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ARTICLE

Investigation of serum vaspin, visfatin, chemerin and IL-18 levels in migraine patients

Investigação dos níveis séricos de vaspina, visfatina, quemerina e IL-18 em pacientes com migrânea

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ABSTRACT

Background: Migraines are headaches caused by changes in the trigeminovascular metabolic pathway. Migraine headache attacks are associated with neurovascular inflammation, but their pathophysiological mechanisms have not been fully explained. **Objective**: To investigate the relationship between serum vaspin, visfatin, chemerin and interleukin-18 (IL-18) levels and the frequency of attacks in migraine headache. **Methods**: Three groups were established: migraine with aura (n = 50), migraine without aura (n = 50) and control group (n = 50). The migraine diagnosis was made in accordance with the International Classification of Headache Disorders-III beta diagnostic criteria. The analyses on serum vaspin, visfatin, chemerin and IL-18 levels were performed using the enzyme-linked immunosorbent assay method. **Results**: The serum vaspin, visfatin, chemerin and IL-18 levels were found to be significantly higher in the migraine patients than in the control group ($p < 0.01$). No statistically significant differences in serum vaspin, visfatin, chemerin and IL-18 levels were found among the migraine patients during attacks or in the interictal period ($p>0.05$). The serum visfatin and chemerin levels of the migraine patients were positively correlated with their serum IL-18 levels ($p < 0.01$), while their serum chemerin and visfatin levels were positively correlated with their serum vaspin levels ($p < 0.05$). **Conclusions**: This study showed that these biomarkers may be related to migraine pathogenesis. Nonetheless, we believe that more comprehensive studies are needed in order to further understand the role of vaspin, visfatin, chemerin and IL-18 levels in the pathophysiology of migraine headaches.

Keywords: Chimerin 1; Interleukin-18; Inflammation; Migraine without Aura; Pathogenesis Homeopathic; Vaspin; Nicotinamide Phosphoribosyltransferase.

RESUMO

Antecedentes: A migrânea é causada por alterações nas vias metabólicas do sistema trigeminovascular. Crises de migrânea estão associadas à inflamação neurovascular, mas seus mecanismos patofisiológicos ainda não são totalmente explicados. **Objetivo**: Investigar a relação entre níveis séricos de vaspina, visfatina, quemerina e interleucina-18 (IL-18) e a frequência de crises de migrânea. **Métodos**: Três grupos foram formados: migrânea com aura (n = 50), migrânea sem aura (n = 50) e grupo controle (n = 50). A migrânea foi diagnosticada de acordo com os critérios da Classificação Internacional das Cefaleias (ICHD-III). As análises dos níveis séricos de vaspina, visfatina, quemerina e IL-18 foram realizadas utilizando-se o método imunoenzimático (ELISA). **Resultados**: Os níveis séricos de vaspina, visfatina, quemerina e interleucina-18 (IL-18) foram significativamente mais elevados em pacientes com migrânea do que no grupo controle ($p < 0.01$). Nenhuma diferença estatisticamente significativa foi observada nos níveis séricos de vaspina, visfatina, quemerina e interleucina-18 (IL-18) entre os pacientes com migrânea durante crises ou no período interictal ($p>0,05$). Os níveis séricos de visfatina e quemerina em pacientes com migrânea se correlacionaram positivamente com os níveis séricos de IL-18 ($p < 0,01$), ao passo que os níveis séricos de quemerina e visfatina se correlacionaram positivamente com os níveis séricos de vaspina ($p < 0,05$). **Conclusões**: Este estudo demonstrou que estes biomarcadores podem estar relacionados à patogênese da migrânea. Contudo, acreditamos que estudos mais abrangentes são necessários a fim de melhor compreendermos o papel dos níveis de vaspina, visfatina, quemerina e IL-18 na fisiopatologia da migrânea.

Palavras-chave: Quimerina 1; Interleucina-18; Inflamação; Enxaqueca sem Aura; Patogênese Homeopática; Vaspina; Nicotinamida Fosforribosiltransferase.

