

Investigation of Migraine- Related Intracerebral White Matter Lesions

Doctoral (Ph.D.) Thesis

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University of Pécs, Medical School

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Current knowledge of migraine and migraine-related white matter lesions

Introduction

Migraine is defined by the International Headache Society (IHS) as a recurrent primary headache disorder, usually unilateral and pulsatile in nature with moderate to severe pain, with attacks lasting for 4-72 hours, and may associate with aura, nausea, vertigo and autonomic symptoms in adulthood.

Migraine Prevalence

Migraine is more common in adults (11%, lifetime 15%) than in children/adolescents (7%, lifetime 5%), with a decreasing prevalence (6%, lifetime 8%) in adults over the age of 60 years. In all categories, migraine is more prevalent in women than in men, with 14% vs 6% in adults, 9% vs 7% in children/adolescents and 8% vs 3% in the elderly.

Migraine Pathophysiology

The trigemino-vascular system provides an important pain-transmission link between the vascular (dural and cortical) and neuronal (brainstem and thalamus) regions. Since the posterior and lateral regions of the hypothalamus

is activated in the early premonitory phase of migraine, it is likely that the hypothalamus is a key organ in the initiation of migraine headache by activation of different brainstem structures. Cortical spreading depression (CSD) starts in the occipital cortex, and it is an appearance of depolarization waves of the neurons and neuroglia that propagate across the gray matter at a velocity of 2–5 mm/min. CSD is a dramatic failure of brain ion homeostasis, efflux of excitatory amino acids (e.g., glutamate) from nerve cells, and increased energy metabolism. CSD is present not just in aura patients, but in aura-free migraineurs, as well. CSD may activate the meningeal nociceptors of trigeminal sensory afferents, resulting in a release of vasoactive neuropeptides (CGRP, SP, NKA, PACAP, VIP). This process leads to the activation of the second-order neurons in the trigeminocervical complex, the third order neurons of the thalamus, and the fourth-order neurons in the sensory cortex (central sensitization). Blood flow is increased in the brainstem nuclei, called “migraine generators” (locus coeruleus, periaqueductal grey matter, raphe nuclei). Cranial parasympathetic fibres are activated in the superior salivatory nucleus in the brainstem. Postganglionic parasympathetic fibres project to the lacrimal, nasal mucosa and salivary glands, and the craniofacial vasculature, and induce lacrimation and rhinorrhoea. The descending pain modulatory pathway activity is decreased, and it may cause more intensive pain.

Migraine as a Vascular Risk Factor

Migraine has been shown to be a risk factor for subclinical brain lesions, ischemic stroke, and cardiovascular diseases.

Definition of Intracerebral White Matter Lesions

White matter lesions (WMLs) were considered if they were visible as hyperintense areas on T2-weighted and FLAIR images without hypointensity on T1-weighted scans and were larger than 3 mm and appeared in at least two consecutive slices.

Location of White Matter Lesions

WMLs can be located in either cerebral hemisphere, in any of the supratentorial cerebral lobes and in the infratentorial brainstem and the cerebellum. Supratentorially they can be further categorized as being located subcortically with U-fibres, in the deep white matter, periventricularly or in the corpus callosum.

Radiological Features of Migraine Lesions

Our research group also examined 17 migraineurs and 17 healthy control subjects using advanced MRI techniques, as follows: T1- and T2-weighted and 3D-FLAIR images,

diffusion weighted images (DWIs) and perfusion weighted images (PWIs), proton magnetic resonance spectroscopy and T1 and T2 relaxation time measurements. We detected significantly increased apparent diffusion coefficient (ADC) values in WMLs compared to normal white matter and controls. This indicates elevated levels of random water molecule motion inside the lesions which can indicate tissue damage. In vivo T1 and T2 relaxation times were prolonged, and it can indicate an increased extracellular water fraction. ¹H-MRS investigation of lesions showed decreased N-acetyl-aspartate (NAA) and decreased creatine and phosphocreatine (Cr) concentrations. Decreased NAA can indicate axonal loss while decreased Cr can reflect tissue degeneration with impaired intracellular energy metabolism. PWI study found mildly reduced intralesional relative cerebral blood flow (rCBF) and relative cerebral blood volume (rCBV), which can also be indicative of axonal and glial cellular loss. These findings indicated that WMLs could be the consequence of microvascular ischemic injury in migraine.

