Journal of the Neurological Sciences 398 (2019) 204–209

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Paradoxical association between age and cerebrovascular reactivity in migraine: A cross-sectional study

Mi Ji Lee[a], Soohyun Cho[a], Sook-Young Woo[b], Chin-Sang Chung[a,*]

[a] Department of Neurology, Neuroscience Center, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea
[b] Biostatistics Team, Statistic and Data Center, Samsung Medical Center, Seoul, Republic of Korea

ARTICLE INFO

Keywords:
Migraine
Cerebrovascular reactivity
Endothelial dysfunction
Stroke
Young age

ABSTRACT

Background: Previous studies reported an increased risk of ischemic stroke in younger migraineurs. We aimed to investigate the association between age and cerebrovascular reactivity (CVR) to vasodilatory stimuli in cerebral arteries in patients with migraine and normal controls.

Methods: In this cross-sectional study, we recruited 248 patients with migraine and 105 normal controls at Samsung Medical Center between October 2015 and July 2018. CVR was measured interictally by using the transcranial Doppler breath-holding test. For the arteries which showed a correlation between age and CVR, we conducted univariable and multivariable linear regression analysis to assess the independent effect of age on CVR. The path analysis was performed to assess mediating effects of the age of onset and disease duration on the age-CVR association.

Results: Patients had reduced CVR in all tested arteries compared to normal controls. A correlation between age and CVR was present in the posterior cerebral artery (PCA) only in patients (Pearson's correlation coefficient = 0.160, $p = 0.012$). In patients, younger age was independently associated with lower CVR in the PCA (multivariable B = 0.003, 95% CI = 0.0002–0.005, $p = 0.033$ adjusted for sex, migraine subtype, and headache frequencies). The path analysis showed that the age of onset fully mediated the effect of age on PCA CVR, while longer disease duration negatively modified the effect of age of onset (p for interaction = 0.018).

Conclusions: In migraineurs, younger age was associated with CVR reduction in the PCA. Younger age of onset may be a hidden risk factor mediating the paradoxical association between age and CVR. This association might explain an increased risk of stroke in younger migraineurs.

1. Introduction

Migraine is the most common neurological disorder, affecting 10% to 15% of the adult population. Migraineurs are at increased risk for cardiovascular events, including ischemic stroke, hemorrhagic stroke, myocardial infarction, and cardiovascular mortality [1–6]. Several studies indicate that the risk of stroke is greater in younger migraineurs than in older ones [4,7,8]. However, it is still unknown why younger migraineurs are susceptible to stroke [9].

Cerebral endothelial dysfunction has been reported in patients with migraine in several studies [10–13]. Endothelium-dependent vasodilation measured by using cerebrovascular reactivity (CVR) to hypercapnic stimuli is impaired in the posterior circulation of migraineurs, where ischemic stroke occurs more frequently in migraineurs [11,14,15] [16]. Thus, reduced CVR might be a key link between migraine and ischemic stroke. Furthermore, reduced CVR precedes the development of white matter hyperintensity, which is also prevalent in patients with migraine [17]. Taken together, the increased risk of stroke in young patients with migraine may be associated with reduced CVR. In addition, there can be a hidden mediator which explains the paradoxical association between younger age and CVR.

In this study, we aimed to investigate the association between age and CVR in patients with migraine in comparison with normal controls (NCs). We also sought the biological explanation of this association. To test if age affects CVR directly or indirectly (i.e. fully or in part mediated by confounders), we established path models to investigate the mediating effects of age-related variables (i.e. age of onset and disease duration) on the association between age and CVR.

* Corresponding author at: Samsung Medical Center, Sungkyunkwan University School of Medicine, Neurology, 81 Irwon-Ro, Gangnam-Gu, 06531 Seoul, Republic of Korea.
E-mail address: cspaul@naver.com (C.-S. Chung).

https://doi.org/10.1016/j.jns.2019.01.039
Received 26 September 2018; Received in revised form 8 January 2019; Accepted 23 January 2019
Available online 24 January 2019
0022-510X/

2. Materials and methods

2.1. Subjects

We recruited consecutive first-visit Korean patients with migraine at the Samsung Medical Center headache clinic between October 2015 and March 2017.

Inclusion criteria were as follows: 1) adults aged 21–60 years; 2) diagnosis of 1.1 migraine without aura (MO) or 1.2 migraine with aura (MA), based on the International Classification of Headache Disorders (ICHD)-3 beta [18]; 3) absence of diagnosed vascular risk factors such as hypertension, diabetes, dyslipidemia, cardiac disease, stroke, and current or past history of smoking; and 4) no current use of any regular medications including migraine preventive agents. Patients with medication overuse were excluded.

