

Features of Gender Differences in Patients with Migraine

Bahtigul Holmuratova*, Nilufar Rashidova, Gulnora Rakhmatullayeva,
Khanifa Khalimova, Dilshoda Akramova

Department of Neurology and Medical Psychology, Tashkent Medical Academy, Uzbekistan

Abstract Background: Among the primary headaches migraine is the most common. The clinical symptoms of this disease are different between men and women. In this difference, the gender characteristics of the male and female are very important. This review aims to determine gender differences among migraine patients. **Methods:** 178 patients with migraine were registered using visual analogue (VAS) scale, MIDAS scale and HALT index. A molecular genetic study was also carried out with the study of the C634G gene of VEGF. Gender types of patients were identified by Sandra Bem's schema. **Results:** The intensity of headaches according to the VAS in patients with the feminine type was $8,3 \pm 0,085$, patients with the masculine type experienced slightly less intense pain – $5,4 \pm 0,20$. Evaluation of the daily activity of patients with migraine according to the MIDAS revealed intense headaches in patients with the feminine type, which highly disrupted the daily activity of patients - $20,7 \pm 0,19$. The average score for the HALT index in patients with the feminine type was $18,7 \pm 0,14$. For the C634G polymorphism of the VEGF gene, the distribution of actual genotypes in the group of patients and the control sample corresponded to that expected at RCM equilibrium ($p > 0,05$). **Conclusion:** The presence of the unfavorable 634G allele of the VEGF gene in the genotype contributes to more frequent detection of the feminine type. The highest scores of MIDAS are observed in patients with the feminine type.

Keywords Migraine, Headaches, Gender, Gene, Attack, Primary headache, Features, Pain, Patients, Feminine, Masculine

1. Introduction

Currently, gender differences in patients with migraine (M) are relevant [1]. At the same time, the term "gender" is usually used to refer to such personality characteristics as masculinity ("masculinity") and femininity ("femininity"), due to the influences of the socio-cultural environment, i.e. stereotypes, ideas existing in society about which personal qualities (psycho-behavioral pattern) correspond to the male and which female [2,4,5]. Consequently, people are committed to traditional gender roles to varying degrees [3]. Differences between men and women in certain reactions, including responses to pain stimulation, are largely due not only to the biological characteristics of men and women, but also to different degrees of severity of masculinity and femininity in them. It has been shown that persons with low femininity and masculinity are more common in different types of primary headaches [7,8]. In addition, migraine patients are more common in women (both men and women). However, despite certain attempts to study the influence of sex and gender differences on the characteristics of headache, many questions remain unanswered, since the identification

of gender characteristics allows us to refine the prognosis of migraine headaches [9,10].

2. Methods

179 patients with migraine (M) were examined. We prospectively enrolled consecutive patients diagnosed with M and diagnosis was based on the ICHD-3 [1]. All examined patients underwent clinical and neurological examination, including scales: the visual analogue VAS scale, the quality of life of patients with migraine using the MIDAS scale, and the calculation of days lost due to headache using the HALT scale. A molecular genetic study was also carried out with the study of the C634G gene of VEGF.

3. Results

The results of calculating the intensity of headache according to the VAS scale and the associated decrease in the quality of life of patients according to the MIDAS scale, and the days lost due to headache according to the HALT index showed in Table 1.

The intensity of headaches according to the VAS in patients with the feminine type was 8.3 ± 0.085 , patients with the masculine type experienced slightly less intense pain - 5.4 ± 0.20 . Evaluation of the daily activity of patients with

* Corresponding author:

dr.bakhtigul@gmail.com (Bahtigul Holmuratova)

Received: Aug. 9, 2023; Accepted: Aug. 30, 2023; Published: Sep. 12, 2023

Published online at <http://journal.sapub.org/ajmms>

migraine according to the MIDAS revealed intense headaches in patients with the feminine type, which highly disrupted the daily activity of patients - 20.7 ± 0.19 , while in patients of the masculine type there was a significant impairment of daily activity with a score of 10, 4 ± 0.16 associated with headache. The average score for the HALT index in patients with the feminine type was 18.7 ± 0.14 , which corresponded to IV, the highest level, which means a high need for medical care, while in patients with the masculine type - 16.1 ± 0.14 points, which corresponds to level III, these patients also need treatment. It should be noted that the higher the scores in patients on the MIDAS, the higher the scores of the HALT index, which means that these patients have a pronounced impairment in the quality of life that requires medical treatment.