Changes of migraine-related white matter lesions after three years

Although the follow-up study mainly showed worsening in the status of brain WMLs, occasional regression of these abnormalities was also observed in some cases. A lower

baseline migraine attack frequency was associated with a tendency of decrease in WML number at three-year follow-up, implying a possible long-term relationship between the headaches and these imaging abnormalities. This longitudinal MRI study found clinically silent brain white matter hyperintensities to be predominantly progressive in nature.

Serum L-arginine and Dimethylarginine Levels in Migraine Patients with Brain White Matter Lesions

Introduction

Migraine is an independent risk factor for the development of WMLs and infarcts. WMLs are more prevalent in migraine patients than in the general population and they can develop at any time during the active migraine years. It was discussed how migraine, especially with aura, carries an increased risk for cerebro- and cardiovascular diseases that cannot be explained by traditional risk factors. Although histopathological data are lacking in migraine, the microvascular ischemic injury theory was supported by our previous quantitative MRI data demonstrating intralesional tissue damage consistent with previous studies of WMLs of ischemic origin. In addition, our longitudinal assessment of the same migraine patient

group showed intralesional and intracerebral progression of WMLs over time.

A vascular aetiology, such as impairment of the L-arginine/nitric oxide (NO) pathway with vascular endothelial dysfunction could explain the development and progression of WMLs and could also provide a link between migraine and ischemic stroke or coronary heart disease. Endothelial NO-synthase (eNOS) utilizes L-arginine to generate the strong vasodilator, anti-atherogenic NO. Methylated analogues of L-arginine, symmetric and asymmetric dimethylarginine (SDMA and ADMA) are modulators of the L-arginine/NO pathway. Both ADMA and SDMA levels are associated with an increased cardiovascular risk and mortality. ADMA has also been found to be a marker of oxidative stress and endothelial dysfunction in migraine.

Despite the growing evidence of oxidative stress and vascular endothelial activation in migraine, the abovementioned biomarkers of endothelial dysfunction have not been comprehensively analysed in relation to WMLs. Therefore, *our objective* was to quantify the L-arginine, ADMA and SDMA serum concentrations of migraine patients with or without cerebral WMLs in a headache-free period, to detect group differences between lesional and non-lesional migraineurs, to investigate the effect of migraine characteristics, and to determine the differences between migraine patients and controls.

Patients and Methods

A total of 109 migraineurs (93 females, mean age 36.7 ± 10.8 years, age range 19-65 years), 82 without and 27 with aura subtypes were prospectively enrolled in the study. As controls, 56 subjects were screened, and 46 age-matched healthy subjects (33 females, mean age 37.3 ± 10.5 years, age range 20-65 years) were enrolled. All included participants underwent a brain 3T-MRI study. WMLs were detected in 43 migraineurs, whereas no WMLs or other structural abnormalities were found in the rest of the studied population including controls. Migraine patients were divided into two subgroups based on presence of WMLs (L+) or absence of those (L-). Serum levels of L-arginine, ADMA and SDMA were quantified from fasting blood samples taken by venepuncture from the antecubital vein in all enrolled participants.

Results

Age

There were no significant differences in age between the whole migraine group and healthy controls. The Kruskal-Wallis test revealed significant differences in age among patients with WML, patients without WML and healthy controls ($P < 0.001$). Post-hoc testing indicated significant differences between all possible pairs of the three groups

($P < 0.05$). Significant differences were not found between lesional subgroups, nor between non-lesional subgroups.

Control group

Since the study subgroups were not age-, and gender-matched, the healthy control group was investigated first by multiple linear regression. There were no significant effects of either age or gender on ADMA, SDMA or L-arginine concentrations; there were no interactions between age and gender.