Healthy subjects aged 21–60 years, who 1) had no history of migraine or any memorable headache in life, 2) were not diagnosed with hypertension, diabetes, dyslipidemia, cardiac disease, or stroke, and had no history of current or past smoking, and 3) were not on any regular medications, were recruited as NCs via posters and personal referrals between October 2015 and July 2018. The Samsung Medical Center Institutional Review Board approved this study. All patients and controls completed the informed consent form.

2.2. Clinical evaluation

Patients were evaluated using the structured headache questionnaire and a clinical interview. Age of onset, disease duration, monthly headache days, migraine subtype (MO vs MA), and chronicity (episodic vs chronic migraine) based on the ICHD-3 beta [18] were determined by two headache neurologists (M.J.L. and C-S.C.).

2.3. Evaluation of cerebral endothelium function

CVR was measured interictally using transcranial Doppler (TCD) with breath holding maneuver. Before the TCD examination, all patients and controls completed a screening questionnaire to evaluate their most recent headache attack. Patients were considered interictal if they did not have migraine headache or take acute abortive medication during the previous 48 h.

We used the Pioneer TC 8080 ultrasound device (Nicolet Vascular, Madison, WI, USA) for the TCD study. Two experienced neurophysiologists blinded to the patient information performed the TCD studies. The TCD examination included bilateral middle cerebral arteries (MCAs: measured at four different depths of 46–64 mm), bilateral posterior cerebral arteries (PCAs: measured at one depth of 64–70 mm), and the basilar artery (BA: measured at four different depths of 80–104 mm at the suboccipital window). The cerebral blood flow velocities (CBFVs) of each vessel represented the maximal mean flow velocities.

After identifying the depth and angle of the maximal flow velocities, patients underwent a breath-holding maneuver. Patients were instructed to breath normally before holding their breath and avoid a Valsalva maneuver during the examination. The CBFVs monitored during and after 30 s of breath holding confirmed that the depth and angle were unchanged. We recorded the flow velocity at the end of the breath holding (CBFV-BH). To determine the CVR, the breath-holding index was calculated as the percentage increase in the CBFV divided by the duration of breath holding (30 s) using the following equation: breath-holding index = [(CBFV-BH – baseline CBFV)/(baseline CBFV × 30 s)] × 100. Breath-holding tests were repeated up to three times according to patients' compliance.

2.4. Statistical analysis

For the bilateral arteries (MCAs and PCAs), the mean breath-holding index of both sides was calculated and used for the entire analyses. Breath-holding indices were square root-transformed to fit the normal distribution when used in the linear regression model.

We compared CVR between patients and NCs using the Student's *t*-test (univariable analysis) and the analysis of covariance (ANCOVA) to adjust covariates such as age and sex. Then, we performed the Pearson's correlation analysis to assess the relationship between age and CVR in patients and NCs, respectively. We conducted univariable and multivariable linear regression analyses adjusted for sex, monthly headache days, migraine subtype, and baseline mean flow velocities. Effects of age, age of onset and disease duration on CVR were determined through path analysis. We calculated effect sizes (i.e. standardized beta coefficients) and *p*-values of each variable and direct, indirect, and mediating effects between variables in each path model. We assessed the model fits using Chi-square (degree of freedom [DF]), goodness of fit (GFI), comparative fit index (CFI), and root mean square error of approximation (RMSEA). The interaction analysis was also performed to test synergistic effects between significant variables.

Statistical analyses were conducted by using commercially available SPSS version 18.0 software (SPSS Inc., Chicago, IL, USA). The Amos version 18.0 software (SPSS, Chicago, IL) was used for all path analyses using the maximum likelihood estimation. Differences with a two-tailed p-value < 0.05 were considered statistically significant. Data were presented as mean (SD), beta (95% confidence interval), or number (%).

3. Results

3.1. Study participants

During the study period, 248 patients with migraine (206 with MO and 42 with MA; 228 episodic and 20 chronic migraine) and 105 NCs were included in the study. The mean age was 42.4 ± 10.21 (range, 21–60) and 37.7 ± 11.23 (range, 21–60) years in patients and NCs, respectively (Table 1). Total 168 (81.6%), 33 (78.6%), and 61 (85.9%) subjects were females in MO, MA, and NC subjects, respectively. The mean numbers of headache days and moderate/severe headache days were 8.3 ± 7.46 and 4.6 ± 4.76 per month respectively in the patient group. The mean age of onset was 31.6 ± 12.37 years with a mean disease duration of 11.2 ± 9.29 years.

