ORIGINAL ARTICLE

Association between serum levels of homocysteine with characteristics of migraine attacks in migraine with aura

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Background: Evidences have shown that migraine with aura (MA) is associated with elevated homocysteine levels but, few studies have evaluated the relationship between homocysteine levels and characteristics of migraine attacks such as severity, frequency, duration and headache diary result (HDR). Thus, in this study, we investigated the association between homocysteine levels and characteristics of migraine attacks in patients with MA. **Materials and Methods:** This cross-sectional study was carried out in Isfahan city, Iran, in February 2013. Fasting serum levels of homocysteine were measured in 130 MA patients (31 males and 99 females) aged 15-60 years. Severity, frequency and duration of migraine attacks, as well as HDR, were determined in each patient according to international headache society criteria by a neurologist. Linear and ordinal logistic regression tests were used to evaluate the relationship between serum homocysteine levels and characteristics of migraine attacks. **Results:** There is no significant association between serum levels of homocysteine with severity, frequency, duration and HDR. This association was not significant after adjustment of confounding variables such as age, body mass index (BMI) and family history of migraine. However, serum homocysteine levels were significantly associated with HDR among males after adjustment for age, BMI and family history of migraine (P = 0.01). **Conclusion:** Significant relationship between homocysteine levels and characteristics of migraine attacks such as severity, frequency, duration and HDR were not found. However, after adjustment of confounding variables, we found a significant positive relationship between homocysteine levels and HDR among men.

Key words: Duration, frequency, homocysteine, migraine, severity

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INTRODUCTION

Migraine is a debilitating, progressive and chronic neurovascular disorder that affects approximately 6% of males and 18% of females worldwide.[1-3] The characteristics of migraine attacks are head pain, nausea, vomiting, photophobia, phonophobia, neck pain and muscle tension.[4,5] Migraine headache can be severe and throbbing and often happens unilateral.[4-6] Other related symptoms are alteration in sensory sensitivity, autonomic dysfunction, dysregulation of mood and focal neurological symptoms.[7] There are two types of migraine: Migraine with aura (MA) and migraine without aura. Both types have the same symptoms, but one-third of migraine patients are faced to transient neurological symptoms that most often involving the visual system that is defined as aura.[7] Approximately, 2 times higher risk of ischemic attacks has been reported in migraine patients.[8] Migraine is more frequent in midlife with 3-fold more prevalence in women.[9] The prevalence of migraine in European adults is 14.7% and in Asian countries is 3% in men and 10% in women.[4-10] In Iran, migraine is one of the most common types of headache.[11] Evidences show that a migraine prevalence is 9.5% in South of Iran, which is considered as high.[12]

Homocysteine is an amino acid that is acted as an intermediate substance in methionine metabolism. High levels of homocysteine are associated with vascular damages such as thrombosis, atherosclerosis, and some ischemic diseases, such as myocardial infraction and ischemic stroke.[13-15] Increased levels of homocysteine can be associated with genetic defects such as methylenetetrahydrofolate reductase (MTHFR) mutation and micronutrient deficiencies such as reduced levels of pyridoxine, folate and cobalamin.[16]

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Recent studies have shown that hyperhomocysteinemia is associated with migraine, especially with MA.[17] Moreover, hyperhomocysteinemia stimulates the initiation of migraine attacks through changes in pain threshold.[18] Therefore, serum homocysteine concentration may be associated with severity and frequency of migraine. Several evidences indicated that higher levels of homocysteine are related to higher severity and frequency of migraine attacks,[19] whereas others showed no relationship between homocysteine levels and frequency of this attacks.[20] These studies are limited to western countries, and data in this regard are scarce in Asian countries. In addition, no studies were evaluated the association between homocysteine levels with duration of migraine attacks and headache diary result (HDR). Hence, the aim of this study is to assess the relationship between homocysteine levels and characteristics of migraine attacks such as severity, frequency, duration and HDR in MA.

MATERIALS AND METHODS

Study population

This is a cross-sectional study which is done in Isfahan city, Iran, in February 2013. The target population consisted of migraine patients referred to Khorshid and ImamMosa Sadr clinics. Initially, 136 MA patients aged 15-60 years who were 105 women and 31 men were selected, but 6 patients were withdrawn from collaboration. The remaining 130 patients included 31 males and 99 females, with a mean age of 34.1 ± 0.94 years, received a complete assessment and were considered for analysis. Written informed consent was obtained from all subjects.