Categorical data

Regarding the gender of subjects, and the presence of comorbid disorders, no significant differences were found among the groups.

Migraine characteristics

Compared to lesion-free migraineurs, patients with WMLs had a longer disease duration (L+ vs. L-, $P < .001$), including subgroups in general (Kruskal-Wallis $P = 0.002$). Those with WML also had a higher number of lifetime headache attacks (L+ vs. L-, $P = 0.004$), including the subgroups again (Kruskal-Wallis $P = 0.003$). The attack frequency of patients with aura was lower than of

migraineurs without aura (L+A- vs. L-A+, $P = 0.002$; L-A+ vs. L-A-, $P < 0.001$).

L-arginine levels

Markedly higher blood serum concentrations were measured in the migraine groups than in the control group. Statistically significant differences were not found between the migraine groups.

ADMA levels

L+ migraine patients showed higher serum concentrations than L- patients and controls. L+A+ patients had higher serum ADMA levels than L+A- ($P = 0.009$), L-A+ ($P < 0.001$), L-A- ($P < 0.001$) patients and controls ($P < 0.001$). In the L+A- group elevated serum levels were found in comparison to the L-A- ($P = 0.009$) and the control groups ($P = 0.017$). The highest ADMA serum levels were detected in the L+A+ group. A significant positive correlation was found between age and ADMA level in lesion-free migraineurs ($P = 0.006$), while this relationship was absent in patients with WML and controls.

SDMA levels

SDMA levels of L+ migraineurs were higher than L- patients ($P < 0.001$) and controls, but the latter comparison

was not statistically significant ($P = 0.06$). The SDMA serum levels were higher in the L+A+ patients than in the L-A+ ($P < 0.001$) and L-A- ($P = 0.006$) patients and controls ($P = 0.003$). Higher serum concentrations were detected in the L+A- patient group than in the L-A+ ($P = 0.003$) and L-A- ($P = 0.029$) patient groups. The highest SDMA plasma levels were detected in the L+A+ group.

Binary logistic regression analysis

The logistic regression model was statistically significant, $\chi^2(22) = 48.56$, $P < 0.0005$. The model explained 51.0% (Nagelkerke R^2) of the variance in WMLs and correctly classified 79.8% of WMLs. ADMA levels were the most significant independent predictors of WML presence, with more than a 21-fold higher likelihood of exhibiting WML in those with a 1 $\mu\text{mol/L}$ elevation in ADMA ($\text{Exp(B)} = 21.49$, $P = 0.038$). Patients with aura were 1.21 times more likely to have WML than patients without aura ($P = 0.041$). Increasing age was associated with an increased likelihood of exhibiting WML ($\text{Exp(B)} = 1.09$, $P = 0.045$). None of the other examined variables added significantly to the model.

Discussion

The main finding of the present study is the elevated serum ADMA concentration in migraine patients with WMLs

outside the attack period. ADMA levels were the best predictor of WMLs, independent of other significant factors such as age and estimated life-time headache attack number. Higher SDMA serum levels distinguished lesional migraine patients from lesion-free patients, while the elevated L-arginine concentrations differentiated migraineurs from controls.

Age, vascular risk factors, migraine characteristics

Increasing age was associated with an increased likelihood of exhibiting WMLs, and older age proved to be a predictor of higher ADMA and SDMA in migraineurs with lesions. Since positive correlation was found between age and disease duration, and there were no significant effects of age on ADMA and SDMA concentrations in controls, long duration of migraine, rather than older age, may explain the elevation of dimethylarginines.

Increased plasma ADMA concentrations have been associated with the presence of numerous vascular risk factors and chronic diseases such as obesity, hypertension, diabetes, dyslipidaemia, hyperhomocysteinemia, ischemic heart disease, transient ischemic attack, silent brain infarcts, ischemic stroke, renal and liver failure, smoking and physical inactivity. Vascular risk factors were rare in both patients and controls in our study, and all of them were treated during

the study period. It is known that lipid-lowering therapy and smoking cessation reverse the endothelial dysfunction, if present. Therefore, a significant influence of vascular risk factors on the findings is unlikely.