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INTRODUCTION

Migraines are headaches that are brought on by alterations in the trigeminovascular system. Migraine attacks are related to neurovascular inflammation of the cerebral and extracerebral vessels; however, their pathophysiology mechanisms are still unknown[1]. It has been reported that migraines are connected to various metabolic disorders, such as obesity, dyslipidemia and hyperinsulinemia[2].

Vaspin, also known as serpin, is a member of the serine protease inhibitor family. This molecule is synthesized from visceral adipose tissue in Otsuka Long-Evans Tokushima Fatty rats at the age when obesity and insulin plasma concentrations reach their peak[3,4]. Vaspin is a member of the adipokine family, which is isolated from both visceral and subcutaneous white adipose tissue. Various studies in the literature have stated that activation of vaspin mRNA expression in human adipose tissue may be a compensatory mechanism related to obesity and insulin resistance. It has also been reported that vaspin is suppressed by tumor necrosis factor-alpha (TNF-α), leptin and resistin[5,6].

Visfatin/pre-B cell colony-enhancing factor-1/nicotinamide phosphoribosyl transferase, which is broken down and activated via c-terminals, is a protein synthesized as an inactive form of prochemerin[7,8].

Chemerin has been found to be associated with paracrine/autocrine signals. Differentiation of chemerin also regulates glucose uptake by accelerating lipolysis in adipocytes[9,10].

Interleukin-18, which is a member of the IL-1 family, is a proinflammatory cytokine. Prointerleukin-18 is synthesized as an inactive precursor molecule and is transformed into an active form through intracellular cysteine protease or the caspase-1 enzyme. This enzyme also initiates the process of converting IL-1β into its active form. IL-18, which was originally called interferon gamma (IFN-γ) inducing factor, is a strong stimulant of IFN-γ and has an important effect on host defense. Thus, IL-18 has been shown to play a role in the pathogenesis of many inflammatory and autoimmune diseases[11].

In reviewing literature review, we found that there were very few studies relating to migraine disease and these biomarkers. The aim of the present study was to investigate the relationship between serum vaspin, visfatin, chemerin and IL-18 biomarker levels and occurrences of migraine disease.

METHODS

One hundred migraine patients and fifty age and sex-matched control participants were enrolled in this study. The migraine patients were clinically assessed by a neurologist at the Department of Neurology of Dicle University. The migraine diagnosis was made in accordance with the International Classification of Headache Disorders-III beta diagnostic criteria[12]. It was determined that 50 patients had migraines without aura, while the remaining 50 patients had migraine with aura.

The patients in the migraine group were divided into two subgroups: migraine in the attack period (with or without aura) (n = 40) and migraine in the interictal period (with or without aura) (n = 60). The control group was composed of healthy individuals who had no headaches of any kind.

The attack frequency of the migraines was recorded as the number of attacks per month. The body mass index of the participants was measured in accordance with the recommendations of the World Health Organization. The exclusion criteria comprised occurrences of the following: thyroid dysfunction, diabetes, metabolic diseases, cardiovascular diseases, chronic illnesses, renal diseases, infectious diseases or pregnancy.

This study was approved by the ethics committee of Dicle University (2017/216), and written informed consent was obtained from all participants prior to their inclusion in the study. It was conducted in accordance with the Declaration of Helsinki.

Biochemical analysis

Blood samples were taken from the control group and from the migraine group. Among the migraine patients, this was done both when they were experiencing migraine headaches and when they were not. The venous blood samples were instantly centrifuged at 3000 rpm for 10 min at 4 °C and then poured into Eppendorf tubes. The serum samples were transferred on ice and stored at -80 °C for three months until the end of the study period.

The serum vaspin, visfatin, chemerin and IL-18 levels were measured using commercially available enzyme-linked immunosorbent assay kits (YL Biont, China). The absorbance was read at 450 nm and recorded using an absorbance microtiter plate reader (ELx800™; BioTek Instruments, USA). The serum glucose, total protein, albumin, globulin, cholesterol and triglyceride levels were determined using routine colorimetric methods in an autoanalyzer (Roche Modular Autoanalyzer; Roche, Tokyo, Japan).

