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Influence of an epigenetic diet on migraine patients

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ABSTRACT

Objective. Migraine is a common type of primary headache disorder, distinguished by recurrent attacks of moderate to severe unilateral throbbing pain. The goal of this study is to analyze the epigenetic influences of diet and their effects on patients with migraine headaches.

Materials and methods. 130 patients with migraine headaches were analyzed (13.7% male and 86.3% female). The subjects were divided into two groups; Group A patients subsequently followed an epigenetic diet enriched with 5 mg of folic acid. Group B patients didn't follow any type of diet.

Results. When analyzing the data before the start of the study, it was found that the average concentration of folic acid in Group A was 2.8+3.6 ng/ml, which was significantly lower than in Group B (p=0.003). The average level of homocysteine was significantly different in both groups (p=0.04). Furthermore, a significant decrease in the intensity and frequency of headache was found (p = 0.02; p = 0.04), and a decrease in the average level of anxiety according to the Hamilton Anxiety Scale was found (from 15.0+3.5 points to 9+2 points) (p=0.03).

Conclusion. A significant effect from homocysteine and folic acid levels in migraine patients on headache severity and quality of life was observed.

Keywords: migraine, epigenetic diet, folic acid, homocysteine

INTRODUCTION

Migraine is a common type of primary headache disorder characterized by periodic attacks of severe unilateral throbbing pain, accompanied by common symptoms such as nausea, vomiting, photophobia, and phonophobia [1]. Considering the frequency of occurrence, the International Headache Society classifies migraines as either episodic or chronic. Dietary factors, among other factors, are now thought to play a role in several putative mechanisms of headache development. In particular, diet can influence the modulation of neuropeptides, neuroreceptors and ion channels, the sympathetic nervous system and glucose metabolism, and nitric oxide release and vascular vasodilation [2].

Recently, there have been accumulating reports on the positive effects of an epigenetic diet with migraine headaches, which involves the modification of DNA and proteins by influencing the work of genes with the help of certain foods, without touching the sequence of the genetic code [3]. Certain dietary factors that increase susceptibility to migraines have direct links to epigenetic mechanisms. Dietary components can block the mechanisms that produce migraines or contribute to the prevention of attacks, in particular, through DNA methylation in the CGRP gene [4,5]. An epigenetic diet, a term coined by Hardy and Tollefsbol in 2011, is intended to target the cellular epigenetic profile and specifically mediate its changes induced by environmental factors [6]. Nutrition can change a person's epigenetic profile, but the question of how to specifically regulate one's profile with the help of an epigenetic diet is not yet sufficiently studied and remains open, which opens up the possibility of influencing migraine occurrence or severity through an epigenetic effect [7].

It has been shown that folic acid (folicin, vitamin B9), is one of the B vitamins involved in one-carbon metabolism and DNA methylation, and has a beneficial effect on migraines. Folic acid is necessary for many cellular effects, such as synthesis of nucleo-

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sides and methylation of biomolecules, including DNA [8,9]. As mammals, humans cannot synthesize folic acid and must consume it through food, either as a component of a natural diet, fortified food, or dietary supplement. Dietary folate is metabolized to 5-methyltetrahydrofolate (5mTHF, the monoglutamyl form) by methylenetetrahydrofolate reductase (MTHFR). This reaction is important for the remethylation of homocysteine to methionine, providing methyl groups for DNA methyltransferases to methylate DNA [10]. Several other nutrients, including vitamins B2, B6, and B12, riboflavin, and choline, are important for maintaining the one-carbon flux required for DNA methylation [11]. That is why a folate deficiency can provoke the appearance of disorders in the nervous system [12,13]. Excess homocysteine can be harmful to blood vessels and lead to endothelial cell damage and changes in blood properties, which may be important in the pathogenesis of cardiovascular disorders and migraines [14,15].

Therefore, deficiency of folate and vitamins B6 and B12 leads to hypomethylation of DNA, which is believed to play a role in the pathogenesis of migraines as a result of interactions with MTHFR [16].

OBJECTIVE

To study the effect of an epigenetic diet on frequency and intensity of migraine headache attacks, indicators of psycho-emotional status, and quality of life of migraine patients.

MATERIAL AND METHODS

130 people aged from 18 to 55 were examined (average age 38.6±8.3), among them 13.7% were men, 86.3% were women. Patients under the age of 18 and pregnant women were not included in the study. Migraine patients were divided into 2 groups: Group A – patients who followed an epigenetic diet enriched with 5 mg of folic acid, Group B – patients who did not follow any type of diet. Patients were divided into groups based on the available level of folic acid (reference values 4.6-18.7 ng/ml). Group A included 75 patients with a low level of folic acid, Group B - 55 patients with a normal level of folic acid.