In the present study, migraine patients with WMLs had a longer disease duration than non-lesional patients, and it was associated with a higher number of lifetime headache attacks. The number of lifetime headache attacks proved to be an independent predictor of WMLs, while the presence of aura indicated higher ADMA levels in migraineurs. Beyond the investigated migraine parameters, there are other factors such as attack intensity and duration, and frequency and severity of the CSD, which may have an influence on lesion formation. In concordance with previous studies, the interictal elevation of L-arginine and dimethylarginines in lesional patients indicate that oxidative stress can be present in both the ictal and interictal phases in migraine.

Effects of migraine on the biosynthesis and metabolism of dimethylarginines and L-arginine

The concentration of ADMA is regulated mainly by degradation in the endothelial cells by the dimethylarginine dimethylaminohydrolase-2 isoform (DDAH-2). Since DDAH-2 is sensitive to oxidative stress triggered by the excessive generation of NO, under pathophysiological conditions, e.g., cardiovascular

diseases and migraine, reactive O₂ species inhibit DDAH-2 activity with corresponding accumulation of ADMA. It is conceivable that the NO-caused vasodilatation is overbalanced by the increased amount of ADMA during migraine headache which may lead to a reduced bioavailability of NO, vasoconstriction with cerebral hypoperfusion and endothelial dysfunction. Since elevation of NO and ADMA concentrations are not restricted to the ictal state, inhibition of eNOS can also be present in a headache-free period. Chronic endothelial dysfunction has a role in mediating impaired cerebral autoregulation, and in the small perforating cerebral blood vessels it could result in poor white matter blood supply and the accumulation of white matter injury.

Conclusion

Elevated ADMA levels may impact the pathogenesis of migraine-related WMLs by influencing cerebrovascular autoregulation and vasomotor reactivity. Higher SDMA concentrations may indirectly influence NO synthesis by reducing substrate availability. Elevated L-arginine serum levels might reflect an increased demand for NO synthesis.

Influence of Hemispheric White Matter Lesions and Migraine Characteristics on Cortical Thickness and Volume

Introduction

Cortical thickness is both a marker of neurological development and a reflection of cortical function. The cerebral cortex contains high neuronal density, and its thickness varies from 1.5 mm to 5 mm. Both the pyramidal neurons and the interneurons travel through the white matter within the hemisphere during prenatal brain development, and both types of cortical neuronal cells receive projection fibres from the thalamus, and association and commissural fibres from other cortical areas.

Migraine is a primary headache disorder that may cause structural and functional alterations in the cerebral cortex. Migraine-related intracerebral WMLs are likely to be microvascular in nature and can be found in all four lobes implicating the deep white matter, the subcortical, the periventricular and the callosal commissure locations. Based on the above-mentioned data, we hypothesized that the WMLs – areas of focal axonal and glial cell (astrocyte, oligodendrocyte, microglia) injuries in association with decreased intracellular energy metabolism due to impairment of mitochondria – may cause cortical changes in migraine. For that reason, we investigated migraine

patients with or without WMLs *to assess* the effects of these tissue damages on cortical thickness and volume. In this respect, the potential role of migraine characteristics was tested, as well. Female patients were selected, because migraine is much more prevalent in adult women than men and to avoid the gender-related differences (e.g., longer headache duration, higher intensity of attacks, more frequent nausea, phonophobia and photophobia in women) existing between women and men.

