MIGRAINE, CAROTID STIFFNESS AND GENETIC POLYMORPHISM

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SUMMARY – Recently migraine has been associated with increased arterial stiffness, procoagulant state, increased incidence of cerebral white matter lesions (WML) and stroke. Our aim was to compare the characteristics of migraineurs to headache free controls regarding their functional carotid ultrasound parameters. Sixty patients (45 women) with migraine (mean age 40.42±10.61 years) were compared with 45 controls (30 women) with no prior history of repeating headache (mean age 38.94±5.46 years) using E-tracking software on Alpha 10 ultrasound platform. Student's t-test was used on statistical analysis with alpha <0.05. All tested carotid vascular parameters were worse in patients with migraine including increased intima-media thickness, greater carotid diameter and carotid diameter change, as well as several arterial stiffness indices. Additionally, patients with migraine had greater incidence of homozygous mutations for procoagulant genes (MTHFR (C677T), PAI-1 and ACE I/D) than expected. Computed tomography and magnetic resonance imaging of the brain showed WML in 11 patients, four of them migraine with aura patients. Since we established increased carotid stiffness and higher frequency of procoagulant gene mutations in migraineurs, we propose prospective ultrasound monitoring in such patients, especially those with detected WML, in order to timely commence more active and specific preventive stroke management strategies.

Key words: *Migraine disorders; Carotid artery diseases; Vascular stiffness; Atherosclerosis; Stroke*

Introduction

Migraine is a common disabling primary headache and a neurovascular disorder. Several epidemiologic studies addressed migraine as an independent risk factor for ischemic cerebrovascular disease[1,2]. A meta-analysis by Schurks *et al.* states that migraine was associated with a twofold higher risk of ischemic stroke apparent only among people who had migraine with aura (MA), those aged less than 45, smokers, women in general, and women using oral contraceptives[1]. Interestingly, there was no association between migraine and myocardial infarction or death due to cardiovascular disease[1]. In addition, results of a large prospective cohort suggest that women with MA are at an increased risk of experiencing transient ischemic attack (TIA) or ischemic stroke, but with good functional outcome[2]. A recently published review confirmed the association between migraine, particularly MA, and ischemic stroke, while implicating several pathophysiological mechanisms of the ischemic event genesis[3]. It has also been confirmed that genetic polymorphisms of the following factors: factor V Leiden, factor V (H1299R), prothrombin G20210A, factor XIII (V34L), β-fibrinogen, MTHFR (C677T), MTHFR (A1298C), APO E, PAI-1, HPA-1 and ACE I/D, are most likely implicated in the foundation of stroke related to migraine[3].

Cerebrovascular disease in very early stages manifests as endothelial dysfunction, increase of arterial stiffness and increase in the intima-media thickness

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(IMT)[4]. Vascular endothelium is involved in four opposite regulatory mechanisms: vasodilatation-vasoconstriction, growth inhibition-growth promotion, antiaggregation-proaggregation, and anti-inflammatory-proinflammatory action. Alterations in these mechanisms may serve as a common mechanistic pathway to both migraine and cerebrovascular disease[4]. Results of the MIRACLES study, published in 2011, showed substantial prevalence of hypertension-migraine comorbidity with a higher probability of cerebrovascular events, compared to simply hypertensive patients[5]. In a study by Nagai *et al.,* migraine in the elderly was identified as a possible clinical manifestation of enhanced arterial stiffness[6]. So far, changes in arterial stiffness have been most often associated with systolic hypertension or pulse wave velocity (PWV) increase. Namely, PWV is generally regarded as one of the closest representations of changes in arterial mechanics caused by provocative factors, and is the gold standard of arterial stiffness measurement. Increase in PWV was also labeled as an independent predictor of cerebrovascular disease occurrence[7].

E-tracking® is semi-automated software for arterial wall biomechanical evaluation[8]. The purpose of this study was to explore viscoelastic common carotid artery characteristics in patients with migraine using several E-tracking® computed parameters and compare them with headache free controls in search for the possible evidence for early functional disbalance and subclinical atherosclerotic damage.