The diagnosis of migraine headaches was confirmed according to the criteria of the International Headache Society [17]. Before the study, all participants were assessed using the Work Disability Assessment Scale (MIDAS) [18], which provides the ability to determine the number of productive days lost due to migraine headaches in the previous 3 months (i.e., migraine disability). Also, the frequency of headache was determined in all patients, the intensity of headache was assessed using a visual analog scale/VAS [19,20]. Assessment of changes in psycho-emotional status was carried out using Hamilton's Anxiety and Beck's Depression Scales [21]. All scales were used at the beginning and end of the study.

The folic acid and homocysteine content in blood was determined in all migraine patients with migraines using an immunochemical method with electrochemiluminescence detection. As for homocysteine, its reference values are up to 15 μmol/l. All examinations were carried out in the morning on an empty stomach. All study subjects provided written informed consent and the study was approved by the Institutional Ethics Committee.

Statistical data processing was performed using the GraphPad Prism version 9.3.0 program. The probability of the obtained results was assessed at a significance level of at least 95% ($p<0.05$). In order to clarify the significance of the relationship between the indicators of the two samples, the correlation coefficients r was determined.

RESULTS

When analyzing the data before the start of the study, it was found that the average concentration of folic acid in Group A was 2.8 + 3.6 ng/ml and was significantly lower than in Group B ($p=0.003$), where the average level of folic acid was 6.5 +5.1 ng/ml, which corresponds to the norm (Table 1). The average level of homocysteine in both groups differed significantly ($p=0.04$): in Group A the average level of homocysteine was increased (17.8 + 2.5 μmol/l), and in Group B it was normal (9.5 + 3 .6 μmol/l). The average rate of participants with high migraine frequency and intensity did not differ significantly between the two study groups at baseline ($p>0.05$).

TABLE 1. Clinical characteristics of patient groups at the beginning of the study

	Group A (n=75)	Group B (n=55)	p *
Folic acid (ng/ml)	2,8 ± 3,6	6,5 ± 5,1	0,003
Homocysteine (μmol/l)	17,8 ± 2,5	9,5 ± 3,6	0,04
VAS scoure	7,8 ± 4,3	5,3 ± 3,2	0,67
Hamilton's Anxiety Scales	15 ± 3,5	10 ± 4,0	0,39
Beck's Depression Scales	10,3 ± 2,6	12,8 ± 3,3	0,48
Frequency of attacks	7,09 ± 3,5	5,8 ± 4,1	0,09
MIDAS	13,7 ± 4,4	8,5 ± 5,2	0,035

** p <0,05*

In Group A, the average score on the Hamilton Anxiety and Beck Depression Scales were 15.0+3.5 points and 10.3+2.6 points, respectively. Group B differed, reflecting average scores on the above scales of 10+4.0 points and 12.8+3.3 points respectively. Re-

garding the determination of the average degree of social and household maladjustment according to the MIDAS Scale, significant differences were found (p=0.035): in Group A, the average level corresponded to the III degree of maladjustment (13.7+4.4), and in Group B to the II degree (8.5+5.2).

In Group A, against the background of using an epigenetic diet enriched with folic acid, the average level of folic acid increased significantly (p = 0.001), and the average level of homocysteine decreased significantly (p = 0.003) (Table 2). Regarding headache indicators, a significant decrease in the intensity and frequency of headache was found in patients from Group A (p = 0.02; p = 0.04), while in Group B, the average level of frequency and intensity of headache did not undergo significant changes. A general decrease in the average level of anxiety according to the Hamilton Scale was observed in Group A after 3 months of the study (from 15.0+3.5 points to 9+2 points) (p=0.03). Regarding the average indicators on the MIDAS Scale, there was a significant decrease in the average score in Group A (13.7+4.4 to 8.5+3.6 points) (p= 0.009).

TABLE 2. Clinical characteristics of group A before and after the study

	Group A (n=75) before the study	Group A (n=75) after the study	p *
Folic acid (ng/ml)	2,8 ± 3,6	5,3 ± 4,1	0,001
Homocysteine (µmol/l)	17,8 ± 2,5	12,06 ± 3,2	0,003
VAS score	7,8 ± 4,3	4,7 ± 2,9	0,02
Hamilton's Anxiety Scales	15,0 ± 3,5	9,2 ± 2,7	0,03
Beck's Depression Scales	10,3 ± 2,6	12,8 ± 3,3	0,48
Frequency of attacks	7,09 ± 3,5	3,8 ± 2,8	0,04
MIDAS	13,7 ± 4,4	8,5 ± 3,6	0,009

**p <0,05*

As a result of the correlation analysis, a direct relationship between the level of homocysteine and the score on the Hamilton Anxiety Scale (Figure 1) and the MIDAS Scale was established in migraine patients from Group A (r = 0.697, p = 0.001; r = 0.557, p = 0.02).

As well as a negative correlation between the level of folic acid and the score on the Beck Depression Scale (r = -0.54, p = 0.025) (Figure 2).