3.2. CVR comparison between patients and controls

Patients with migraine showed lower CVR in the examined arteries (Table 1; $p = 0.038$, 0.001, and 0.001 for MCAs, PCAs, and BA, respectively). These associations were significant after the Bonferroni correction for multiple comparisons.

Table 1
Demographics and CVR of patients and controls.

	Patients (n = 248)	Controls (n = 105)	P value	Adjusted P value[a]
Age	42.4 (10.21)	37.7 (11.23)	< 0.001	
Female sex	201 (81.0%)	86 (81.9%)	0.850	
MCA BHI, mean	1.11 (0.328)	1.19 (0.311)	0.038	0.042
PCA BHI, mean	1.13 (0.397)	1.29 (0.403)	0.001	< 0.001
BA BHI	0.94 (0.403)	1.09 (0.358)	0.001	< 0.001

Cerebrovascular reactivity was measured with breath-holding index (BHI) in each artery. In bilateral arteries, BHIs were averaged.
Abbreviations: MCA = middle cerebral artery, BHI = breath-holding index, PCA = posterior cerebral artery, BA = basilar artery.
[a] Adjusted for age and sex.

Table 2
Correlations between age and cerebrovascular reactivity of the posterior cerebral artery.

	Patients (n = 248)		Normal control (n = 105)	
	Pearson's correlation Coefficient	P value	Pearson's correlation coefficient	P value
MCA BHI, mean	0.026	0.689	−0.029	0.772
PCA BHI, mean	0.160	0.012*	0.017	0.867
BA BHI	0.076	0.233	0.038	0.677

Cerebrovascular reactivity was measured as breath-holding index (BHI) in each artery. In bilateral arteries, BHIs were averaged.
Abbreviations: MCA = middle cerebral artery, BHI = breath-holding index, PCA = posterior cerebral artery, BA = basilar artery.
* $p < 0.05$.

3.3. Correlation between age and CVR

The correlations between age and CVRs are summarized in Table 2. In patients, the mean PCA CVRs positively correlated with age, showing lower CVR in younger patients ($p = 0.012$). CVRs in the MCA and BA did not correlate with age in patients. In NCs, no correlation existed between age and CVR in all tested vessels.

3.4. Determinants of impairments in the CVR of the posterior cerebral artery

Univariate and multivariate linear regression analysis for the PCA CVR were tested in patients and NCs (Table 3). In patients with migraine, only the age (B = 0.003, 95% CI 0.0002 to 0.005, $p = 0.033$) showed an independent association with the PCA CVR. Sex, migraine subtype, monthly headache days, and baseline CBFV were not associated with the PCA CVR. When stratified by sex, the association between age and the PCA CVR remained significant in 201 female migraineurs (B = 0.003, 95% CI = 0.0001–0.005, $p = 0.043$ adjusted for MWA and headache days) but it was insignificant in 47 male migraineurs (B = 0.001, 95% CI = −0.003–0.005, $p = 0.747$ adjusted for MWA and headache days). In NCs, there was no significant predictor of the PCA CVR.

3.5. Path analysis

In patients with migraine, we tested the effects of age and age-related variables (i.e. age of onset and disease duration) on PCA CVR using the path analysis (Fig. 1). In Model 1, age had a direct effect on the PCA CVR (standardized beta coefficient = 0.197; Fig. 1A). Model 2 showed that age of onset had a greater effect size on the PCA CVR than age (standardized beta coefficient = 0.243; Fig. 1B). Disease duration was not independently associated with the PCA CVR when the effect of age was not taken into consideration (Model 3; Fig. 1C). When the age of onset was considered as a mediator between age and the PCA CVR (Model 4; Fig. 1D), it fully explained the effect of age on PCA CVR. Specifically, the total effect of age (standardized beta coefficient = 0.194) was smaller than the direct effect of age of onset (standardized beta coefficient = 0.204), suggesting that the indirect effect via age of onset (standardized beta coefficient = 0.133) was only significant to account for the effect of age (Table 4). When disease duration was regarded as a mediator (Model 5; Fig. 1E), it partially mediated the effect of age via inverse correlation (standardized beta coefficient = −0.169). Subsequently, the total effect of age (standardized beta = 0.194) was reduced compared with the direct effect (standardized beta = 0.235; Table 4). All the five models showed good fits (Fig. 1F). Estimated effect sizes of each path model are summarized in Table 4.

3.6. Interaction analysis

The interaction analysis showed that the disease duration modified the effect of age of onset on the PCA CVR with a negative coefficient (Beta = −0.0003, SE = 0.0003, p for interaction = 0.018).