Statistical analyses

The Statistical Package for the Social Sciences (SPSS), version 17.0, was used to conduct the statistical analysis. The descriptive statistics were presented as means, standard deviations and frequency distributions. The categorical data were compared using the chi-square test, while the continuous data were compared using Student's t test. The correlation analysis was carried out using Pearson's correlation test. The results are presented in Tables 1, 2 and 3. P-values less than 0.05 were accepted as statistically significant.

Table 1. Baseline characteristics of serum vaspin, visfatin, chemerin and IL-18 levels in migraine patients and the control group.

Characteristics	Control group (n = 50)	Migraine group (n = 100)	p value
Age(years)	25.6 ± 7.1	28.5 ± 8.1	0.086
Sex (female/male)	28/22	60/40	
Height (cm)	1.6 ±08	1.6 ± 0.0	0.073
Weight (kg)	66.2 ± 17.3	66.4 ± 14.6	0.950
BMI (kg/m^2)	23.3 ± 4.4	24.3 ± 4.4	0.200
Visfatin (ng/ml)	8.8 ± 4.6	23.8 ± 21.7**	< 0.001
IL-18 (ng/ml)	11.9 ± 7.3	27.1 ± 35.1*	0.003
Chemerin (ng/ml)	119.8 ± 36.7	241.4 ± 253.4*	0.001
Vaspin (pg/ml)	0.5 ± 0.3	1.3 ± 1.7*	0.002
Albumin (mg/dl)	5.0 ± 0.3	5.1 ± 0.3	0.228
Cholesterol (mg/dl)	157.8 ± 26.8	162.6 ± 33.7	0.391
Glucose (mg/dl)	94.8 ± 27.8	76.9 ± 20.2**	< 0.001
HDL (mg/dl)	49.2 ± 16.2	45.3 ± 10.3	0.074
Total protein (mg/dl)	8.3 ± 0.4	8.2 ± 0.3	0.708
Triglycerides (mg/dl)	123.4 ± 74.9	149.7 ± 62.6*	0.025
Globulin (mg/dl)	3.2 ± 0.2	3.2 ± 0.4	0.444

Notes: Data are expressed as (mean ± SD); SD: standard deviation. $p < 0.001$**, $p < 0.05$*: the degree of significance of the comparison between the patient and control groups.

Table 2. Comparison of serum vaspin, visfatin, chemerin and IL-18 levels between migraine subgroups and control group.

Characteristics	Control group (n=50)	Migraine with aura (n = 50)	Migraine without aura (n=50)	p value
Visfatin (ng/ml)	8.9 ± 4.7	21.2 ± 20.8**	27.4 ± 31.8**	< 0.001
IL-18 (ng/l)	11.9 ± 7.3	47.4 ± 174.5*	26.6 ± 34.8*	0.012
Chemerin (ng/ml)	119.9 ± 36.8	234.9 ± 229.7 *	261.1 ± 383.7 *	0.017
Vaspin (pg/ml)	0.52 ± 31	1.2 ± 1.67 *	1.31 ± 1.86 *	0.011
Albumin (mg/dl)	5.05 ± 0.37	5.20 ± 0.41 *	5.05 ± 0.29 *	0.048
Cholesterol (mg/dl)	155.3 ± 34.6	166.1 ± 35.3	159.4 ± 32.4	0.284
Glucose (mg/dl)	94.8 ± 27.8	77.2 ± 18.0**	75.1 ± 22.1 **	< 0.001
HDL (mg/dl)	49.2 ± 16.2	45.7 ± 11.4	45.2 ± 45.2	0.221
Total protein (mg/dl)	8.3 ± 0.44	8.3 ± 0.37	8.2 ± 0.37	0.206
Triglycerides (mg/dl)	123.4 ± 74.9	144.1 ± 56.9	155.5 ± 68.4	0.057
Globulin (mg/dl)	3.2 ± 0.2	2.9 ± 1.4	3.1 ± 0.3	0.253

Notes: Data are expressed as (mean ± SD); SD: standard deviation; $p < 0.001$**, $p<0.05$* the degree of significance of the comparison between the patient and control groups

Table 3. Comparison of serum vaspin, visfatin, chemerin and IL-18 levels between migraine subgroups.

