis of reaching movements. Ann Neurol. 2001; 49(5):668–72. [PubMed: 11357959]
37. Harno H, Hirvonen T, Kaunisto MA, Aalto H, Levo H, Isotalo E, et al. Subclinical vestibulocerebellar dysfunction in migraine with and without aura. Neurology. 2003; 61(12):1748–52. [PubMed: 14694041]
38. Kruit MC, Launer LJ, Ferrari MD, van Buchem MA. Brain stem and cerebellar hyperintense lesions in migraine. Stroke. 2006; 37(4):1109–12. [PubMed: 16497982]
39. Kwa VI, Stam J, Blok LM, Verbeeten B Jr. T2-weighted hyperintense MRI lesions in the pons in patients with atherosclerosis. Amsterdam Vascular Medicine Group. Stroke. 1997; 28(7):1357–60. [PubMed: 9227683]
40. Chabriat H, Mrissa R, Levy C, Vahedi K, Taillia H, Iba-Zizen MT, et al. Brain stem MRI signal abnormalities in CADASIL. Stroke. 1999; 30(2):457–9. [PubMed: 9933287]
41. Tzourio C, Tehindrazanarivelo A, Iglesias S, Alperovitch A, Chedru F, d'Anglejan-Chatillon J, et al. Case-control study of migraine and risk of ischaemic stroke in young women. Bmj. 1995; 310(6983):830–3. [PubMed: 7711619]
42. Carolei A, Marini C, De Matteis G. History of migraine and risk of cerebral ischaemia in young adults. The Italian National Research Council Study Group on Stroke in the Young. Lancet. 1996; 347(9014):1503–6. [PubMed: 8684100]
43. Buring JE, Hebert P, Romero J, Kittross A, Cook N, Manson J, et al. Migraine and subsequent risk of stroke in the Physicians' Health Study. Arch Neurol. 1995; 52(2):129–34. [PubMed: 7848119]
44. Merikangas KR, Fenton BT, Cheng SH, Stolar MJ, Risch N. Association between migraine and stroke in a large-scale epidemiological study of the United States. Archives of Neurology. 1997; 54(4):362–8. [PubMed: 9109736]
45. Crassard I, Conard J, Bousser MG. Migraine and haemostasis. Cephalalgia. 2001; 21(6):630–6. [PubMed: 11531894]
46. Tietjen GE, Al Qasmi MM, Athanas K, Dafer RM, Khuder SA. Increased von Willebrand factor in migraine. Neurology. 2001; 57(2):334–6. [PubMed: 11468324]
47. Tzourio C, El Amrani M, Poirier O, Nicaud V, Bousser MG, Alperovitch A. Association between migraine and endothelin type A receptor (ETA -231 A/G) gene polymorphism. Neurology. 2001; 56(10):1273–7. [PubMed: 11376172]
48. Dreier JP, Kleeberg J, Petzold G, Priller J, Windmuller O, Orzechowski HD, et al. Endothelin-1 potently induces Leao's cortical spreading depression in vivo in the rat: a model for an endothelial trigger of migrainous aura? Brain. 2002; 125(Pt 1):102–12. [PubMed: 11834596]
49. Goadsby, PJ. Pathophysiology of migraine: a disease of the brain. In: Goadsby, PJ.; Silberstein, SD., editors. Headache. Boston: Butterworth-Heinemann; 1997. p. 5-25.
50. Eggers AE. New neural theory of migraine. Med Hypotheses. 2001; 56(3):360–3. [PubMed: 11359360]
51. Resnick S, Reyes-Iglesias Y, Carreras R, Villalobos E. Migraine with aura associated with reversible MRI abnormalities. Neurology. 2006; 66(6):946–7. [PubMed: 16567723]
52. Iizuka T, Sakai F, Yamakawa K, Suzuki K, Suzuki N. Vasogenic leakage and the mechanism of migraine with prolonged aura in Sturge-Weber syndrome. Cephalalgia. 2004; 24(9):767–70. [PubMed: 15315534]
53. Smith M, Cros D, Sheen V. Hyperperfusion with vasogenic leakage by fMRI in migraine with prolonged aura. Neurology. 2002; 58(8):1308–10. [PubMed: 11971111]
54. Ghabriel MN, Lu MX, Leigh C, Cheung WC, Allt G. Substance P-induced enhanced permeability of dura mater microvessels is accompanied by pronounced ultrastructural changes, but is not dependent on the density of endothelial cell anionic sites. Acta Neuropathol (Berl). 1999; 97(3): 297–305. [PubMed: 10090678]
55. Gursoy-Ozdemir Y, Qiu J, Matsuoka N, Bolay H, Bermpohl D, Jin H, et al. Cortical spreading depression activates and upregulates MMP-9. J Clin Invest. 2004; 113(10):1447–55. [PubMed: 15146242]