Patients and Methods

The investigation was performed on 60 migraine patients (45 women) and 45 controls (30 women) with no prior history of repeating headache. Study patients were randomly selected from a pool of our episodic migraine patients evaluated in the last quarter of 2009. Controls were randomly selected from clinically healthy individuals within the same age range (18-55 years) examined in our cerebrovascular laboratory during the same period. Participants signed the informed consent previously approved by the Hospital Ethics Committee and underwent standard neurological examination. Migraine questionnaire was filled in by migraine patients providing the following information: age, sex, age at migraine onset, number of migraine days *per* month, headache duration per episode, maximum pain severity using visual analog scale (VAS), coexistence of other headaches, migraine triggers, presence of aura, and migraine therapy administered. Additional information noted in all study subjects included years of education, marital status, smoking (with pack-year assessment for active smokers), alcohol consumption, hypertension (if present), diabetes mellitus (if present), heart disease (if present), use of contraceptives, body height, and body weight. The following parameters were calculated: life-time migraine duration (yrs), pulse pressure (PP, difference between systolic and diastolic blood pressure values), body mass index (BMI), and pack-year number for the group of active smokers (one pack of cigarettes smoked *per* day for one year). Laboratory blood analysis was performed as screening only for migraine patients with the following parameters: hemoglobin, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), red blood cell count, leukocyte count, total cholesterol, LDL, HDL, triglycerides, and haplotype analysis for factor V Leiden, factor II (prothrombin G20210A), MTHFR (C677T), PAI-1, ACE I/D and APO E. Migraine patients were also asked to undergo magnetic resonance imaging (MRI) to establish the potential presence of cerebral white matter lesions (WML).

Color coded flow imaging carotid Doppler (CDFI) and E-tracking were performed on Alpha-10 (Aloka Co., Ltd., Tokyo, Japan) with 13 MHz linear transducer in B and M modes using standard protocols and E-tracking® system. Noninvasive brachial blood pressure (BP) was measured thrice on the right arm in supine position after five minute bed rest with an Omron digital automatic oscillometric BP monitor. The mean BP was used for E-tracking®. Data collection was performed by a single investigator who was not informed on the patient's involvement in this study and with respect to the Recommendations of the Task Force for arterial stiffness during headache free intervals[9]. All measurements were performed on distal common carotid artery (CCA; 1.5 cm proximally to carotid bifurcation) in supine position with head elevation of up to 30° and side tilt of 30° to the left and then to the right. The following ultrasound parameters were evaluated: carotid IMT, systolic and diastolic carotid inter-adventitial diameters (CID) and difference

Table 1. Descriptive statistics of patients with migraine and controls

	Age (yrs)	Sex		BW (kg)	BH (m)	BMI (kg/m^2)	Smoking (n)				P-y	BP (mm Hg)		PP (mm Hg)	IMT (mm)		CID (mm)		CIDc (mm)				***BSI***	
		F	M				1	2	3	4		SBP	DBP		R	L	R	L	R	L	R	L	R	L
Migraineurs																								
Mean	39.35			72.19	1.70	25.04*					11.4	123.07*	79.17*	43.91	0.49*	0.50*	7.05*	7.01*	0.43*	0.36*	7.90*	8.13*		
SD	9.95			3.54	0.07	4.13					13.31	12.81	10.07	9.33	0.13	0.13	0.74	0.93	0.14	0.12	2.92	3.31		
CI (95%)	2.63	45	15	3.58	0.02	1.09	22	1	4	33	3.52	3.39	2.66	2.47	0.03	0.03	0.17	0.22	0.03	0.10	0.69	0.78		
Controls																								
Mean	37.80			70.13	1.72	23.71					13	116.78	74.56	42.22	0.41	0.44	6.46	6.36	0.58	0.58	5.64	5.46		
SD	4.72			12.11	0.09	2.71					8.97	7.99	6.73	5.39	0.06	0.08	0.73	0.72	0.19	0.19	1.99	2.03		
CI (95%)	0.02	30	15	3.36	0.02	0.75	6	8	2	29	2.49	2.21	1.86	1.49	0.02	0.02	0.20	0.20	0.05	0.05	0.55	0.56		