Inclusion and exclusion criteria

Data on age, sex, medical history, family history of migraine and consumption of vitamin supplements were collected. Inclusion criteria consist of having history of migraine for a long time (>5 years), current diagnosis of MA and 1-year history of severe, recurrent and long-lasting migraine attacks (at least one attack per month lasting 4 h). The presences of certain disorders such as chronic heart disease, previous stroke and chronic renal failure, which may increase homocysteine levels, were determined in each subject. All these conditions, as well as consumption of Vitamin-B supplements, were as exclusion criteria. The migraine patients who have an affected first- and second-degree relative were considered as family history of migraine

Measurements

Weight, height and body mass index (BMI) were measured for all participants by someone except the researcher in the Khorshid and Emam Mosa Sadr clinics. Weight was measured by a digital scale with minimum clothing and without shoes with a precision of 100 g. Height was measured in a standing position without shoes by a tape measure with the nearest 0.5 cm. BMI was determined by dividing body weight (kg) on height (meter square). Serum levels of homocysteine were measured by enzyme immunoassay in Yaran laboratory, Isfahan, Iran. Blood samples were taken in the morning after a 12 h fast. Hyperhomocysteinemia was defined as serum levels higher than 15 μmol/l in men and higher than 10 μmol/l in women.

Migraine assessment

The diagnosis of the migraine patients was conducted by an experienced neurologist according to the international headache society (IHS) criteria (headache classification committee of the IHS 2004).[7] Characteristics of migraine attacks such as headache severity, frequency and duration were determined. The visual analog scale was used to measure the migraine severity.[21,22] In this method, headache severity ranks from 1 to 10 and each patient should select one number between 1 and 10 for severity of his headache. Frequency was considered as the number of attacks per month. Mean duration (hour) of migraine attacks was considered as the duration. Moreover, the HDR was measured by the following equation: Duration of headache × frequency of migraine attacks.[21]

Statistical methods

Quantitative variables are expressed as mean, and standard error of mean and qualitative variables are shown as frequency (percent). To determine the differences in demographical characteristics between men and women, we used independent-samples *t*-test. The relationship between continuous quantitative and ordinal dependent variables with predictor variables were evaluated using linear and ordinal logistic regression, respectively. During the fitting of ordinal logistic regression, the proportional odd assumption or parallel lines test was checked using Chi-square test and then the cumulative probabilities of ordered categories response variables as a linear function of the covariates were modeled. All statistical analysis was conducted using SPSS (version 18) statistical software (SPSS, Inc., Chicago, IL, USA).

RESULTS

Table 1 presents the demographical characteristics of patients. Mean serum homocysteine levels in migraine patients were 8.6 ± 0.25 μmol/l and 27 patients (2 males and 25 females) had hyperhomocysteinemia. There is no significant difference in mean age (P = 0.84), serum homocysteine levels (P = 0.07), severity (P = 0.84), frequency (P = 0.65) and duration (P = 0.06) of migraine attacks as well as HDR (P = 0.18) between males and females. However, mean of BMI (P = 0.02) and the proportion of family history of migraine (P = 0.002) were higher among females than males.

The relationship between serum levels of homocysteine and characteristics of migraine attacks in crude and adjusted models is shown in Tables 2-5. There was no significant association between serum levels of homocysteine and severity, frequency, duration and HDR ($P > 0.2$). This association remained nonsignificant even after adjustment of confounding variables such as age, BMI and family history of migraine ($P > 0.2$). In addition, sex-stratified analysis revealed no significant relationship between serum homocysteine levels and characteristics of migraine attacks including severity, frequency, duration and HDR either in crude or adjusted models. However, serum levels of homocysteine was positively associated with HDR among males after adjustment of age, BMI and family history of migraine ($P = 0.01$).

DISCUSSION

In this study, we found a significant positive association between serum levels of homocysteine and HDR among males after adjustment for confounding variables such as age, BMI and family history of migraine. However, no significant relationship was found between serum levels of homocysteine and characteristics of migraine attacks such as severity, frequency and duration either in crude or adjusted models. This is the first study to examine the association between serum homocysteine levels and characteristics of migraine attacks including duration and HDR in patients with MA.