Table 1. Evaluation of headache intensity and quality of life of patients

SCALE	Feminine type n=136 (45,9%)	Masculine type n=43 (14,5%)
VAS	$8,3 \pm 0,085$	$5,4 \pm 0,20$
MIDAS	$20,7 \pm 0,19$	$10,4 \pm 0,16$
HALT index	$18,7 \pm 0,14$	$16,1 \pm 0,14$

Study of the C634G polymorphism of the VEGF gene, which has 3 genotypic variants: C/C, C/G and G/G. Genotype 634C/C is wild - major, G/G minor, is relatively rare in the population.

The distribution of the actual and theoretical frequencies of the genotypes of the C634G polymorphism of the VEGF gene and their correspondence to the RCM population equilibrium was carried out separately in groups of patients with migraine of the feminine and masculine types.

For the C634G polymorphism of the VEGF gene, the distribution of actual genotypes in the group of patients and

the control sample corresponded to that expected at RCM equilibrium ($p > 0.05$). Thus, the expected and observed frequency of the C/C genotype in the group of patients were almost similar, i.e. 0.57 and 0.58, respectively. The expected frequency of the heterozygous C/G genotype was 0.37 versus 0.35 observed, the expected frequency of the unfavorable homozygous G/G genotype was 0.06 versus 0.07 observed.

The expected and observed frequency of occurrence of C/C, C/G and G/G genotypes in the control group were: 0.75/0.76, 0.23/0.21 and 0.02/0.02, respectively, Table 2.

The following are the results of the analysis of gene diversity (Table 3.) for the C634G polymorphism of the VEGFA gene according to the following criteria: the calculated expected heterozygosity (h_{exp}), and the relative deviation of the observed heterozygosity (h_{obs}) from the expected one (h_{exp}), in the main and population samples.

The relative deviation (D) of the expected heterozygosity from the observed one was calculated using the formula: $D = (h_{obs} - h_{exp}) / h_{exp}$, где h_{obs} и h_{exp} – observed and expected heterozygosity, respectively.

In the main group, a relatively high heterozygosity for the studied polymorphism was revealed, $h_{exp} = 0.37$ and $h_{obs} = 0.35$ ($0.37 < H_{exp} < 0.4$), which indicates a moderate genetic diversity of this polymorphism.

In the population sample, h_{exp} and h_{obs} corresponded to the values of 0.23 and 0.21, which corresponds to the low gene diversity of the population for this polymorphism.

In the main and control samples, the coefficient of the relative deviation of the observed heterozygosity from the expected C634G polymorphism of the VEGFA gene turned out to be negative, i.e. $D < 0$ ($D = -0.05$ and -0.04 , respectively), which indicates a lack of heterozygotes, the level of which corresponds to moderate (Table 4).

Table 2. Frequency distribution of the genotypes of the C634G polymorphism of the VEGFA gene in accordance with RCM in the group of patients

Gene	Polymorphism	Genotype	Distribution of genotypes		χ^2	P
			Expected	Observed		
VEGFA	rs 2010963	C/C	0,57	0,58	0,045	0,4
		C/G	0,37	0,35	0,272	
		G/G	0,06	0,07	0,415	

Table 3. Frequency distribution of the genotypes of the C634G polymorphism of the VEGFA gene in accordance with the Hardy-Weinberg equilibrium in the control group

Gene	Polymorphism	Genotype	Distribution of genotypes		χ^2	P
			Expected	Observed		
VEGFA	rs 2010963	C/C	0,75	0,76	0,009	0,5
		C/G	0,23	0,21	0,114	
		G/G	0,02	0,02	0,379	

Table 4. Difference between expected and observed frequencies of heterozygosity

Groups	h_{exp}	h_{obs}	D *
Main groups	0,37	0,35	-0,05
Control group	0,23	0,21	-0,04

Note: $D = (0,35 - 0,37) / 0,37 = -0,05$ for main group;
 $D = (0,21 - 0,22) / 0,22 = -0,04$ for control group

The next stage of the work was the analysis of associations of alleles and genotypes of the C634G polymorphism of the VEGFA gene by feminine and masculine types.