DISCUSSION

When analyzing the results of this study, the normalization of the level of folic acid and a significant decrease in the level of homocysteine were found in Group A against the background of the use of an epigenetic diet enriched with folic acid. This was accompanied by a significant decrease in the intensity of headaches and a decrease in the frequency of migraine attacks, as well as an improvement in the quality of life in migraine patients. The obtained results are somewhat consistent with the data of Menon and co-authors [22], who showed that folic acid supplementation of 1 mg proved to be useful for the prevention of migraine attacks, quality of life and psycho-emotional background. A direct relationship was also established between homocysteine levels and the level of anxiety, as well as the score on the MIDAS Scale. The detected changes may indicate that the damaging effect of hyperhomocysteinemia may underlie the adverse effect of the latter on neurons in the brain of patients [6]. As mentioned earlier, an excess of homocysteine can be harmful to blood vessels and play a role in the pathogenesis of migraines, especially in migraines presenting with aura [23]. However, the direct relationship between homocysteine levels and migraines are still a matter of debate, especially since only a few studies have evaluated homocysteine levels in migraineurs [24].

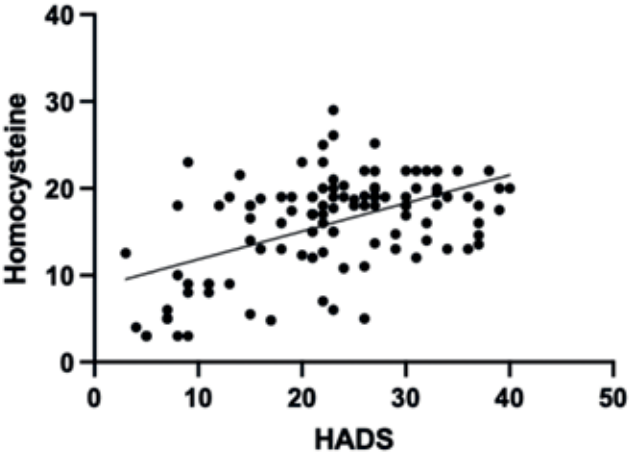

FIGURE 1. Correlation analysis between homocysteine level and Hamilton anxiety scale score in patients in group A

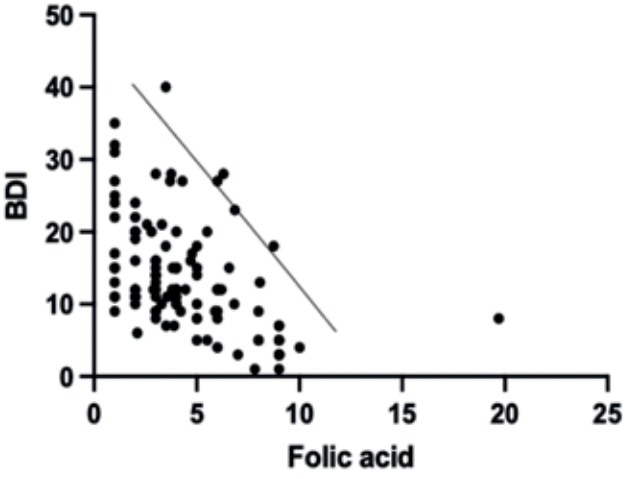

FIGURE 2. Correlation analysis between the level of folic acid and the Beck depression scale score in patients in group A

In this study, the use of folic acid in certain dosages in patients with migraines was established under the condition of its initial deficiency, and plays an important role in reducing the level of homocysteine and reducing the symptoms associated with migraines. Also, the revealed negative correlation between the level of folic acid and the score on the Beck Depression Scale, may indicate the likely significant role of folic acid for the normal psychoemotional state of patients with migraines. Consequently, folate deficiency leads to DNA hypomethylation, which is thought to trigger migraine attacks and may exacerbate pain and contribute to depressive disorders [25]. Taken together, folic acid is required for DNA methylation, and its presence in the diet has been reported to have a beneficial effect on migraines [22]. Further research is needed to understand the feasibility of using vitamin supplements that include different doses of folic acid, vitamin B 6, and B 12, not only in reducing migraine headache symptoms, but also in their long-term effects on migraines.

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CONCLUSIONS

Dietary intervention for disease is always attractive because it is rarely associated with serious side effects. However, even a simple diet contains many components that can interact with many genes in different ways. This can lead to results where it's difficult to determine the exact casual relation.

A significant effect of homocysteine and folic acid in migraine patients on headache severity and quality of life was established.

The role of epigenetic modifications for migraines isn't fully known, but epigenetics is considered a promising direction in the preventive treatment of this complex, disabling disease.

The use of an epigenetic diet in the prevention and treatment of diseases, the pathogenesis of which is associated with a change in the epigenetic profile, requires further study because it's difficult to predict the final effect from the diet due to the low specificity of such a diet, and its effects on the epigenome, accompanied with the vast number of interactions between the active components of a diet.

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