A higher prevalence of migraine in patients with cardiac syndrome x compared to patients with cardiovascular disease and healthy control

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Research Article

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Abstract

Background

Cardiac syndrome X(CSX), is a type of ischemic heart disease, that is characterized by angina-like chest pain, without any evidence of significant coronary vascular abnormalities. Some evidence has revealed a significant association between migraines, particularly migraine with aura, with cardiovascular diseases (CVDs). In this case-control study, the prevalence of migraine and the role associated risk factors were compared between the patients with CSX, CVD, and healthy control individuals.

Methods

The patients with CSX (n = 70), CAD (n = 70), and healthy individuals (n = 70) were enrolled in this study. For each enrolled subject, demographic and clinical data were collected. The prevalence of migraine and associated risk factors were determined in each group.

Results

The prevalence of migraine in the CSX group (40%) was significantly higher compared to those of CVD (24%) (p = 0.047) and healthy controls groups (21%) (p = 0.017). In the control subjects, but not in the CVD and CSX groups, the female gender was a significant risk factor for migraine. The prevalence of migraine with aura was significantly higher in patients with CSX (20%) compared to patients with CVD (8%) (p = 0.045). The family history of migraine was significantly higher in patients with CSX (57.0%) compared to patients with CVD (31.0%) and the control group (35.7%) (p = 0.004).

Conclusions

The results of this study revealed a significantly higher prevalence of migraine in patients with CSX. The findings also showed a familial aggregation of migraine in the patients with CSX, suggesting a role of genetic factors in predisposing CSX patients to migraine.

Introduction

Migraine is a prevalent debilitating neurovascular disorder, affecting more than 1 billion people globally. Migraine attack usually consists of four different phases including prodrome, aura, headache, and postdrome phases. The headache phase is associated with several symptoms including photophobia, nausea, vomiting, and fatigue which disturb daily activities and reduce the quality of life of migraineurs (1). The burden of migraine, however, is not restricted to the headache phase and patients may suffer from several symptoms such as hypersensitivity, phonophobia, photophobia, and vestibular disorders in the interictal phase, the phase between migraine attacks (2, 3). Although the exact molecular and cellular

mechanisms underlying migraine pathogenesis are not completely understood, several reasonable explanations have been proposed. At the molecular level, the critical role of calcitonin-gene-related peptides (CGRPs) in the pathogenesis of migraine has been documented and CGRP receptor antagonists and monoclonal antibodies against CGRP or its receptors have revealed substantial efficacy in the treatment of migraine attacks (4). In addition to CGRP receptors, numerous studies have indicated the high efficacy and safety of 5-HT_{1F} receptor agonists such as Lasmiditan in the treatment of migraine (5). At the cellular level, prior studies have described the role of mitochondrial dysfunction in the pathogenesis of migraine. The correlation of migraine with mitochondrial genome polymorphisms and biomarkers of oxidative stress are amongst the evidence that indicates the possible contribution of mitochondrial dysfunction to migraine pathology (6). A wide range of risk factors has been identified for migraine. Multiple investigations have concluded the important role of genetic factors in migraine development including familial aggregation of migraine, a high concordance rate of migraine in monozygotic twins, and the association between several genetic polymorphisms with the increased risk of migraine (7). The association of migraine with demographic characteristics such as sex and age have also been described. Women are at a higher risk of migraine development than men which could be related to differences in sex hormone fluctuations or psychological factors. Although migraine can occur at any age, their prevalence rate exhibits an age-dependent manner, increases from early life to middle age, and then gradually declines (8). Clinical and experimental data have revealed the association of migraine with numerous comorbidities including cardiovascular, psychiatric, neurologic, as well as inflammatory disorders. The association with these comorbidities complicates the diagnosis, increases the risk of progression to chronic migraine, limits treatment options, and lowers the quality of life of migraineurs. Therefore, understanding migraine comorbidities is very important because it can help to determine possible common or overlapping pathological mechanisms of diseases and can lead to the development of new diagnostic and therapeutic strategies (9). A growing body of evidence has revealed a significant association between migraines, particularly migraine with aura, with cardiovascular diseases (CVDs) such as ischemic heart disease, myocardial infarction, angina, and arrhythmia (10). Because alteration in blood flow is involved in the pathogenesis of migraines and CVDs, this association can be described by inadequate blood flow to the heart or brain due to genetic factors, endothelial dysfunction, and coagulation abnormalities (11). Cardiac syndrome X (CSX), is a type of ischemic heart disease, that is characterized by angina-like chest pain, and ST segment depression during exercise, without any evidence of significant coronary vascular abnormalities at coronary angiography (12). CSX is more prevalent in postmenopausal women. Although the potential risk factors for CSX have not yet been fully elucidated, several mechanisms may involve including microvascular abnormalities (13) and mitochondrial dysfunction. Because these abnormalities have been proposed in the etiology of migraine, we have suggested a link between migraine and CSX in our previous study (14). In this study, we have extended our previous study to a larger population of CSX patients. Furthermore, the association of several risk factors, notably sex and familial aggregation are evaluated.