56. Dohmen C, Sakowitz OW, Fabricius M, Bosche B, Reithmeier T, Ernestus RI, et al. Spreading depolarizations occur in human ischemic stroke with high incidence. Ann Neurol. 2008; 63(6): 720–8. [PubMed: 18496842]
57. Welch KM, Nagesh V, Aurora SK, Gelman N. Periaqueductal gray matter dysfunction in migraine: cause or the burden of illness? Headache. 2001; 41(7):629–37. [PubMed: 11554950]
58. Kruit MC, Launer LJ, Overbosch J, van Buchem MA, Ferrari MD. Iron accumulation in deep brain nuclei in migraine: a population-based magnetic resonance imaging study. Cephalalgia. 2008 (in press).
59. DaSilva AF, Granziera C, Snyder J, Hadjikhani N. Thickening in the somatosensory cortex of patients with migraine. Neurology. 2007; 69(21):1990–5. [PubMed: 18025393]
60. DaSilva AF, Granziera C, Tuch DS, Snyder J, Vincent M, Hadjikhani N. Interictal alterations of the trigeminal somatosensory pathway and periaqueductal gray matter in migraine. Neuroreport. 2007; 18(4):301–5. [PubMed: 17435592]
61. Shechter A, Stewart WF, Silberstein SD, Lipton RB. Migraine and autonomic nervous system function: a population-based, case-control study. Neurology. 2002; 58(3):422–7. [PubMed: 11839842]
62. Havanka-Kanniainen H, Tolonen U, Myllyla VV. Autonomic dysfunction in adult migraineurs. Headache. 1986; 26(8):425–30. [PubMed: 3771211]
63. Havanka-Kanniainen H, Tolonen U, Myllyla VV. Autonomic dysfunction in migraine: a survey of 188 patients. Headache. 1988; 28(7):465–70. [PubMed: 3243708]
64. Havanka-Kanniainen H. Cardiovascular reflex responses during migraine attack. Headache. 1986; 26(9):442–6. [PubMed: 3781830]
65. Pogacnik T, Sega S, Pecnik B, Kiauta T. Autonomic function testing in patients with migraine. Headache. 1993; 33(10):545–50. [PubMed: 8294192]
66. Boiardi A, Munari L, Milanesi I, Paggetta C, Lamperti E, Bussone G. Impaired cardiovascular reflexes in cluster headache and migraine patients: evidence for an autonomic dysfunction. Headache. 1988; 28(6):417–22. [PubMed: 3170188]
67. Mikamo K, Takeshima T, Takahashi K. Cardiovascular sympathetic hypofunction in muscle contraction headache and migraine. Headache. 1989; 29(2):86–9. [PubMed: 2708041]
68. Gotoh F, Komatsumoto S, Araki N, Gomi S. Noradrenergic nervous activity in migraine. Arch Neurol. 1984; 41(9):951–5. [PubMed: 6477230]
69. Yakinci C, Mungen B, Er H, Durmaz Y, Karabiber H. Autonomic nervous system function in childhood migraine. Pediatr Int. 1999; 41(5):529–33. [PubMed: 10530067]
70. Thijs RD, Kruit MC, van Buchem MA, Ferrari MD, Launer LJ, van Dijk JG. Syncope in migraine: the population-based CAMERA study. Neurology. 2006; 66(7):1034–7. [PubMed: 16606915]
71. Lipton RB, Pan J. Is migraine a progressive brain disease? Jama. 2004; 291(4):493–4. [PubMed: 14747508]
72. Tietjen GE. Stroke and migraine linked by silent lesions. Lancet Neurol. 2004; 3(5):267. [PubMed: 15099537]
73. Rocca MA, Colombo B, Pagani E, Falini A, Codella M, Scotti G, et al. Evidence for cortical functional changes in patients with migraine and white matter abnormalities on conventional and diffusion tensor magnetic resonance imaging. Stroke. 2003; 34(3):665–70. [PubMed: 12624289]
74. Ardila A, Sanchez E. Neuropsychologic symptoms in the migraine syndrome. Cephalalgia. 1988; 8(2):67–70. [PubMed: 3401918]
75. Farmer K, Cady R, Bleiberg J, Reeves D. A pilot study to measure cognitive efficiency during migraine. Headache. 2000; 40(8):657–61. [PubMed: 10971662]
76. Hooker WD, Raskin NH. Neuropsychologic alterations in classic and common migraine. Arch Neurol. 1986; 43(7):709–12. [PubMed: 3729750]
77. Le Pira F, Zappala G, Giuffrida S, Lo Bartolo ML, Reggio E, Morana R, et al. Memory disturbances in migraine with and without aura: a strategy problem? Cephalalgia. 2000; 20(5): 475–8. [PubMed: 11037744]
78. Mulder EJ, Linssen WH, Passchier J, Orlebeke JF, de Geus EJ. Interictal and postictal cognitive changes in migraine. Cephalalgia. 1999; 19(6):557–65. [PubMed: 10448542]