Subjects and Methods

Between 2010 and 2017, a total of 161 female patients fulfilling the International Headache Society (IHS) classification criteria for migraine with or without aura were prospectively screened from the Outpatient Headache Clinic of the Department of Neurology, Medical School, University of Pécs, Hungary. At the time of the study period, all migraineurs had recurrent headaches, and none of them were on chronic prophylactic therapy. For acute migraine treatment, eletriptan, sumatriptan, ibuprofen, diclofenac, acetylsalicylic acid and/or acetaminophen were utilized. The demographic and clinical data of migraineurs were the following: mean age 39.3 ± 12.5 , range 18-73 years; disease duration 15.6 ± 11.9 , range 1-57 years; attack frequency/month 5.6 ± 4.5 , range 0.2-14.8; total number of estimated lifetime migraine attacks (average monthly attack number $\times 12 \times$

number of migraine disease years to date) 966 ± 1158 , range 12-6840; $n = 52$ with WMLs (L+ patients); $n = 63$ with aura. Migraineurs had no other types of headaches. None of the included migraine patients' headache or aura was unilaterally side-locked in nature. Magnetic resonance imaging (MRI) was performed in a headache-free period for each patient. Medical comorbidities that could influence migraine characteristics or lead to the formation of WMLs were excluded (hypertension, diabetes mellitus, kidney disease, hepatopathy, high LDL-cholesterol, hyperuricemia, elevated CRP level, thyroid gland disease, systemic autoimmune disease, smoking, cardiac source of embolism, obesity). Based on self-report, all migraineurs were right handed. As controls, 40 age-matched healthy female subjects were included (mean age 38.3 ± 10.0 , range 19-66 years). Controls were recruited by family physicians in Baranya County, Hungary. Similar to migraine patients, all controls were right-handed. All control subjects were free of headache, and their brain MRI studies did not show any structural abnormalities.

Results

There was no significant difference in age between the whole migraine (including both L+ and L- patients) and the control groups ($P = 0.738$). The Kruskal–Wallis test revealed significant age differences among migraine

subgroups (L+ and L-) and controls ($P = 0.001$). Post-hoc testing indicated that L+ subgroup was significantly older than the L- ($P = 0.0003$) and the control ($P = 0.018$) groups. Disease duration ($P = 0.003$), the total number of migraine attacks ($P = 0.022$) and the rate of aura ($P = 0.0003$) were also significantly higher in L+ patients than in L- patients.

The left and right differences in lobar and insular volumes/thicknesses (i.e., lateralities) were not different among our groups (L+, L-, control); $P = 0.626, 0.965, 0.425, 0.859$ and 0.989 for the frontal, parietal, temporal, occipital and insular thicknesses and $P = 0.598, 0.252, 0.855, 0.732$ and 0.136 for the frontal, parietal, temporal, occipital and insular volumes, respectively. Cortical thickness and volume measurements of the five lobes were not statistically different among our three groups (L+, L-, control).

Age showed a significant negative association with both thickness and volume in each examined lobe ($P < 0.001$). Intracranial volume (ICV) showed a significant positive association with the volumes of all regions ($P < 0.001$). There were no significant group*age, group*total ICV or age*ICV interactions in the performed analyses.

In the whole migraine group, none of the migraine characteristics were selected by stepwise linear regression as significant predictors of cortical thickness or volume. Only age (for both thickness and volume) and ICV (for

volume) were identified as significant predictors ($P < 0.001$).

Focusing on the L+ patients, none of the binarized total or lobar lesion number/volume variables were selected by stepwise linear regression as significant predictors of the insular or lobar thicknesses/volumes.

Discussion

In this study, we investigated a homogeneous (female migraineurs without medical comorbidities) migraine group to explore the potential effects of WMLs and migraine characteristics on cortical lobar thickness and volume. The WMLs and clinical characteristics failed to show any effects on the lobar cortical measures. When the lesion + group was divided into two subgroups by median split of total and lobar lesion number and volume, the cortical measurements (thickness and volume) did not show any significant difference between the groups with low vs. high lesion number/volume by stepwise linear regression. Only age and ICV proved to be significant predictors; the former for both cortical thickness and volume, while the latter for cortical volume.

The lack of the impact of WMLs on cortical thickness and volume may be the consequence of the not reaching the critical size of injured white matter territory, the intralobar separations of lesions with differences in distributions, or less severe intralesional tissue damage.