Patients and Methods

Patient population

This case-control study was performed from March to October 2021. Adult patients, aged between 18–70 years old, with a history of angina chest pain, abnormal cardiac tests including exercise test, SPECT MPI, and normal angiography results were classified in the CSX group (n = 70), and if showed more than 50% coronary artery involvement in angiography were categorized in CAD group (n = 70). Seventy healthy individuals without any history of previous illness, with a normal ECG, were randomly selected as the control group. Severe valvular heart diseases, previous coronary artery diseases, diabetes mellitus, congenital heart disease, hypertension, and cardiomyopathy were exclusion criteria for the control and CSX groups. The patients with a history of severe anxiety, depression, and headache that unrelated to migraine were excluded from the study. The study protocol was approved by the Ethics Committee of Bandar-Abbas University of Medical Sciences. The protocol was explained to the patients and written informed consent was obtained from all the patients. For each enrolled subject, demographic and clinical data were collected. The presence of migraine in the subjects and their parents, siblings, and children was evaluated using a Migraine Screen Questionnaire (MS-Q) based on the International Headache Society (IHS) criteria (15).

Statistical analysis:

SPSS software (Version 15) was used to analyze the data. Continuous variables were presented as mean ± standard deviation (SD) and categorical variables were presented as frequency. The Chi-square test was used to compare qualitative variables between groups. Mann-Whitney and One-way ANOVA tests were used to compare continuous variables between groups. Binary logistic regression was used to determine the significant associations between the risk factors and migraine. A p-value less than 0.05 was considered a significant difference.

Results

Table 1 shows various clinical and demographic characteristics of the healthy patients enrolled in this study. The mean age and BMI were not significantly different among the studied groups. The prevalence of migraine in all studied subjects was 34.3% (n = 60) of which 61.7% of the subjects (n = 37) were female and 38.3% were male (n = 23) (p = 0.035). The prevalence of migraine in the CSX group was 40% which was significantly higher compared to those of CVD (24%) (p = 0.047) and healthy controls groups (21%) (p = 0.017). In the control subjects with migraine, the number of female subjects (n = 13; 86.7%) was significantly higher than males with migraine (n = 2; 13.3%) (p = 0.002), however, in the CVD and CSX groups the frequencies of males and females with migraine were not significantly different. The prevalence of migraine with aura was significantly higher in patients with CSX (20%) compared to patients with CVD (8%) (p = 0.045). Family history of migraine was observed in 40(57.0%) patients with CXS which was significantly higher compared to patients with CVD (31.0%) and the control group (35.7%) (p = 0.004). Table 2 reveals and compares various characteristics between patients with (n = 60) and without migraine(n = 150). No significant difference was observed in the mean age and BMI of the

subjects with and without migraine. Significant higher percentages of family history of migraine and female sex were observed in the patients with migraine compared to those in subjects without migraine. The prevalence of obesity and smoking was not significantly different among subjects with and without migraine. The results of logistic regression models are summarized in Table 3. The data showed that family history was the only significant predictor of migraine in all cases (OR 4.88, 95% CI: 2.56–9.30; $p < 0.0001$). In the control group, predictors of migraine included female sex (OR 7.25, 95% CI: 1.43–36.70; $p < 0.017$) and family history (OR 4.08, 95% CI: 1.11–14.95; $p < 0.034$). Furthermore, the data showed that family history was the only predictor of migraine in the CVD (OR 7.00, 95% CI: 2.11–23.13; $p < 0.01$) and CSX group none of the evaluated factors were a predictor of migraine.