4. Discussion

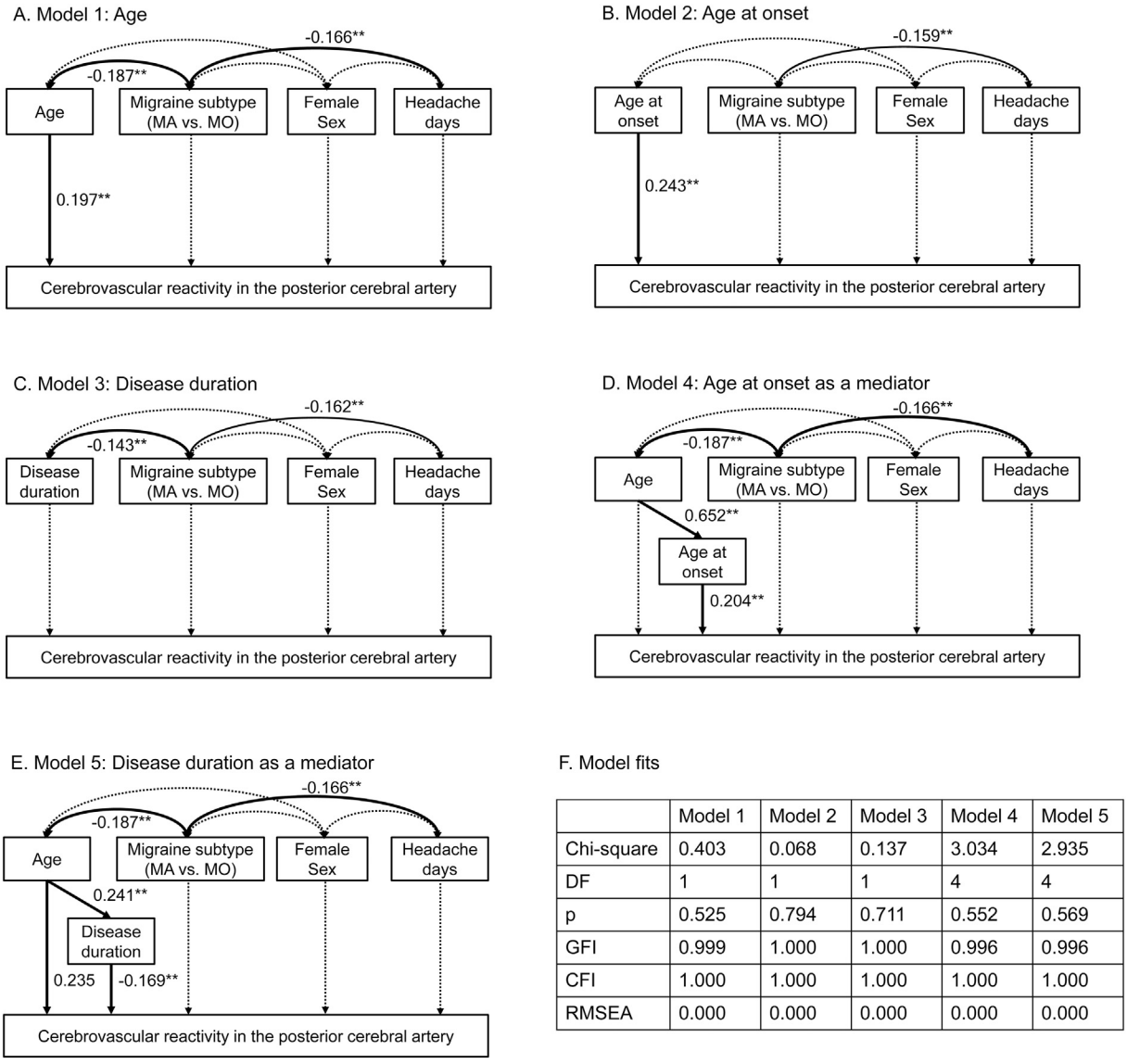
The major findings of this study are that 1) migraine is associated with reduced CVR compared to normal controls, 2) younger age is associated with reduced CVR of the PCA only in patients with migraine, 3) the association between age and the PCA CVR is fully mediated by the age of onset (i.e. younger age of onset fully explains reduced PCA CVR in younger migraineurs), and 4) longer disease duration negatively modified the effect of age of onset on the PCA CVR (i.e. when the age of onset is same, migraineurs who has longer disease duration will be currently old age and have less reduced PCA CVR than expected in younger migraineurs with shorter disease duration). Younger age of onset might be a hidden active risk factor of cerebral endothelial dysfunction in migraineurs and possibly contribute to increased risk of stroke in younger migraineurs. Disease duration might modify the effect of onset age, additionally explaining a lower stroke risk in older

Table 3
Factors associated with cerebrovascular reactivity in the posterior cerebral artery.