Although the clinically silent brain WMLs are predominantly progressive in nature, smaller lesions may improve in size or even disappear. In addition, the normal-appearing white matter did not show MRI signs of tissue injury in migraine patients with or without WML.

The negative association of age with cortical thickness and volume raises the possibility that WMLs are age-related. WMLs can develop at any age during the active migraine years, and their presence does not correlate with age. Disease duration and attack frequency are the main indicators for brain damage in migraine. Usually, ageing associates with longer disease duration and higher lifetime attack number, and these factors may increase the risk of oxidative stress-related endothelial injury and atherosclerosis. Furthermore, a wide range of vascular risk factors contribute to lesion formation. In the present study, both migraineurs and controls lacked any medical comorbidity, thus the role of ageing in lesion development is less likely.

Conclusions

In summary, we investigated a female migraine group, and found that neither the lesions nor other clinical characteristics have a detectable effect on cortical thickness and volume of bilateral intracerebral lobes. Cortical thicknesses were equivalent within the range of ± 0.1 mm. Only age and ICV proved to be significant

predictors; the former for both cortical thickness and volume, while the latter for cortical volume.

New Findings

1. The elevated ADMA levels in lesional migraineurs may indicate a role of migraine-related vascular endothelial dysfunction in the development of WMLs, supporting the ischemic injury theory of WML formation. These findings indicate that elevated ADMA concentrations may be a risk factor for clinically silent brain WMLs and point out the necessity of therapeutic interventions. SDMA may also have a role in lesion formation by indirect inhibition of NO bioavailability. The higher L-arginine serum concentrations might reflect an increased demand for NO synthesis in migraine. Migraine may be a systemic factor of vascular endothelial injury during the active headache years.

2. We investigated a female migraine group and found that neither the lesions nor other clinical characteristics have a detectable effect on cortical thickness and volume of bilateral intracerebral lobes. Only age and ICV proved to be significant predictors; the former for both cortical thickness and volume, while the latter for cortical volume. These are good news for migraineurs.

Publications Related to the Thesis

1. Influence of hemispheric white matter lesions and migraine characteristics on cortical thickness and volume. **Komáromy H**, He M, Perlaki G, Orsi G, Nagy SA, Bosnyák E, Kamson Olayinka D, John F, Trauninger A, Pfund Z. *J Headache Pain*. 2019 Jan 10;20(1):4. doi: 10.1186/s10194-019-0959-2. **Impact Factor (2018): 3.403**
2. Serum L-arginine and dimethylarginine levels in migraine patients with brain white matter lesions. Erdélyi-Bótor S, **Komáromy H**, Kamson DO, Kovács N, Perlaki G, Orsi G, Molnár T, Illes Z, Nagy L, Kéki S, Deli G, Bosnyák E, Trauninger A, Pfund Z. *Cephalalgia*. 2017 May; 37(6):571-580. doi: 10.1177/0333102416651454. **Impact factor: 3.882**

Other Publications Related to the Topic of Headache

3. Risk factors of migraine-related brain white matter hyperintensities: an investigation of 186 patients. Trauninger A, Leél-Ossy E, Kamson DO, Pótó L, Aradi M, Kövér F, Imre M, **Komáromy H**, Erdélyi-Botor S, Patzkó A, Pfund Z. *J Headache Pain*. 2011 Feb;12(1):97-103. doi: 10.1007/s10194-011-0299-3. **Impact Factor: 2.427**

Other Publications

4. Intrauterine diagnosis and pathology of fetal choroid plexus carcinoma--a case study. Joó GJ, Reiniger L, Papp C, Csaba A, **Komáromy H**, Rigó J Jr. *Pathol Res Pract*. 2014 Dec; 210(12):1156-9. doi: 10.1016/j.prp.2014.01.009. **Impact Factor: 1,397**

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„There are two things parents should give their children roots and wings. Roots to give them bearing and a sense of belonging, but also wings to help free them from constraints and prejudices and give them other ways to travel (or rather, to fly).” (Johann Wolfgang von Goethe)

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