Table 1
Comparison of various characteristics between patients and control group

Variables	Control(a)	CVD(b)	CSX(c)	p values		
				a vs b	a vs c	b vs c
Age (years); (mean ± SD)	50.2 ± 10.0	51.2 ± 9.0	51.5 ± 8.0	0.529	0.410	0.846
BMI (kg/m^2); (mean ± SD)	25.0 ± 3.9	26.2 ± 4.4	26.5 ± 5.3	0.0.08	0.120	0.846
Obesity (BMI ≥ 30); n (%)	6(8.6)	12(17.1)	16(22.9)	0.130	0.02	0.398
Female Sex; n (%)	36(51.4)	35(50.0)	36(51.4)	0.866	0.866	1.0
Smoking; n (%)	7(10)	35(50.0)	36(51.4)	< 0.001	< 0.001	0.866
Migraine; n (%)	15(21.0)	17(24.0)	28(40)	0.687	0.017	0.047
Migraine with aura; n (%)	9(13)	6(8)	14(20)	0.412	0.254	0.045
Family history; n (%)	25(35.7)	22(31.0)	40(57.0)	0.591	0.011	0.002
Abdominal pain in their children; n (%)	8(11.4)	8(11.4)	15(21.4)	0.919	0.137	0.172

BMI: Body Mass Index, CVD: Cardiovascular disease, CSX: Cardiac syndrome X, n: number

Table 2

Comparison of various characteristics between subjects with and without migraine

Variables	Subjects with migraine (n = 60)	Subjects without migraine (n = 150)	p values
Age (years); (mean ± SD)	50.3 ± 8.7	51.3 ± 9.2	0.508
BMI (kg/m^2); (mean ± SD)	25.8 ± 4.0	25.9 ± 4.8	0.989
Obesity (BMI ≥ 30); n (%)	7(11.7)	27(18.0)	0.320
Female Sex; n (%)	37(61.6)	70(46.6)	0.035
Smoking; n (%)	25(41.6)	53(35.3)	0.241
Family history; n (%)	41(68.3)	46(30.7)	P < 0.001

BMI: Body Mass Index, n: number

Table 3
Predictors of migraine in the logistic regression model

Group	Predictors	OR	CI (95%)	P value
All case	**Family history**			
	YES	4.879	2.56–9.30	< 0.0001
	NO	-	-	-
Control	**sex**			
	Female	7.254	1.43–36.70	0.017
	Male	-	-	-
	Family history			
	YES	4.080	1.11–14.95	0.034
	NO	-	-	-
CVD	**Family history**			
	YES	7.000	2.12–23.15	0.001
	NO	-	-	-
CSX	**Family history**			
	YES	2.750	0.99–7.62	0.052
	NO	-	-	-

CVD: Cardiovascular disease, CSX: Cardiac syndrome X.

Discussion

A growing number of studies have revealed mitochondrial deficits in the brain and muscles of migraineurs (6). Mitochondrial dysfunction is also considered a feature of patients with CSX(Hsiu-Bao); therefore, it is speculated that this common feature, mitochondrial dysfunction, can lead to comorbidity between migraine and CSX. The results of the present study displayed a higher prevalence of migraine in the patients with CSX compared to healthy control and the patients with CVD. Furthermore, a higher frequency of family history of migraine was observed in the patients with CSX compared to CVD and healthy control, suggesting a possible role of genetic factors in predisposing CSX patients to migraine. Several studies have indicated comorbidity between migraine, particularly migraine with aura, and CVD. Although the exact mechanism is not clearly understood, changes in blood flow led to insufficient blood flow to the heart and brain a common feature of CVD and migraine (11, 16). However, our data revealed that the prevalence of migraine in the patients with CVD was not significantly different from that