The frequencies of occurrence of allelic and genotypic variants of the polymorphic marker C634G of the VEGF gene (international code -rs 2010963) among the entire cohort of patients, distributed according to the degree of development of femininity and the control group, are shown in Table 4. It has been established that the C634G polymorphism of the VEGF gene is associated with the development of the feminine type. Thus, the functionally unfavorable 634G allele statistically significantly prevailed in patients compared with the control group (24.7% vs. 13.1%, respectively). The favorable allele 634C, on the contrary, was highly significantly more common in the group of conditionally healthy donors compared to patients: 86.9% versus 75.3% at ($\chi^2=15.4$; $P<0.05$; $OR=2.2$, 95% CI 1.47-3.239).

4. Discussion

In this article, the gender types of migraine were studied. Particularly the effect of gender has been studied and has been found to be of considerable value in the clinical course of migraine. The feminine type plays a central role here, but it is assumed that this is only part of the mechanism. Some therapeutic strategies have been developed based on this knowledge. However, there is currently no evidence to support gender-specific treatment strategies for migraine. There are some limitations to be considered. This study was clinic-based and the data cannot estimate the prevalence of M in the general population. The findings require further study and cannot be extrapolated to the general population directly.

5. Conclusions

Thus, the presence of the unfavorable 634G allele of the VEGF gene in the genotype contributes to more frequent detection of the feminine type. At the same time, the highest scores in patients with migraine according to the MIDAS are observed in patients with the feminine type, therefore, the higher the scores of the HALT index, which indicates severe impairments in the quality of life of the examined patients, requiring medical treatment.

REFERENCES

- [1] Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2018; 38: 1-211.
- [2] Borsook D, Erpelding N, Lebel A et al (2014) Sex and the migraine brain. *Neurobiol Dis* 68: 200–214.
- [3] Осипова, В. В. Первичные головные боли: методические рекомендации / В. В. Осипова. – М., 2017. – 27 с.)
- [4] “Gender aspects of CGRP in migraine” Alejandro Labastida-Ramírez*, Eloísa Rubio-Beltrán, Published October 30, 2017.
- [5] Christine R. Starr 1 & Eileen L. Zurbriggen1 “Sandra Bem’s Gender Schema Theory After 34 Years: A Review of its Reach and Impact” 2017 year, 76:566–578, Springer Science.
- [6] Buse DC, Scher AI, Dodick DW, et al. Impact of migraine on the family: Perspectives of people with migraine and their spouse/domestic partner in the CaMEO study. *Mayo Clin Proc.* 2016; doi: 10.1016/j.mayocp.2016.02.013. [Epub ahead of print].
- [7] Hanifa Mukhsinovna Halimova, Nilufar Safoyevna Rashidova, Bakhtigul Nurmammedovna Holmuratova «Gender characteristics and features of the course of primary headaches» *Journal of Biomedicine and Practice.* 2021, vol. 6, issue 1, pp.64-68.
- [8] Level of Anxiety in male and female migraineurs seeking medical assistance. The 3rd International Forum on Pain Medicine (Montreal, Canada, June 28 — July 1, 2007). — Montreal, 2007. — P. 23.
- [9] Migraine in man: 11th World Congress on Pain (Sydney, Australia, August 21-26, 2005). — Sydney, 2005. — P.112.
- [10] Влияние гендера на болевой порог мужчин и женщин при мигрени без ауры // Интернет-журн. «Головная боль» [Электронный ресурс]. — 2007. — № 1. Соавт.: Данилов А.Б., Голубев В.Л.
- [11] Calhoun AH, Batur P (2017) Combined hormonal contraceptives and migraine: An update on the evidence. *Clev Clin J Med* 84:631–638.
- [12] Амелин А.В. Мигрень (патогенез, клиника, лечение) / А.В. Амелин, Ю.Д. Игнатов, А.А. Скоромец и др. — М.: МЕДпресс-информ, 2011. — 265 с.
- [13] Laurell K, Artto V, Bendtsen L, et al. Premonitory symptoms in migraine: A cross-sectional study in 2714 persons. *Cephalalgia.* 2016; 36: 951-959.