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CLINICAL AND VEGETATIVE PARAMETERS IN PATIENTS WITH MIGRAINE, DEPENDING ON GENOTYPE

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Resume

109 sick with migraine are clinical neurologically examined, which were divided into 2 groups: the first group sick with migraine with aura (n - 22); the second group - sick with migraine without aura (n - 87). In addition, a PCR (polymerase chain reaction) study method was used to divide patients by genotype. The results of the study showed an increase in disease symptoms, depending on the pathological (VV) genotype from the normal (AA) genotype.

Key words: *migraine, genotype, migraine with aura, migraine without aura, MTHFR (methylenetetrahydrofolate reductase)*

КЛИНИКО-ВЕГЕТАТИВНЫЕ ПОКАЗАТЕЛИ У БОЛЬНЫХ С МИГРЕНЬЮ В ЗАВИСИМОСТИ ОТ ГЕНОТИПА

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Резюме

Обследовано 109 больных мигренью, в зависимости от генотипа которые были разделены на 2 группы: первая группа больные мигренью с аурой (n - 22); вторая группа - больные мигренью без ауры (n - 87). Для распределения больных по генотипу проводилось полимеразная цепная реакция. По данным исследование от нормального (АА) к патологическому (VV) генотипу клиника мигрени с аурой, то есть классическая мигрень, имеет тенденцию к утяжелению, с преобладанием вегетативной дисфункции.

Ключевые слова: *мигрень, генотип, мигрень с аурой, мигрень без ауры, МТГФР (метилентетрагидрофолат редуктаза).*

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МИГРЕН БИЛАН КАСАЛЛАНГАН БЕМОРЛАРНИНГ ГЕНОТИПГА БОҒЛИҚ ҲОЛДАГИ КЛИНИК-ВЕГЕТАТИВ КЎРСАТКИЧЛАРИ

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Резюме

Мигрен билан касалланган 109 та бемор 2 та гуруҳга бўлиниб, аурали мигрен (n-22) ва аурасиз мигрен (n-87) клиник неврологик текширишлар ўтказилди. Бундан ташқари беморларни генотип бўйича тақсимлаш учун ПЗР (полимеразали занжир реакцияси) тадқиқот усули ўтказилди.Тадқиқот натижалари нормал (АА) генотипдан патологик (VV) генотипга қараб, касаллик белгиларининг ўсиб боришини кўрсатади.

Калит сўзлар: *мигрен, генотип, аурали мигрен, аурасиз мигрен, МТГФР (метилентетрагидрофолат редуктаза).*

Relevance

In the last decade, the concept of migraine has undergone significant changes, due to the rapid growth of scientific research on the study of epidemiology, genetics, pathogenesis and treatment of this disease. According to epidemiological studies conducted in various countries, from 3 to 16% suffer from migraine, and according to some reports up to 30% of the population [1, 2, 4, 5, 10, 11, 13]. At the same time, men make up from 2 to 15%, and women from 6 to 25% of the entire population. The ratio of men to women is 1: 2.5 or 2: 4 [1, 2, 3, 6, 7,].

The role of heredity in the origin of migraine has long attracted the attention of researchers. Frequent indications of the presence of migraine in several generations of close relatives, as well as the appearance of the disease at an early age, indicate the important role of hereditary, genetic factors in the origin of this disease. Genealogical studies show that if both parents had migraine attacks, the risk of disease of descendants reaches 60-90%. If only mother suffered from migraine, then the risk of morbidity is 72%, if only father - 20% [1, 2, 8, 11, 12].

Thus, there is various evidence of the involvement of genetic factors in the origin of migraine, but their significance and role remain clearly undefined. Of course, migraine can result from more than one genetic defect. It is likely that new genetic studies will significantly expand the understanding of the etiology of migraine, improve the diagnosis and treatment of this disease.

Materials and methods

The studies were carried out on the basis of a sample of migraine patients (migraine with aura (MA) n = 22, migraine without aura (MWA) n = 87), in the amount of 109 people, aged 16 to 53 years, who were admitted to the Khorezm regional hospital №1.

Previously, all patients were examined to establish verification of the diagnosis of migraine. The survey was conducted by the staff of the Department of Neurology and Psychiatry of Urgench branch of TMA. PCR studies were carried out at the Center for Genomic Technologies (CGT) at the Institute of Genetics and Experimental Plant Biology (IG and EPB) of the Academy of Sciences of the Republic of Uzbekistan (AS RUz) and in the laboratory of the Mamun Academy in Khiva. The material for DNA was venous blood from the ulnar vein with a volume of 1 ml.