Normal control (n = 105)	Univariate		
	B	95% CI	P value
Age (y)	0.000	−0.003–0.003	0.961
Female sex	−0.061	−0.148–0.026	0.170

Migraine (n = 248)	Univariate			Multivariate		
	B	95% CI	P value	B	95% CI	P value
Age (y)	0.002	0.001–0.004	0.036	0.002	0.00001–0.004	0.038
Female sex	−0.018	−0.072–0.035	0.504	0.015	−0.039–0.070	0.582
Migraine with aura	0.012	−0.045–0.069	0.673	0.016	−0.042–0.075	0.580
Monthly headache days	−0.003	−0.006–0.000	0.051	−0.002	−0.006–0.001	0.104

The dependent variable was the square root-transformed mean breath-holding index of the bilateral posterior cerebral arteries.



F. Model fits

	Model 1	Model 2	Model 3	Model 4	Model 5
Chi-square	0.403	0.068	0.137	3.034	2.935
DF	1	1	1	4	4
p	0.525	0.794	0.711	0.552	0.569
GFI	0.999	1.000	1.000	0.996	0.996
CFI	1.000	1.000	1.000	1.000	1.000
RMSEA	0.000	0.000	0.000	0.000	0.000

Fig. 1. Path analysis.
Significant associations ($p < 0.05$) are indicated with bold arrows and standardized beta coefficients highlighted with asterisks. The dependent variable was the square root-transformed breath-holding index of the posterior cerebral artery of the more impaired side. (A) Age showed a significant effect on the PCA CVR. (B) Age of onset showed a greater effect on the PCA CVR. (C) Disease duration was not a significant factor when considered alone. (D) Age of onset fully mediated the effect of age on the PCA CVR. In this model, the direct effect of age became insignificant. (E) Disease duration negatively mediated the effect of age on the PCA CVR. (F) Model fits were excellent for each model.

Table 4
Summary of effect sizes.

	Independent variable	Dependent variable	Estimate	S.E.	Beta	P value	Direct effect	Indirect effect	Total effect
Model 1	Age	PCA CVR	0.003	0.001	0.197	0.003	0.197	NA	0.197
Model 2	Age of onset	PCA CVR	0.004	0.001	0.243	< 0.001	0.243	NA	0.243
Model 3	Disease duration	PCA CVR	−0.002	0.001	−0.118	0.078	−0.118	NA	−0.118
Model 4	Age	PCA CVR	0.001	0.001	0.061	0.48	0.061	0.133	0.194
	Age	Age of onset	0.773	0.060	0.652	< 0.001			
	Age of onset	PCA CVR	0.003	0.001	0.204	0.017			
Model 5	Age	PCA CVR	0.004	0.001	0.235	< 0.001	0.235	−0.001	0.194
	Age	Disease duration	0.222	0.059	0.241	< 0.001			
	Disease duration	PCA CVR	−0.003	0.001	−0.169	0.011			

The dependent variable was the square root-transformed breath-holding index of the posterior cerebral artery of the more impaired side.

migraineurs.

4.1. CVR, endothelial dysfunction and risk of stroke

This is the first study to evaluate the contribution of age-related factors on CVR in young migraineurs. Evidences suggested the presence of endothelial dysfunction and increased arterial stiffness in patients with migraine [10–13,19–21]. While there have been controversial reports on systemic endothelial dysfunction, cerebral endothelial dysfunction has been reported to be impaired in migraineurs even in the absence of the systemic endothelial dysfunction [11,22–24]. CVR to hypercapnic stimuli is commonly used to assess dynamic cerebral endothelial function because the endothelium is a major structure responsible for CO2-induced vasodilatory response [25].

Endothelium is a key regulator of vascular homeostasis, playing a direct role in the balance of tissue oxygen supply and metabolic demand via regulation of vessel tone and diameter [26]. Although endothelial dysfunction may not directly cause stroke, it can impair the detection and rapid vasodilatory response to hypoxia or hypercapnia [26,27]. Endothelial dysfunction can also impair the development of collateral channels in response to ischemia [28,29]. Therefore, endothelial dysfunction may increase the risk of ischemic stroke of any cause [30].

