HEADACHE & FACIAL PAIN SECTION

Original Research Article
Duration of Migraine Is Associated with Cardiac Diastolic Dysfunction

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Abstract

Objective. **Migraine is a common type of headache
accompanied or preceded by signs of central and
autonomic nervous system dysfunction. Autonomic
dysfunction has been suggested to be a potential
contributor to impaired cardiac diastolic function.
Cardiac diastolic dysfunction is characterized by
normal left ventricular contractility but impaired
ventricular relaxation. It is a growing clinical entity
implicated in morbidity and mortality due to heart
failure. The aim of this study was to determine if any
relationship exists between migraine and diasto-
lic dysfunction.**

Methods. **Migraineurs (N = 55), and age- and sex-
matched healthy controls (N = 52) were evaluated
by conventional and tissue Doppler echocardio-
graphy. Migraine-related disability in the previous 3
months was assessed by the Migraine Disability
Assessment questionnaire. Baseline characteris-
tics were recorded, and blood samples were
collected.**

Results. **The groups did not differ in terms of sex
or age. The migraine group had higher lipid levels
compared with the control group. Diastolic dys-
function was significantly higher among the 30
migraineurs with a history of migraine of 10 years
or more compared with the 25 migraineurs with a
history of less than 10 years, (P = 0.003). In logistic
regression analysis, migraine duration was shown
to be an independent predictor of diastolic dys-
function (odds ratio 1.130, 95% confidence interval,
P = 0.044).**

Conclusions. **Cardiac diastolic dysfunction is asso-
ciated with migraine. A long history of migraine is an
independent predictor of diastolic dysfunction.**

Key Words. **Headache; Risk Factor; Hyperlipi-
demia; Quality of Life; Burden of Disease**

Introduction

A headache of usually unilateral and throbbing type, lasting 4–72 hours, accompanied by nausea, vomiting, photophobia, and phonophobia, worsening with physical activity, and with aura (reported in 20% patients) not attributed to another disorder is called migraine [1]. Migraine is a common primary headache with a prevalence of 15–17% in females and 6% in males [2]. It may be triggered by a variety of environmental factors all thought to activate meningeal nociceptors, and is further associated with a local neurogenic inflammatory response [3]. Moreover, skipping a meal, stress, and sleep disturbances are thought to activate the hypothalamus, perifornical areas, and stria terminalis, which converge on the superior salivatory nucleus and parasympathetic sphenopalatine ganglion, leading to increased sensitivity of the meningeal nociceptors [4]. Brainstem activation is observed during a migraine attack, mainly in the dorsal pons [5]. Autonomic nervous system (ANS) symptoms characterized by nausea, vomiting, flushing, pallor, diarrhea, diaphoresis, or polyuria may accompany acute migraine attacks due to activation of the hypothalamus and brainstem autonomic nuclei [6]. Autonomic dysfunction in migraine is shown by many studies based on sudomotor axon reflex, changes in blood pressure measurements and heart rate variability during resting and active standing, deep breathing, the Valsalva maneuver, and the tilt-table test [7,8]. Results of pupillometry or sweating tests are controversial; they report either sympathetic hypofunction or hyperfunction in migraine [9,10]. However, there is overall agreement that an autonomic dysregulation is present in migraine [8].

ANS regulates heart rate and cardiac contractility by dual effects of the sympathetic and parasympathetic nerves. Comprehensive electrocardiographic analyses have provided more information in terms of the detection of abnormalities in heart rate variability related to the ANS dysfunction in migraineurs [11].

Cardiac diastolic dysfunction is characterized by normal left ventricular contractility but impaired ventricular relaxation [12]. Numerous conditions such as diabetes mellitus, obesity, hypertension, advanced age, cardiomyopathy, constrictive pericarditis, coronary heart diseases, and sleep apnea are associated with diastolic dysfunction [13]. To the best of our knowledge, the relationship between migraine and diastolic dysfunction has not been studied. In this age- and sex-matched, case-control study, we aimed to determine if any relationship exists between migraine and diastolic dysfunction.

Methods

The subjects enrolled had an adequate level of understanding of the questionnaires, were aged between 18 and 60 years, and had given written consent. The study was approved by the Local Ethical Committee. Migraine was diagnosed by two neurologists according to The International Classification of Headache Disorders: 2nd edition criteria [1]. Subjects who were older than 60 years;

who had a history of diabetes, renal disease, cardiomyopathy, coronary heart disease, valvular heart disease, hypertension, or obesity; or were taking any migraine prophylactic medications such as antihypertensives were excluded due to their effects on cardiac diastolic function. The control group consisted of age- and sex-matched healthy volunteers, who were admitted to the neurology outpatient clinic due to symptoms unrelated to headache, syncope, stroke, or cardiovascular disease. A detailed form that included demographic characteristics, the diagnosis, clinical characteristics, and Migraine Disability Assessment questionnaires (MIDAS) [14] were assessed by the neurologists. MIDAS is a quickly applied, 5-item questionnaire that evaluates the disability and impact of migraine headaches on daily living in the past 3-month period. All subjects gave baseline blood samples.