As a result of genotyping of patients with migraine and in studying the clinical and neurological status of patients with migraine, the following groups were identified depending on the genotype: group 1 (n = 25) - patients with MA and MWA with a normal genotype (AA); Group 2 (n = 62) - patients with MA and MWA with a heterozygous genotype (VA); Group 3 (n = 18) - patients with MA and MWA with a homozygous pathological genotype (VV);

Clinical and neurological examination included the study of patient complaints, an in-depth study of neurological status.

To determine the vegetative supply, all examined filled out “the questionnaire for identifying signs of vegetative changes” (Vein

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A.M., 1998), according to which the SVD was set when the total score was over 15.

Kerdo index - according to the formula: VI = (1 – D / P) ×100%, where: D - diastolic pressure, P - pulse.

Minute blood volume (MBV) was determined by the method of Lillier-Strandra and Zander (in liters). MBV = A / Dsr. ×HSS, where

Amplitude AP = APsystole. - APdiastol.

APav. = $\frac{\text{APsystol. + APdiastol.}}{2}$, A / Dav. = $\frac{\text{Amplitude AP}\times 100}{\text{APav.}}$

Research results and discussion

Headache intensity was studied on a 10-point visual analogue scale, as well as on the basis of a headache diary filled by patients. The symptoms of photophobia, phonophobia, as well as nausea and vomiting, associated with a migraine attack, were evaluated on a 3-point scale. We compared the data obtained in patients with migraine depending on the genotype (table. 1).

As can be seen from table 1, the intensity of the cephalgic syndrome according to the visual analogue scale was significantly (P <0.001) during migraine attack manifested in patients with migraine with heterozygous (AV 6.34 ± 0.12 points) and pathological (VV 7.22 ± 0 , 15 points) genotype compared with the normal (AA) genotype (5.2 ± 0.14 points). The intensity of the manifestations of concomitant symptoms (photophobia, phonophobia and nausea) was also significantly (P <0.005 and P <0.001) more manifested in patients with a pathological (VV) genotype compared to the normal (AA) genotype. In relation to vomiting, the reliability between the groups was not (P>0.005) revealed, however, the tendency to increase the severity of the symptom score from normal (AA) to pathological (VV) genotype observed (1.24 ± 0.14 and 1.61 ± 0, 26 points respectively).

In other words, the data obtained indicates that, with the accumulation of the pathological gene MTHFR Ala222Val (from the normal (AA) to the pathological (VV) genotype), the clinical course is more severe, migraine attacks are more manifested as the main and accompanying clinical signs.

When analyzing factors provoking a migraine attack in patients with migraine, depending on the genotype, it was revealed (Table 2) that a reliable (P <0.005 and P <0.001) tendency to increase the influence of provoking factors from the normal (AA) to pathological (VV) genotype is revealed of the following factors: physical overstrain, overwork, irregular meals in the form of food omissions, alcohol intake, long, tiring ride in vehicles, sharp light, sound (watching TV shows, sharp sounds) olfactory irritations (even the smell of perfumes), cold factors, changes in sleep regimen and somatic diseases. With respect to factors such as emotional stress and changes in the weather and geomagnetic situation, no significant differences were revealed, however, a tendency to increase the influence of these factors from the normal (AA) to the pathological (VV) genotype was observed.

Thus, from the survey it can be concluded that most external provoking factors have a significant tendency to increase the influence from the normal (AA) to the pathological (VV) genotype of the MTHFR Ala222Val gene.

We studied the vegetative status in patients with migraine, depending on the genotype, using the questionnaire table (survey), the Kerdo index, and MBV (table 3).

When analyzing the quantitative point assessment of the severity of SVD, it was found that according to the questionnaire, the average score significantly

(P <0.005 and P <0.001) increased from the normal (AA) to the pathological (VV) genotype (30.08 ± 0.73 and 38.06 ± 0.92 points, respectively).

According to the indicators of the Kerdo index and MBV, no significant differences were detected. However, according to the indicators of the Kerdo index from normal (AA) to pathological (VV) genotype, there was an unreliable tendency to increase in parasympathetic patients (from -0.93 ± 1.63 to -2.21 ± 2.31%, respectively).

The analysis of the study of the vegetative status in patients with migraine, depending on the genotype, showed that from the normal (AA) to the pathological (VV) genotype of the MTHFR Ala222Val gene, there is a higher point severity of this syndrome with an increase in the tendency to parasympathetic direction, and in our opinion this is due with the depletion of the vegetative nervous system as a result of frequent migraine attacks.