Heterogenous mechanisms may contribute to the increased risk of stroke in migraineurs. Genetic associations, cortical spreading depression, which leads to subclinical ischemia, coagulation abnormalities, and comorbidities such as active patent foramen ovale and arterial dissection have been proposed as mechanisms of stroke in migraineurs [3,7,31]. In addition, cardioembolic stroke is increased among elderly with a history of MA [32]. Although not a single cause explains the increased risk of stroke in migraineurs, endothelial dysfunction can predispose migraineurs to diverse types of ischemic stroke [25,33]. Reduced CVR may explain the lower ischemic threshold reported in experimental models of migraine, additively or synergistically with cortical excitability and spreading depolarization [34]. Our findings are in line with a recent study result that ischemic stroke in migraineurs has more “no-mismatch” patterns (i.e. smaller size of salvageable penumbra), suggesting a vulnerability to incorporate the penumbra into the ischemic core [35].

4.2. Age of onset: implications for the pathogenesis of migraine

Previous studies demonstrated that the risk of ischemic stroke is greater in young migraineurs [1,4,8,36]. However, recent studies showed conflicting results [6,37]. In this study, we assumed that age itself might not be a real risk factor. Rather, we determined the effects of age-related variables, i.e. the age of onset and disease duration, which were unmeasured in previous population-based studies.

In our study, younger age of onset was directly associated with a lower PCA CVR. It fully mediated the effect of age on PCA CVR. Two possible hypotheses may explain this association. First, endothelial dysfunction may increase the susceptibility to the development of migraine in earlier life. Second, endothelial dysfunction can also result from early-onset migraine, which leads to longer disease suffering and repeated aura attacks. In our study, however, MA subtype or headache frequency around the time of CVR measurement was not independently associated with PCA CVR, supporting the first hypothesis. However, our observational study is only hypothesis-generating. Yet it has not been documented whether endothelial dysfunction is involved in the pathogenesis of migraine [38]. The role of cerebral endothelial dysfunction in migraine pathogenesis should be investigated in future studies. In addition, our data did not explain the effect of MA, which increases the risk of stroke in migraine. Mechanisms other than CVR, such as coagulation abnormality, cortical spreading depression, and genetic susceptibility, should be considered in future studies on MA.

4.3. Impact of disease duration: implications for migraine progression

Our study showed that longer disease duration has a synergistic effect with age of onset on the PCA CVR. This finding might not be an aging phenomenon alone but a migraine-specific mechanism, considering that aging did not significantly impair CVR in NCs in our study. Our results suggest that endothelial dysfunction may progress in predisposed patients as migraine persists over a long time-period. Repeated migraine attacks, the use of acute migraine medication, and exaggerated vascular aging are possible hypotheses that explain the association between longer disease duration and worse CVR. Although controversial, deep white matter hyperintensity, which is associated with lower CVR, also progresses over time in migraineurs [17,39]. Longitudinal studies are needed to identify the progression of endothelial dysfunction and its consequences in patients with migraine.

4.4. Strengths and limitations

Our study has several strengths. This is the first study to suggest a possible hypothesis of age-specific risk of stroke patients with migraine, providing new insights into age of onset and disease duration. We included a relatively large number of unselected consecutive patients. The path analysis showed a good fit of the models.

Our study also has limitations. First, the study subjects were recruited from a single university hospital, which might not represent the general migraine population. Second, NCs were not recruited by the age- and sex-matching to patients. We statistically adjusted age and sex in group comparison to overcome this limitation. Third, our cross-sectional analysis does not reveal a cause-and-effect relationship. We did not provide separate information for migraine with vs. without aura and female vs. male migraineurs, which are well-known risk factors of increased risk of stroke in migraineurs. In addition, we only estimated headache frequency around the time of CVR measurement, which does not reflect a lifetime severity of migraine. Fourth, we excluded patients with vascular risk factors. Although it reduced the effect of possible confounders, our study participants may not be representative of overall population of patients with migraine. In addition, we did not perform screening tests of vascular risk factors to select patients and NCs. Fifth, we did not measure markers of systemic endothelial function. Thus, our findings cannot explain the overall vascular events (e.g. cardiac ischemic events) in migraineurs. Finally, we did not conduct end-tidal CO_2 monitoring after the breath-holding maneuver. Although breath holding is a widely accepted non-invasive method to study hypercapnia-induced vasodilation, a more sophisticated approach to deliver quantitative stimuli, such as prospective end-tidal CO_2 targeting, is desirable in confirmatory studies.

5. Conclusion

In this study, younger migraineurs had a greater CVR impairment in the PCA, mediated by younger age of onset. Longer disease duration negatively modified the effect of age of onset on the PCA CVR. Reduced CVR, an indirect measure of cerebral endothelial dysfunction, may predispose younger migraineurs to increased risk of stroke.

Financial support

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIP) (No. 2017R1A2B2009086 and 2017R1A2B4007254). Yuhan company and DongA ST supported the data management in part.

Conflict of interest/disclosures

None.