*p<0.05
SD = standard deviation; CI = confidence interval; F = female; M = male; BW = body weight; BH = body height; 1 = active smokers; 2 = occasional smokers (less than one cigarette a day); 3 = former smokers (minimum one year abstinence); 4 = never smokers; P-y = pack-year; BP = blood pressure; SBP = systolic blood pressure; DBP = diastolic blood pressure; PP = pulse pressure; IMT = intima-media thickness; CID = diastolic carotid inter-adventitial diameter; CIDc = change in carotid inter-adventitial diameter; BSI = beta stiffness index; R = right; L = left.

between the two (CIDc), carotid beta stiffness (BSI) index, elasticity coefficient (Ep), arterial compliance (AC), augmentation index (AI) and one-point beta pulse wave velocity (bPWV) bilaterally[9].

Descriptive statistics and frequency tables were created. Quantitative data were analyzed by Kolmogorov-Smirnov test to verify the normality of distribution and Bartlett-Box test was used to check homoscedasticity of variance. SPSS (version 8.0 for Windows) was used to compare the means of continuous variables with Student's t-test for independent samples or, if appropriate, Mann-Whitney U-test (for 2 groups) was substituted, both at a threshold value of 0.05 (two-tailed p value).

Results

In our group of migraineurs (n=60) there were 45 women (mean age 40.42±10.61 years), while in the control group (n=45) there were 30 women (mean age 38.94±5.46 years). Descriptive statistics is shown in Table 1. The mean life-time headache duration was 16.24±12.20 years (CI 2.86): in 46 patients beginning in adolescence and adulthood, in two patients beginning in puberty and in seven patients with later onset (after 40 years); five patients could not recollect the age of migraine onset. MA was reported by 19 patients (32%). The mean number of headache days *per* month was 9.82±9.37 (CI 2.20), range 1-30, and the mean pain severity on VAS was 7.52±1.15 (CI 0.27). Twenty-eight patients reported to have an additional headache (most often tension type headache). The average headache period duration in patient group ranged from 30 minutes to 7 days. Most of the patients resorted to therapy with nonsteroidal antiinflammatory drugs (NSAIDs) (n=43), two received intravenous (iv) therapy, one was taking ergotamine, one was without medication aid, and only 13 were taking triptans. Thirteen patients reported no migraine triggers; of the remaining, 28 patients pointed to multiple triggers and 19 opted for only one trigger. Single triggers were categorized as follows: physical conditions (n=19), weather change (n=15), stress (n=14), premenstrual syndrome (PMS, n=13), emotions (n=5), ovulation (n=5), food and drink (n=5) and menstruation (n=4). We would like to emphasize that the most prevalent migraine triggers (n=22) were those associated with menstrual cycle (3 single triggers).

Additionally, 24 patients had 14 years, 28 had 12 years, 4 had 16 years and the remaining four patients had 8 years of schooling. There were 44 married, 13 single and 3 divorced patients. Twenty-seven patients claimed they did not take alcoholic drinks and 33 reported having occasional drink. There were 3 hypertensive patients, all medicated and well controlled (repeated BP measurements revealed normal values); two patients were diabetic (one treated with diet and one with oral medication; blood glucose measurement showed normal values in both cases). None of the patients had cardiac disease. There were 22 (37%) active smokers among migraineurs with the mean pack-year number 11.4±13.31. Four women were taking oral contraceptives.

Blood sample measurements of inflammation parameters like ESR, leukocyte count and CRP were all within the normal laboratory values, as were red blood cell count and hemoglobin values. Total cholesterol was 5.63±1.21 mmol/L (CI 0.32), LDL 3.50±1.10 mmol/L (CI 0.30), while HDL and triglycerides were 1.50±0.50 mmol/L (CI 0.10) and 1.38±0.99 mmol/L (CI 0.26), respectively. The mean waist circumference was 85.63±13.66 cm (CI 3.61).