Conventional and tissue Doppler echocardiography were performed by cardiologists who were blind to the clinical status of the subjects. The echocardiographic assessments were performed during headache-free intervals in migraineurs. Cardiac diastolic dysfunction is characterized by normal left ventricular contractility but impaired ventricular relaxation [12]. There are four basic echocardiographic patterns of diastolic dysfunction graded from I to IV in which the mildest form is grade I. Grade II diastolic dysfunction is called pseudonormal filling dynamics and is considered a moderate diastolic dysfunction. Grade III and IV diastolic dysfunctions represent restrictive filling dynamics [15,16]. In the present study, a Vingmed System echocardiography unit (Vivid 7 Pro, General Electric, Horten, Norway) was used. A sample volume of 2 mm was placed between the mitral leaflet tips, E and A velocities were measured, and the E/A ratio was calculated. Using continuous-wave Doppler tracings, isovolumetric contraction time (ICT), isovolumetric relaxation time (IVRT), and aortic ejection time (ET) were measured. The Doppler-derived myocardial performance index (MPI) (also denoted as the Tei-index) is an index of combined cardiac systolic and diastolic function [17]. It is defined as the sum of ICT and IVRT divided by the ET. Tissue Doppler was employed to measure systolic (S) and diastolic (E′ and A′) mitral annular velocities.

Statistical Analysis

To show a statistically significant difference between migraine and diastolic dysfunction, the required sample size of a minimum of 32 volunteers in each group was calculated (Alpha = 0.05 and Beta = 0.20 [Power 80%]). The data were analyzed with the PASW Statistics version 18 software package (SPSS Hong Kong Headquarters, Quarry Bay, Hong Kong). The normal distribution of variables was verified by the Kolmogorov–Smirnov test. Spearman's rho correlation was used when one or both of the variables were not normally distributed. Comparisons between the groups were made with either Student's t-test or the Mann–Whitney U-test. A chi-square (χ^2) test was used to investigate whether distributions of categorical variables differed within the groups. Logistic regression analyses were conducted according to body mass index (BMI), total cholesterol, and history of migraine duration.

Table 1 Comparisons of baseline characteristics and blood values between the groups

	Migraine (N = 55)	Control (N = 52)	P Value
Sex (number of female/male)	37/15	40/15	0.513
Age (years)	35.87 ± 9.69	35.15 ± 9.12	0.694
Body mass index (kg/m^2)	24.47 ± 3.81	23.46 ± 4.16	0.063
Blood glucose (mg/dL)	91.37 ± 9.33	97.42 ± 23.78	0.581
Hemoglobin (g/dL)	14.07 ± 1.72	13.84 ± 1.39	0.457
Mean platelet volume (fL)	8.63 ± 1.09	8.81 ± 1.19	0.425
C-reactive protein (mg/L)	2.00 ± 2.02	4.01 ± 5.66	0.473
Total cholesterol (mg/dL)	212.49 ± 45.98	179.58 ± 39.04	*0.001
LDL (mg/dL)	133.33 ± 38.56	102.46 ± 33.91	*<0.001
HDL (mg/dL)	56.32 ± 16.59	52.89 ± 17.17	0.152
Triglyceride (mg/dL)	117.76 ± 68.12	128.83 ± 65.66	0.292

* $P < 0.05$.
HDL = high-density lipoprotein; LDL = low-density lipoprotein.
Data are shown as mean ± standard deviation for continuous variables.

Data are shown as mean ± standard deviation for continuous variables and absolute numbers (%) for dichotomous variables. P values less than 0.05 were considered statistically significant.

Results

In this study, 107 subjects were included. Demographic characteristics, and hematological and biochemical parameters of the migraineurs (N = 55) and healthy controls (N = 52) are displayed in Table 1. Age, sex, and BMI did not differ between the groups (all $P > 0.05$). Mean total cholesterol and low-density lipoprotein (LDL)-cholesterol values were higher in the migraineurs compared with the control group as well (212.49 ± 45.98 vs 179.58 ± 39.04, $P = 0.001$ and 133.33 ± 38.56 vs 102.46 ± 33.91, $P < 0.001$, respectively). Blood glucose, C-reactive protein, hemogram, and MPV values did not differ between the groups.