According to published literature, the hypothesis about the participation of the autonomic nervous system in the realization of migraine headache was based on the assumption that parasympathetic influences can cause cranial vasodilation, release of inflammatory mediators, and activation or sensitization of trigeminovascular afferents [6, 7, 9]. The results of our studies confirm that the autonomic nervous system is actively involved in the implementation of migraine headache. One of the most active genes

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associated with migraine is the gene encoding the enzyme 5, 10 - methylenetetrahydrofolate reductase (MTHFR), the MTHFR gene located on chromosome 1 (1p36,3) [10]. One of the most studied mutations in this gene is the replacement of cytosine with thymine at position 677, which we studied in our work.

Thus, it can be concluded that the results of clinical and autonomic studies in patients with migraine, depending on the genotype, showed that with the accumulation of the pathological MTHFR Ala222Val gene (from normal (AA) to pathological (VV) genotype) the following regularity were revealed:

1. Clinically migraine attacks are more expressed as the main and accompanying clinical signs.

2. Most external triggers of migraine have a significant tendency to increase the impact.

3. There is a higher point severity of vegetative dystonia syndrome with an increase in the tendency to parasympathetic direction.

Table 1

The severity in points of the main clinical manifestations in patients with migraine, depending on the genotype

Norm indicator.	Norm.Genotype (AA)	Heterozygous (AV)	Patol. Geno type (VV)	P 1-2	P 2-3	P 1-3
	1	2	3			
The number of examined	25	62	18			
Pain intensity on a VAS	5,76±0,20	6,32±0,14	6,34±0,23	0,001	0,001	0,001
Photophobia	1,88±0,09	2,23±0,06	2,44±0,12	0,05	-	0,05
Phonophobia	1,8±0,1	2,11±0,08	2,44±0,12	0,05	0,05	0,001
Nausea	1,72±0,14	2,13±0,09	2,33±0,11	0,05	-	0,05
Vomiting	1,24±0,14	1,29±0,11	1,61±0,26	-	-	-

Table 3

Vegetative indicators in patients with migraine, depending on the genotype, M ± m

Norm indicator	Geno-type (AA)	Heterozygous (AV)	Patol. Genotype (VV)	P 1-2	P 2-3	P 1-3
	1	2	3			
The number of examined	25	62	18			
Questionnaire table (Point)	30,08±0,73	34,06±0,70	38,06±0,92	0,05	0,05	0,001
Kerdo Index (VI%)	-0,93±1,63	-1,45±1,07	-2,21±2,31	-	-	-
Minute blood volume (liter)	3291,07 ±57,41	3248,42 ±53,38	3363±100,5	-	0,05	-

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Table 2

Characteristics of factors provoking a migraine attack in patients with migraine, depending on the genotype

Provocative factors	Patients with migraine			P 1-2	P 2-3	P 1-3
	Norm Genotype (AA)	Heterozy-gotic (AV)	Patol. Genotype (VV)			
	1	2	3			
The number of examined	25	62	18			
Emotional stress	21 (84,0±7,33)	44 (71,0±5,76)	16 (88,89±7,40)	-	-	-
Physical overstrain	21 (84,0±7,33)	48 (77,4±5,31)	17 (94,4±5,41)	-	0,05	-
Irregular nutrition	11(44,0±9,92)	42 (67,74±5,93)	14 (77,8±9,79)	0,05	-	0,05
Alcohol	5 (20,0±8,0)	20 (32,26±5,93)	12	-	0,05	0,05
Long ride in transport	14 (56,0±9,93)	47 (75,8±5,43)	17 (94,4±5,41)	-	0,05	0,05
Harsh light, sound, olfactory stimulation	16(64,0±9,4)	34 (52,3±6,34)	16 (88,89±7,40)	-	0,05	0,05
Changes in weather and geomagnetic situation	18 (72,0±8,89)	51 (82,26±4,81)	16 (88,89±7,40)	-	-	-
Cold factors	6 (24,0±8,54)	27 (43,55±6,29)	12(66,67±11,11)	-	-	0,05
Change in sleep mode	5 (20,0±8,0)	25 (40,32±10,61)	13 (72,2±5,17)	-	0,05	0,001
Somatic diseases	4 (16,0±7,33)	14 (21,54±10,26)	12 (66,67±4,96)	-	0,05	0,001

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