The mean BP was 123.07±12.81 mm Hg over 79.17±10.07 mm Hg in migraineurs *versus* 116.78±7.99 mm Hg over 74.56±6.73 mm Hg in controls ($p<0.05$). There was no statistically significant PP difference between patients and controls (43.91±9.33 mm Hg *versus* 42.22±5.39 mm Hg). Heart rate was normal in all patients (69.89±8.64 beats/min, CI 2.28).

Color coded carotid Doppler showed plaques in four patients, mild stenosis in one patient and moderate stenosis in one patient, while 54 patients showed no pathology. The mean IMT was normal in both groups, but slightly greater in migraine patients. The same was also found for CID and CIDc. AC in migraineurs showed decreased carotid compliance, while all other markers implied increased arterial stiffness (Table 2), with no side-to-side differences ($p>0.05$).

Genetic polymorphism analysis revealed homozygotic mutations (HoM) for MTHFR (C677T) in three and heterozygous mutation (HeM) in 22 patients, HoM for PAI-1 in 11 and HeM in 22 patients, and HoM for ACE in nine and HeM in 18 patients. Single mutations occurred in 14 patients, coexisting mutations of two aforementioned genes occurred in 12 patients, while another nine patients had three coexisting mutations (11 patients were mutation free). There were no HoM discovered for factor V Leiden, factor II (prothrombin G20210A) and APO E. Only 2 HeM were detected for factor V Leiden and APO E; all other patients were mutation free. Brain MRI was performed in 20 patients (others refused brain imaging): periventricular WML were found in 11 patients, 4 in MA patients, and two patients had evidence of previous small brain stem ischemic lesions.

Table 2. Other functional vascular parameters of migraineurs versus controls

	Ep (kPa)		AC (mm^2/kPa)		AI (%)		βPWV (m/s)	
	R	L	R	L	R	L	R	L
Migraineurs								
Mean	103.64*	107.43*	0.88*	0.85*	9.99	11.11	6.13*	6.21*
SD	38.27	45.19	0.33	0.33	10.50	14.59	1.06	1.24
CI (95%)	8.96	10.59	0.08	0.08	2.46	3.42	0.25	0.29
Controls								
Mean	70.95	68.80	1.10	1.10	NA	NA	5.07	4.98
SD	26.27	26.80	0.40	0.44	NA	NA	0.95	0.95
CI (95%)	7.28	7.43	0.11	0.12	NA	NA	0.26	0.26

*$p<0.01$; NA = not available, there were no side-to-side differences detected; SD = standard deviation; CI = confidence interval; Ep = elasticity coefficient; AC = arterial compliance; AI = augmentation index; βPWV = one-point beta pulse wave velocity; CIDc = carotid inter-adventitial diameter change; R = right; L = left.

Discussion

Migraine patients in this study had significantly higher values of IMT, BSI, Ep, AI and βPWV indicating increased carotid stiffness. AC was decreased compared to controls, as is usually expected in early vascular changes. The average life-time migraine duration in our patients was 16 years, but it was, so far, discovered that functional properties in peripheral arteries are altered even in patients with migraine of a relatively recent onset (<6 years), even more so in muscular arteries[10]. Our previous studies have shown that over time, due to age increase alone, changes of vascular elasticity can be detected and predicted[11]. However, there were no significant differences in our study between the morphological and functional measurements in either CCA or between sexes. A recent study showed results similar to ours, i.e. there was no difference between left and right CCA lumen diameter and IMT despite the fact that men had larger carotid diameters in general[12].