observed in the healthy control group. Similarly, Nemati et al showed the same prevalence of migraine in CVD patients and healthy control subjects (14). They also demonstrated a higher significant prevalence of migraine in patients with CSX (60%) compared to that of the healthy group (22%) and concluded that CSX may be a manifestation of migraine. Their finding is consistent with the results of our study which showed a higher prevalence of migraine in CSX patients (40%) compared to the control group (21%). Several mechanisms can explain the association of CSX and migraine. Vasospasm, endothelial abnormalities, and mitochondrial dysfunction are among possible mechanisms that may connect CSX to migraine (14). Several epidemiological investigations have shown a higher prevalence of migraines in women compared to men (17, 18). In addition, sex-related differences in migraine attacks have been confirmed by the findings of structural and functional brain MRIs (19). Several possible mechanisms include fluctuation in the circulating level of estrogen, genetic factors, as well as sex differences in the exposure and response to the environmental stressor may involve in this issue (18, 20). When we analyzed the control group, the results of binary regression demonstrated female sex is a predicting factor for migraine which is in line with several previous studies (18). However, this result did not observe in the patients with CVD and CSX, suggesting that gender does not play a role in increasing the prevalence of migraine in the patient with CSX. Due to the association of obesity with vascular endothelium damage (21) and the role of endothelial dysfunction in the pathogenesis of CSX (22), it has been postulated that obesity may play a role in the development of CSX. In the present study, no significant difference was observed in the BMI of patients with CSX and healthy control individuals, however, the prevalence of obesity (BMI ≥ 30) was significantly higher in the patients with CSX compared to the control group and Chi-square test revealed that obesity was associated with the increased risk of CSX (odd ratio = 2,95% CI (0.953–4.233). On the other hand, obesity is also considered a risk factor for the development and exacerbation of migraine (23). However, in the present study no significant association was observed between BMI and migraine, and the prevalence of obesity (BMI ≥ 30) was not significantly different in the patients with CSX compared to the control group. Therefore, a higher prevalence of migraine in patients with CSX could not be described as a higher prevalence of obesity in CSX patients. The essential role of genetic factors in the development of migraine have been indicated by numerous studies (24, 25), and heritability of 42% has been estimated for migraine (26). The familial aggregation of migraine as well as familial early age onset and severity of migraines are also confirmed by polygenic risk scores analyses (27, 28). Furthermore, genome-wide association (GWS) studies have identified the association of migraine with more than thirty distinct genomic loci, suggesting the polygenic nature of migraine (29). The results of the present study showed a higher familial history of migraine in the CSX group which suggests the possible role of genetic factors in predisposing CSX patients to migraine.

Conclusions

The results of this study revealed a significantly higher prevalence of migraine in patients with CSX. The findings also showed a remarkable familial aggregation of migraine in the patients with CSX, suggesting a role of genetic factors in predisposing CSX patients to migraine and also common pathology of both

conditions. Due to the Covid19 pandemic a relatively low number of patients and healthy control enrolled in the present study; therefore, further studies with larger populations of CSX patients are needed to confirm the results of this study. In addition, GWS studies are warranted to determine the possible genetic loci that predispose CSX patients to migraine.

Declarations

Ethical Approval: The study received ethics approval from the Ethics Committee of Hormozgan University of Medical Sciences (No: 94-96/374). Informed consent was obtained from all individual participants included in the study.

Consent for publication : Not Applicable

Data availability: The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Competing Interests: The authors declare that they have no competing interests.

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Author Contributions: M.M, E.O and A.GH contributed to the study design and supervision. M.M performed the statistical analysis. M.M, E.O, F.D and A.GH wrote the manuscript. A.GH and SH.A revised the manuscript. All authors read and approved the final manuscript.

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