Acknowledgments

Authors thank Drs. Gyeong-Moon Kim, Sang-Won Seo, Kwang-Yeol Park, and Chang-seok Oh for their scientific comments on this study. We also thank Ms. Miran Jung for data management.

References

[1] M. Etminan, B. Takkouche, F.C. Isorna, A. Samii, Risk of ischaemic stroke in people with migraine: systematic review and meta-analysis of observational studies, BMJ 330 (2005) 63.
[2] T. Kurth, J.M. Gaziano, N.R. Cook, G. Logroscino, H.C. Diener, J.E. Buring, Migraine and risk of cardiovascular disease in women, JAMA 296 (2006) 283–291.
[3] M.J. Lee, C. Lee, C.S. Chung, The migraine-stroke connection, J. Stroke 18 (2016) 146–156.
[4] M. Schurks, P.M. Rist, M.E. Bigal, J.E. Buring, R.B. Lipton, T. Kurth, Migraine and cardiovascular disease: systematic review and meta-analysis, BMJ 339 (2009) b3914.
[5] S. Sacco, R. Ornello, P. Ripa, F. Pistoia, A. Carolei, Migraine and hemorrhagic stroke: a meta-analysis, Stroke 44 (2013) 3032–3038.
[6] T. Kurth, A.C. Winter, A.H. Eliassen, R. Dushkes, K.J. Mukamal, E.B. Rimm, et al., Migraine and risk of cardiovascular disease in women: prospective cohort study, BMJ 353 (2016) i2610.
[7] T. Kurth, H. Chabriat, M.G. Bousser, Migraine and stroke: a complex association with clinical implications, Lancet Neurol. 11 (2012) 92–100.
[8] K.P. Peng, Y.T. Chen, J.L. Fuh, C.H. Tang, S.J. Wang, Migraine and incidence of ischemic stroke: a nationwide population-based study, Cephalalgia 37 (4) (2017) 327–335.
[9] V.L. Feigin, C.M. Lawes, D.A. Bennett, C.S. Anderson, Stroke epidemiology: a review of population-based studies of incidence, prevalence, and case-fatality in the late 20th century, Lancet Neurol. 2 (2003) 43–53.
[10] S.T. Lee, K. Chu, K.H. Jung, D.H. Kim, E.H. Kim, V.N. Choe, et al., Decreased number and function of endothelial progenitor cells in patients with migraine, Neurology 70 (2008) 1510–1517.
[11] R. Rajan, D. Khurana, V. Lal, Interictal cerebral and systemic endothelial dysfunction in patients with migraine: a case-control study, J. Neurol. Neurosurg. Psychiatry 86 (2015) 1253–1257.
[12] X. Rodriguez-Osorio, T. Sobrino, D. Brea, F. Martinez, J. Castillo, R. Leira, Endothelial progenitor cells: a new key for endothelial dysfunction in migraine, Neurology 79 (2012) 474–479.
[13] G.E. Tietjen, N.A. Herial, L. White, C. Utley, J.M. Kosmyna, S.A. Khuder, Migraine and biomarkers of endothelial activation in young women, Stroke 40 (2009) 2977–2982.
[14] D. Perko, J. Pretnar-Oblak, M. Sabovic, B. Zvan, M. Zaletel, Cerebrovascular reactivity to l-arginine in the anterior and posterior cerebral circulation in migraine patients, Acta Neurol. Scand. 124 (2011) 269–274.
[15] V. Gonzalez-Quintanilla, M. Toriello, E. Palacio, M.A. Gonzalez-Gay, J. Castillo, S. Montes, et al., Systemic and cerebral endothelial dysfunction in chronic migraine. A case-control study with an active comparator, Cephalalgia 36 (2016) 552–560.
[16] M.C. Kruit, M.A. van Buchem, P.A. Hofman, J.T. Bakkers, G.M. Terwindt, M.D. Ferrari, et al., Migraine as a risk factor for subclinical brain lesions, JAMA 291 (2004) 427–434.
[17] K. Sam, A.P. Crawley, J. Conklin, J. Poublanc, O. Sobczyk, D.M. Mandell, et al., Development of White matter hyperintensity is preceded by reduced cerebrovascular reactivity, Ann. Neurol. 80 (2016) 277–285.
[18] S. Headache Classification Committee of the International Headache, The International Classification of Headache Disorders, 3rd edition (beta version), Cephalalgia, 33 (2013), pp. 629–808.
[19] S. Sacco, P. Ripa, D. Grassi, F. Pistoia, R. Ornello, A. Carolei, et al., Peripheral vascular dysfunction in migraine: a review, J. Headache Pain 14 (2013) 80.