According to the ICHD-II criteria, among the 55 migraineurs, 23 were diagnosed with episodic migraine with aura, 27 with episodic migraine without aura, and 5 with chronic migraine. The frequency of migraine attacks in episodic migraine and chronic migraine patients were

4.22 ± 3.17 and 17.60 ± 2.30 days/month, respectively. On echocardiographic examinations, atrial and ventricular dimensions were found to be within normal limits. We did not observe any echocardiographic findings of concentric hypertrophy, left atrial enlargement, etc., but two of the migraine with aura patients had patent foramen ovale. Diastolic dysfunction was found in 23.6% of the migraine group (eight had Grade II and five had Grade I) and 3.8% of the control group (one had Grade I and the other had Grade II diastolic dysfunction); the difference between the groups was statistically significant ($P < 0.05$) (Table 2). Among the 13 migraineurs with diastolic dysfunction, 5 had episodic migraine with aura. The mean MPI scores were also significantly higher in migraineurs (0.41 ± 0.10) compared with the control group (0.35 ± 0.05) ($P = 0.014$) (Table 2). In order to assess the effect of migraine burden on diastolic dysfunction, we divided the patients into two groups according to history of migraine of less than 10 years or of 10 years or more. The mean migraine durations of the migraine groups, 10 years or more vs less than 10 years, were 16.60 ± 5.90 and 4.80 ± 2.22 years, respectively. The difference was statistically significant ($t = 9.440$, $P < 0.001$). Migraine patients with a history of 10 years or more were significantly more prone to have diastolic dysfunction as well

Table 2 Continuous wave Doppler-derived parameters and comparisons between the groups

	Migraine (N = 55)	Control (N = 52)	P Value
Diastolic dysfunction, N (%)	13 (23.6%)	2 (3.8%)	*0.004
AET (milliseconds)	300.44 ± 30.43	325.58 ± 33.46	*<0.001
IVRT (milliseconds)	73.27 ± 13.41	70.69 ± 9.91	0.317
ICT (milliseconds)	47.49 ± 15.15	43.50 ± 9.25	0.463
MPI	0.41 ± 0.10	0.35 ± 0.05	*0.010

* $P < 0.05$.
AET = aortic ejection time; IVRT = isovolumetric relaxation time; ICT = isovolumetric contraction time; MPI = myocardial performance index; N = number of patients.

Table 3 The correlation between migraine duration and diastolic dysfunction

Migraine Duration and Number of Patients (N)	≥10 Year (N = 30)	<10 Year (N = 25)	P Value
Diastolic dysfunction (N)	12	1	*0.003

* $P < 0.05$.

($P = 0.003$) (Table 3). There was no significant relationship between MIDAS groups and presence of diastolic dysfunction (Table 4). In the logistic regression analysis, the relationship between diastolic dysfunction and migraine duration was independent of BMI and total cholesterol levels ($P = 0.044$, odds ratio = 1.130, 95% confidence interval = 1.003–1.272) (Table 5).

Discussion

Migraine is associated with ANS symptoms and signs. Diastolic dysfunction is a chronic process associated with autonomic neuropathy or dysfunction [18,19]. To our knowledge, this is the first study designed to assess the relationship between migraine and cardiac diastolic func-

Table 4 Distribution of the migraineurs' MIDAS grades and diastolic dysfunction

MIDAS (N)	Number of Migraineurs *with* Diastolic Dysfunction	Number of Migraineurs *without* Diastolic Dysfunction
Grade 1	2	5
Grade 2	4	6
Grade 3	4	13
Grade 4	3	18

MIDAS = Migraine Disability Assessment Questionnaire; MIDAS Grade 1 = little or no disability; Grade 2 = mild disability; Grade 3 = moderate disability; Grade 4 = severe disability.

Table 5 Results of multivariate analysis of migraine and diastolic dysfunction (logistic regression model without interaction)

	OR (95% CI)	P Value
Migraine duration (year)	1.130 (1.003–1.272)	*0.044
BMI (kg/m^2)	1.157 (0.928–1.444)	0.195
Total cholesterol (mg/dL)	1.015 (0.997–1.033)	0.097

* $P < 0.05$.
BMI = body mass index.
Odds ratio (OR) is statistically significant if confidence interval (CI) does not include 1.

tion. Here, we report that the prevalence of diastolic dysfunction was significantly higher in migraineurs compared with healthy controls. Compared with the healthy controls, lipid levels were also increased in migraineurs. In the logistic regression analysis, a migraine history of 10 years or more was found to be an independent predictor for developing diastolic dysfunction.