Table 1: Demographical characteristics of patients

Variables	Total	Male	Female	*P*
Age (years)	34.1±0.9	33.8±2.09	34.2±1.05	0.84
BMI (kg/m^2)†	25.6±0.4	23.9±0.7	26.1±0.5	0.02
Family history of migraine (%)	80 (61)	12 (38)	68 (68)	0.002
Serum homocysteine (μm/l)	8.6±0.2	9.4±0.5	8.3±0.2	0.07
Migraine severity (range)††	7.16±0.06	7.19±0.1	7.16±0.08	0.84
Frequency (per month)†††	9.8±0.5	10.2±0.8	9.7±0.7	0.65
Duration (h)‡	17.0±1.1	14.4±1.09	17.9±1.4	0.06
HDR‡‡	161.8±12.3	141.3±12.8	168.3±15.7	0.18

Mean ± SEM. †Body mass index; ††Measured by VAS; †††Frequency of attacks per month; ‡Average duration of migraine attacks; ‡‡Headache diary result: Duration of headache × frequency of headache. VAS = Visual analogue scale; SEM = Standard error of mean; HDR = Headache diary result

There are quantitative studies on the association between serum levels of homocysteine and characteristics of migraine attacks such as severity and frequency of migraine, in the present research we found no studies that focus on duration and HDR in this field. In a cross-sectional studies, Kurth *et al*. reported no significant relationship between homocysteine levels and risk of active MA (migraine with high attacks frequency) in women.[23] Menon *et al*. conducted a study on 206 women with MA that their homocysteine levels were higher than average levels in the white population (8.9 μmol/l). After vitamin supplementation, homocysteine concentration decreased significantly but frequency of migraine attacks does not change significantly. However, headache severity and migraine disabilities decreased significantly.[20] Lea *et al*. conducted a similar study on 52 patients with MA with high levels of homocysteine. After vitamin supplementation and lowering homocysteine concentration severity and frequency of migraine attacks and also migraine disabilities decreased significantly.[19] Di Rosa *et al*. conducted a clinical trial on 16 children with MA and high homocysteine levels. After lowering the homocysteine levels by folic acid supplementation, migraine attacks disappeared completely in 10 patients and reduced in six children significantly.[24] Inconsistent results in different studies may be due to differences in subjects diet, physical activity levels and their health status.

In this study, unlike other studies, any significant relationship between homocysteine levels and characteristics of migraine attacks such as severity, frequency, duration and HDR was not observed except for HDR among males after adjustment of confounding variables. Given that few studies have been done in this field, further studies preferably with larger sample size and adjustment of more confounding variables, are needed to shed light our findings.

The pathophysiology of migraine is still unknown. Many studies have indicated that migraine, especially MA, is related to increased levels of homocysteine, and it can be due to a mutation in MTHFR enzyme.[25] This enzyme defect prevents the conversion of 5, 10-methylenetetrafirsthydrofolate to 5-methylenetetrahydrofolate which is essential to methionine synthase that convert the homocysteine to methionine.[26] High levels of homocysteine are associated to endothelial damage such as thrombosis, atherosclerosis

Table 2: OR and 95% CIs for the relationship between homocysteine levels and severity of migraine attacks†

Models	Male		Female		Total	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Crude	1.02 (0.82-1.28)	0.83	1.02 (0.89-1.17)	0.67	1.02 (0.41-1.14)	0.67
Model I	1.00 (0.78-1.29)	0.95	1.03 (0.90-1.17)	0.66	1.02 (0.41-1.51)	0.64
Model II	1.02 (0.78-1.33)	0.86	1.01 (0.87-1.16)	0.86	1.01 (0.89-1.14)	0.83
Model III	0.83 (0.58-1.17)	0.29	1.01 (0.87-1.17)	0.83	0.99 (0.87-1.12)	0.91

†Measured by VAS. Model I = adjusted for age (continuous); Model II = additionally adjusted for BMI (continuous); Model III = further adjusted for family history of migraine; VAS = Visual analogue scale; BMI=Body mass index; OR = Odds ratio; CI = Confidence interval

Table 3: Results of multiple linear regression for relationship between homocysteine levels and frequency of migraine attacks†