79. Bell BD, Primeau M, Sweet JJ, Lofland KR. Neuropsychological functioning in migraine headache, nonheadache chronic pain, and mild traumatic brain injury patients. Arch Clin Neuropsychol. 1999; 14(4):389–99. [PubMed: 14590592]

80. Gaist D, Pedersen L, Madsen C, Tsiropoulos I, Bak S, Sindrup S, et al. Long-term effects of migraine on cognitive function: a population-based study of Danish twins. Neurology. 2005; 64(4):600–7. [PubMed: 15728279]

81. Jelicic M, van Boxtel MP, Houx PJ, Jolles J. Does migraine headache affect cognitive function in the elderly? Report from the Maastricht Aging Study (MAAS). Headache. 2000; 40(9):715–9. [PubMed: 11091288]

82. Pearson AJ, Chronicle EP, Maylor EA, Bruce LA. Cognitive function is not impaired in people with a long history of migraine: a blinded study. Cephalalgia. 2006; 26(1):74–80. [PubMed: 16396669]

83. Ishizaki K, Mori N, Takeshima T, Fukuhara Y, Ijiri T, Kusumi M, et al. Static stabilometry in patients with migraine and tension-type headache during a headache-free period. Psychiatry Clin Neurosci. 2002; 56(1):85–90. [PubMed: 11929575]

84. Terwindt GM, Ophoff RA, Haan J, Vergouwe MN, van Eijk R, Frants RR, et al. Variable clinical expression of mutations in the P/Q-type calcium channel gene in familial hemiplegic migraine. Dutch Migraine Genetics Research Group. Neurology. 1998; 50(4):1105–10. [PubMed: 9566402]

85. Dichgans M, Herzog J, Freilinger T, Wilke M, Auer DP. 1H-MRS alterations in the cerebellum of patients with familial hemiplegic migraine type 1. Neurology. 2005; 64(4):608–13. [PubMed: 15728280]