It is widely accepted that carotid PWV directly reflects arterial stiffness while central pressure or AI is its indirect or surrogate measure. Increase in PWV is attributed to endothelial cell regulation that contributes to structural changes of arterial tunica media that might occur independently, as well. Furthermore, increased aortic PWV in young people was labeled as a possible mechanism underlying the increased CV risk in migraine patients[13]. Similar was recently also confirmed in chronic migraine patients, where both increased arterial stiffness and endothelial dysfunction were discovered[14]. Liman *et al.* confirmed increase in arterial stiffness in migraine patients, even without impairment of peripheral endothelial function[15]. In a study by de Hoon *et al.,* interictally increased arterial stiffness was concluded to suggest that migraine might be part of a more generalized vascular disorder[16]. Recently, multiple linear regression analysis revealed that migraine was an independent determinant of AI after adjustment for confounding factors such as age, sex, body height, systolic BP, hypertension medication, hyperlipidemia, diabetes mellitus and heart rate[6]. Our migraine patients had significantly higher IMT values compared to controls (still within the healthy boundaries) suggesting stratification, i.e. IMT quintiles predicting the risk of stroke[17]. Kovaite *et al.* found that SCORE risk assessment may be used to assess cardiovascular risk as low (<5%) or increased (≥5%) selecting cut-off value of 0.078 mm for IMT and 8.95 m/s for PWV[18]. Our previous study showed that, due to age increase alone, changes of vascular stiffness could be detected and predicted[11]. Still, it has been established that age and sex independently influence both parameters, while BMI and LDL cholesterol independently reflect only carotid IMT changes[19]. The aforementioned parameters are especially important since they mark two separate entities of vascular damage: functional – arterial stiffness (PWV) and morphological – subclinical atherosclerosis (carotid IMT).

Only a few of our patients had conventional vascular risk factors, probably because of their relatively young age. Still, our patients were more prone to smoking (one-third were active smokers) compared to controls. Agreeably, Lopez-Mesonero *et al.* found habitual smoking of 5 cigarettes daily to invoke migraine attacks by one-third more often[20]. Smoking is proatherogenic through blood clot formation, endothelial dysfunction and lipid peroxidation, all persisting long after smoking cessation[21]. Previous studies have stated that diameter increase, IMT increase and plaque formation are early irreversible markers of atherosclerosis, as are systolic BP and PP increase[22]. Additionally, significantly higher BP values, but still within the healthy boundaries, were observed in our migraine patients and recently by Harandi *et al.* proposing the need for greater vigilance in patient screening and management[23]. Both systolic and diastolic BP were equally increased in our patients, so no difference in PP values was detected between the groups.

Additionally, our migraine patients had a high incidence of homozygous and heterozygous mutations for MTHFR, PAI-1 and ACE. Other tested genes (factor V Leiden, factor II (prothrombin G20210A), and APO E) did not differ between our groups, as was also noted by Pizza *et al.*[3] So far, PAI-1 was found significantly lower in migraineurs (along with tPA) supporting involvement of hemostasis in the pathogenesis of migraine[24]. Proatherogenic homozygous ACE mutation is more frequent in migraine with aura and is deemed responsible for the occurrence of migraine attacks and their frequency. Additionally, it seems that this phenomenon is even stronger when associ-

ated with MTHFR gene polymorphism, especially in Caucasians. Furthermore, MTHFR mutation causes mild elevation in homocysteine levels, which in turn causes vascular abnormalities and migraine, as well as trigemino-vascular activation[3]. Migraine susceptibility in MTHFR polymorphism could be explained by ischemia or hypoxia that evoke cerebrovascular incidents, or by increased platelet stickiness. However, increased homocysteine suppresses Na+-K+-ATPase activity in parietal, prefrontal and cingulated cortex of rats, offering the possibility of involvement of both neurons and glia[25]. Lastly, platelet activation and plasma coagulability are increased during migraine attacks, implying that genes affecting vascular endothelial function could play a significant role in cerebral blood flow changes detected in migraineurs[3].