There is growing evidence of an association between migraine and an increased risk for ischemic stroke and other cardiovascular events [20]. Although migraine is reported to be a risk factor for stroke and coronary heart disease, the risk is low in the general population, and it is important to identify which migraineurs will develop these events [21]. The identification of comorbidities in migraineurs is essential in our understanding of the pathophysiology of migraine and assessing the therapeutic options [22]. In a case-control study, the aortic stiffness measured by aortic pulse wave velocity was found to be higher in young migraineurs without significant cardiovascular risk factors [23]. In another study investigating the vascular dysfunction associated with migraine, migraine with aura patients and healthy controls were assessed by carotid intima-media thickness, and endothelial function by using peripheral arterial tonometry [24]. Although the peripheral endothelial function was not impaired, arterial stiffness was found to be greater in migraineurs [24]. The authors concluded that these findings might contribute to the increased stroke risk in migraineurs [24]. Cardiac diastolic dysfunction with preserved ejection fraction is a growing clinical entity implicated in morbidity and mortality due to heart failure [25]. The role of specific treatments for diastolic dysfunction per se is unclear. Therapy is directed to reduce associated risk factors such as obesity, hypertension, and high blood glucose levels. In diabetic patients, decreased myocardial 123I-metaiodobenzylguanidine uptake was shown to be associated with diastolic dysfunction [26]. Recently, in a rat model of insulin resistance with hyperglycemia, sympathetic nervous dysregulation was proposed in the development of diastolic dysfunction in the absence of systolic left ventricular dysfunction as well [27]. However, our migraine patients did not have a history of diabetes, and there was no significant difference in glucose levels compared with the control group. Age is an important factor that influences the prevalence of diastolic dysfunction [28]; thus, we limited our study population to age 60 and under. Hypertension, diabetes, and obesity are implicated in the development of symptomatic myocardial dysfunction in individuals with normal coronary arteries [29]. In our study, we also did not include subjects with a history of hypertension, coronary heart disease, or arrhythmia. Another risk factor for diastolic dysfunction is obesity [30]. Interestingly, migraine is also associated with obesity [31]. It is reported that increased inflammatory mediators, vascular hyperreactivity, adipocytokines, and sympathetic tone are associated with an increase in headache frequency [31]. In our study, migraine patients' BMI values were less than 30 kg/m^2, and there were no significant differences between the migraineurs and the controls. Dyslipidemia, a component of metabolic syndrome, has also been

associated with migraine [32]. In our study, similar to the literature, our migraine group had significantly higher total and LDL cholesterol levels compared with the controls.

In order to support evidence for migraine's impact over the patient's lifetime, we divided our patients into two groups according to migraine history of less than 10 years or of 10 years or more. Diastolic dysfunction was significantly higher in the migraineurs with a history of 10 years or more. Furthermore, in the logistic regression analysis, migraine duration was shown to be an independent predictor of diastolic dysfunction. MIDAS assesses migraine-related disability in the past 3 months. In our study, we did not find a significant relationship between MIDAS scores and diastolic dysfunction. However, being a university hospital, the migraine patients who were referred to us had higher MIDAS scores. Only one patient, reporting a history of migraine of less than 10 years and MIDAS grade 4, had diastolic dysfunction. These findings may further strengthen our hypothesis that a long migraine history may cumulatively contribute to the susceptibility of the migraine sufferers to develop diastolic dysfunction. Still, we think that large-scale prospective studies would provide greater statistical power. In future, new studies investigating the effect of migraine prophylactic medications on diastolic dysfunction might further clarify several issues.

Limitations of the Study

In this study, we did not include tests to evaluate autonomic dysfunction such as heart rate variability, changes in blood pressure measurements during resting and active standing, deep breathing, the Valsalva maneuver, the tilt-table test, sudomotor axon reflex, or sweating tests in our study population. However, based on previous studies, there is overall agreement that an autonomic dysregulation is present in migraine. Our study population consisted of 13 migraineurs with diastolic dysfunction. Large-scale prospective studies are needed to obtain further information if cardiac diastolic dysfunction is a cause or consequence, or simply an epiphenomenon of a persistent autonomic dysregulatory process that is promoted by migraine or is a constitutional factor that promotes persistent migraine.

Conclusion

Migraine has a negative impact on general well-being. Cardiac diastolic dysfunction might represent a footprint of autonomic imbalance in migraineurs with a more than 10-year history. Echocardiography is a practical and noninvasive additional method to define the risk of cardiac disease in patients with a long history of migraine.

Acknowledgments

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