Models	Male		Female		Total	
	β (±SE)	*P*	β (±SE)	*P*	β (±SE)	*P*
Crude	0.09±0.28	0.74	0.13±0.26	0.61	0.12±0.20	0.52
Model I	0.16±0.32	0.61	0.12±0.26	0.62	0.11±0.20	0.58
Model II	0.21±0.22	0.33	0.27±0.26	0.30	0.22±0.20	0.26
Model III	0.36±0.26	0.18	0.26±0.27	0.34	0.21±0.20	0.29

†Frequency of attacks per month. Model I = adjusted for age (continuous); Model II = additionally adjusted for BMI (continuous); Model III = further adjusted for family history of migraine; BMI = Body mass index; SE = Standard error

Table 4: Results of multiple linear regression for relationship between homocysteine levels and duration of migraine attacks†

Models	Male		Female		Total	
	β (±SE)	*P*	β (±SE)	*P*	β (±SE)	*P*
Crude	0.48±0.35	0.17	0.41±0.52	0.43	0.34±0.39	0.39
Model I	0.17±0.37	0.64	0.40±0.52	0.44	0.26±0.39	0.50
Model II	0.32±0.37	0.38	0.22±0.52	0.66	0.20±0.39	0.60
Model III	0.44±0.45	0.34	0.15±0.54	0.78	0.10±0.40	0.79

†Average duration of migraine attacks per hour. Model I = adjusted for age (continuous); Model II = additionally adjusted for BMI (continuous); Model III = further adjusted for family history of migraine; BMI =Body mass index; SE = Standard error

Table 5: Results of multiple linear regression for relationship between homocysteine levels and HDR†

Models	Male		Female		Total	
	β (±SE)	*P*	β (±SE)	*P*	β (±SE)	*P*
Crude	6.94±4.07	0.10	2.68±5.77	0.64	3.10±4.30	0.47
Model I	5.52±4.57	0.23	2.50±5.76	0.66	2.30±4.36	0.59
Model II	7.33±3.70	0.06	3.10±5.79	0.59	3.21±4.29	0.45
Model III	11.75±4.31	0.01*	2.81±6.00	0.64	2.75±4.47	0.54

†HDR: frequency of headache × duration of headache; *Significant level: $P < 0.05$. Model I = adjusted for age (continuous); Model II = additionally adjusted for BMI (continuous); Model III = further adjusted for family history of migraine; HDR = Headache diary result; SE = Standard error

and some disease like cerebrovascular and cardiovascular disease. Moreover, migraine, especially MA, is associated to reduce of cerebral blood flow that produces a propagated depolarization wave into the brain cortex (cortical spreading depression).[27] Therefore, high levels of homocysteine may be involved in reducing of cerebral blood flow and produce of the depolarization wave. Moreover, this condition decreases the transfer of oxygen to the brain and it may act as a stimulator in the onset of headache.[17] Homocysteine-related endothelial damage may also inhibit the release of nitric oxide.[28] In turn, reduced secretion of nitric oxide is associated to abnormal function of vessel walls.[29] that affects the neurovascular function and the coagulant properties of the blood and leads to initiation and maintenance of migraine attacks.[30,31]

This study has several limitations. First, this is the cross-sectional nature of our study; hence, we cannot confer a causal link between serum levels of homocysteine and characteristics of migraine attacks. Further studies are needed to confirm our findings. Second, despite several adjustments, further control for confounding variables such as dietary pattern, medical history and psychosocial factors will be needed to reach an independent association between homocysteine levels and characteristics of migraine attacks.

CONCLUSION

Significant relationship between serum levels of homocysteine and characteristics of migraine attacks such as severity, frequency, duration and HDR were not found. However, after adjustment of confounding variables, we found a significant positive relationship between homocysteine levels and HDR among men. Further studies are required to shed light on our findings.

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AUTHOR'S CONTRIBUTION

OS contributed in definition of intellectualcontent, Literature search, Manuscript preparation, ZM contributed in design, Manuscript editing, Manuscript review, GhA contributed in design, definition of intellectual content, Guarantor, FKh contributed in Defi nition of intellectual content, Clinical studies, Experimental studies, AF contributed in Design, Data analysis, Statistical analysis.

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