Only two of our patients had evidence of previous small and asymptomatic cerebrovascular events in posterior circulation (brain stem ischemia) and there were periventricular WML in 11 patients (four of those in MA patients). Additionally, there was no evidence of occipital brain lesions in our patients, labeled as specific to patients with migraine in the CAMERA study[26]. Still, longitudinal studies are needed to assess whether these lesions have a tendency to progress and would have relevant (long-term) functional or clinical correlates. So far, epidemiologic data showed the risk of cerebrovascular events in migraineurs to be most prominent in the 45-55 age group (approximately twofold) and even more so if the patients are female, smokers and taking oral contraceptives (seven-fold)[27]. Additionally, Lee *et al.* report that this increased risk may be explained by a reduced number of circulating endothelial progenitor cells, a surrogate biologic marker of vascular function[28]. In our patient group, there were no signs of chronic inflammation as proven by laboratory testing, i.e. leukocyte count and CRP levels. CRP can be used as a measure of endothelial health or dysfunction promoted by chronic inflammation, facilitation of lipoprotein-macrophage interaction, all eventually inciting atherosclerosis[29].

Lastly, we would like to state pitfalls of our investigation: small sample size, lack of age, sex and risk factor matching, and lack of isolation of migraineurs with occipital WML or with homozygous mutation of procoagulant genes in comparison to matched controls.

Conclusion

In conclusion, based on the results of this study, we can say that our patients with episodic migraine were at a low risk of cerebrovascular disease, but had started to stratify from expected values of functional vascular parameters thus proving vascular remodeling. Therefore, ultrasound and general health monitoring are advisable so that active preventive measures against potential cerebrovascular disease can be initiated on time. Furthermore, prospective studies should be performed to evaluate the rate of progression of IMT, BSI, Ep, AI, βPWV and AC with respect to genetic polymorphism, thus determining their importance as markers of cerebrovascular and cardiovascular incidents.

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Sažetak

MIGRENA, KAROTIDNA KRUTOST I GENETSKI POLIMORFIZAM

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Nedavno se pojam migrene povezao s povećanom arterijskom krutosti, prokoagulantnim stanjem, povećanim brojem zamijećenih otšećenja bijele moždane tvari te moždanim udarom. Naš cilj je bio usporediti funkcijske karakteristike mjerenja u zajedničkoj karotidnoj arteriji kod bolesnika s migrenom i u kontrolnoj skupini osoba bez učestalih glavobolja. U ispitivanje je bilo uključeno šezdeset ispitanika (45 žena) s migrenom (srednje dobi 40,42±10,61 godina) te 45 ispitanika u kontrolnoj skupini (30 žena) koji u anamnezi nisu imali učestale glavobolje (srednje dobi 38,94±5,46 godina). Mjerenja su provedena putem korisničke potpore E-tracking na ultrazvučnom aparatu Alpha 10. Studentov t-test se koristio za statističku analizu te je alfa bila određena na <0,05. Sve ispitivane vrijednosti bile su lošije kod bolesnika s migrenom uključujući zadebljanu tuniku intime i medije, veći karotidni promjer i promjenu karotidnog promjera, kao i nekoliko indeksa arterijske krutosti. Uz to, bolesnici s migrenom imali su veću učestalost homozigotnih mutacija za prokoagulantne gene (MTHFR (C677T), PAI-1 and ACE I/D) nego što je očekivano. Kompjutorizirana tomografija i magnetska rezonancija mozga zabilježile su oštećenje bijele moždane tvari kod 11 bolesnika, od kojih je 4 imalo migrenu s aurom. Kako smo zabilježili da postoji povećana arterijska krutost te veća učestalost mutacija prokoagulantnih gena kod bolesnika s migrenom, predlažemo da se takve osobe ultrazvučno prate, a osobito one kod kojih već postoji oštećenje bijele moždane tvari, kako bi se na vrijeme mogle poduzeti aktivne specifične mjere prevencije nastanka moždanih krvožilnih bolesti.

Ključne riječi: *Migrenski poremećaji; Karotidna arterija, bolesti; Vaskularna krutost; Ateroskleroza; Moždani udar*