[20] K. Ikeda, T. Hirayama, K. Iwamoto, T. Takazawa, Y. Kawase, Y. Yoshii, et al., Pulse wave velocity study in middle-aged migraineurs at low cardiovascular disease risk, Headache 51 (2011) 1239–1244.
[21] J.N. de Hoon, J.M. Willigers, J. Troost, H.A. Struijker-Boudier, L.M. van Bortel, Cranial and peripheral interictal vascular changes in migraine patients, Cephalalgia 23 (2003) 96–104.
[22] F.H. Vanmolkot, J.N. de Hoon, Endothelial function in migraine: a cross-sectional study, BMC Neurol. 10 (2010) 119.
[23] M. Fischer, C. Gaul, H. Shanib, D. Holle, L. Loacker, A. Griesmacher, et al., Markers of endothelial function in migraine patients: results from a bi-center prospective study, Cephalalgia 35 (2015) 877–885.
[24] J.S. Larsen, E.A. Skaug, U. Wisloff, O. Ellingsen, L.J. Stovner, M. Linde, et al., Migraine and endothelial function: the HUNT3 Study, Cephalalgia 36 (2016) 1341–1349.
[25] S.F. Stevenson, F.N. Doubal, K. Shuler, J.M. Wardlaw, A systematic review of dynamic cerebral and peripheral endothelial function in lacunar stroke versus controls, Stroke 41 (2010) e434–e442.
[26] J.E. Deanfield, J.P. Halcox, T.J. Rabelink, Endothelial function and dysfunction: testing and clinical relevance, Circulation 115 (2007) 1285–1295.
[27] S. Verma, M.R. Buchanan, T.J. Anderson, Endothelial function testing as a biomarker of vascular disease, Circulation 108 (2003) 2054–2059.
[28] S. Brugaletta, V. Martin-Yuste, T. Padro, L. Alvarez-Contreras, J. Gomez-Lara, H.M. Garcia-Garcia, et al., Endothelial and smooth muscle cells dysfunction distal to recanalized chronic total coronary occlusions and the relationship with the collateral connection grade, JACC Cardiovasc. Interv. 5 (2012) 170–178.
[29] L. Yin, V. Ohanyan, Y.F. Pung, A. Delucia, E. Bailey, M. Enrick, et al., Induction of vascular progenitor cells from endothelial cells stimulates coronary collateral growth, Circ. Res. 110 (2012) 241–252.
[30] M. Reinhard, G. Schwarzer, M. Briel, C. Altamura, P. Palazzo, A. King, et al., Cerebrovascular reactivity predicts stroke in high-grade carotid artery disease, Neurology 83 (2014) 1424–1431.
[31] V. De Giuli, M. Grassi, C. Lodigiani, R. Patella, M. Zedde, C. Gandolfo, et al., Association between migraine and cervical artery dissection: the Italian project on stroke in young adults, JAMA Neurol. 74 (2017) 512–518.
[32] X.M. Androulakis, N. Kodumuri, L.D. Giamberardino, W.D. Rosamond, R.F. Gottesman, E. Yim, et al., Ischemic stroke subtypes and migraine with visual aura in the ARIC study, Neurology 87 (2016) 2527–2532.
[33] K. Ogasawara, A. Ogawa, T. Yoshimoto, Cerebrovascular reactivity to acetazolamide and outcome in patients with symptomatic internal carotid or middle cerebral artery occlusion: a xenon-133 single-photon emission computed tomography study, Stroke 33 (2002) 1857–1862.
[34] K. Eikermann-Haerter, Spreading depolarization may link migraine and stroke, Headache 54 (2014) 1146–1157.
[35] A. Pezzini, G. Busto, M. Zedde, M. Gamba, A. Zini, L. Poli, et al., Vulnerability to infarction during cerebral ischemia in migraine sufferers, Stroke 49 (2018) 573–578.
[36] J.T. Spector, S.R. Kahn, M.R. Jones, M. Jayakumar, D. Dalal, S. Nazarian, Migraine headache and ischemic stroke risk: an updated meta-analysis, Am. J. Med. 123 (2010) 612–624.
[37] M. Lantz, J. Sieurin, A. Sjolander, E. Waldenlind, C. Sjostrand, K. Wirdefeldt, Migraine and risk of stroke: a national population-based twin study, Brain 140 (2017) 2653–2662.
[38] J.P. Dreier, J. Kleeberg, G. Petzold, J. Priller, O. Windmuller, H.D. Orzechowski, 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 125 (2002) 102–112.
[39] I.H. Palm-Meinders, H. Koppen, G.M. Terwindt, L.J. Launer, J. Konishi, J.M. Moonen, et al., Structural brain changes in migraine, JAMA 308 (2012) 1889–1897.