	Interictal period (n = 60)	Migraine during attack (n = 40)	p value
Visfatin (ng/ml)	23.9 ± 22.1	23.7 ± 21.3	0.964
IL-18 (ng/l)	25.7 ± 32.9	29.2 ± 38.6	0.622
Chemerin (ng/ml)	255.4 ± 278.7	220.3 ± 211.6	0.500
Vaspin (pg/ml)	1.4 ± 2.0	1.1 ± 1.1	0.391

Notes: Data are expressed as (mean ± SD); SD: standard deviation .

RESULTS

The serum vaspin, visfatin, chemerin, IL-18, albumin and triglyceride levels were significantly higher in the migraine group than in the control group. The serum glucose levels were significantly lower in the migraine group than in the control group ($p < 0.01$). There were no significant differences between the control and migraine groups in terms of serum cholesterol, total protein, albumin, globulin and high-density lipoprotein cholesterol levels ($p > 0.05$) (Table 1).

The serum visfatin and chemerin levels of the migraine patients were positively correlated with their serum IL-18 levels ($p < 0.01$), and their serum visfatin and chemerin levels were positively correlated with their serum vaspin levels ($p < 0.05$). It was determined that the serum vaspin, visfatin, chemerin and IL-18 levels did not correlate with age, disease duration or frequency of migraine headaches ($p > 0.05$) (Table 2). There were no statistically significant differences in serum vaspin, visfatin, chemerin and IL-18 levels between the groups in terms of interictal period and attack period ($p > 0.05$) (Table 3).

DISCUSSION

Migraines are thought to stem from dysfunction of an area in the brainstem that is associated with pain modulation and sensory processing. This area has also been shown to control trigeminocervical nociceptive inputs[13]. Accordingly, pain is understood to be a combination of an altered perception of stimuli and activation of a feed-forward neurovascular dilator mechanism in the first division of the trigeminal nerve[14]. Experimental studies have shown that cortical spreading depression may trigger neurogenic meningeal inflammation and activate the trigeminovascular system[15].

We found that the serum vaspin, visfatin, chemerin and IL-18 levels were higher in the migraine patients than in the control group and that these differences were statistically significant. The serum vaspin, visfatin, chemerin and IL-18 levels in the migraine subgroups were found to be significantly higher than those of the control group. However, there were no statistically significant differences among the patients in terms of interictal periods and attack periods. Furthermore, a positive correlation was observed between serum visfatin levels and serum chemerin and vaspin levels in the migraine group. In our review of the literature, we did not find any studies regarding serum chemerin, vaspin and IL-18 biomarkers in migraine patients. In this regard, this is the first clinical study to investigate the role of these biomarkers in migraine patients.

Visfatin is a pre-B cell clonal factor for highly expressed lymphocyte secretion that is located in the liver, kidney, brain, muscle and adipose tissue. It can induce expression of proinflammatory cytokines, such as IL-1, IL-6 and TNF-α, and can increase the activity of nuclear factor kappa B (Nf-K B)[16,17]. Visfatin increases the production of proinflammatory cytokines and synthesizes adhesion molecules, and it also causes leukocyte activation. When visfatin is expressed, it activates synthesis of IL-6 in dendritic cells and peripheral mononuclear blood cells[18,19]. Several researchers have studied the role of visfatin in acute ischemic stroke and have demonstrated increased plasma visfatin levels in such cases[20,21].

In our review of the literature review, we only found a limited number of studies regarding migraine patients and serum visfatin levels. In a study conducted by Li et al.[22], it was determined that plasma visfatin levels increased in migraine patients during the attack period, compared with the control group. They also found that plasma visfatin levels did not change in the interictal period, in comparison with the control group[22]. In the present study, it was determined that serum visfatin levels in the migraine patients were higher than those in the control group and that this difference was also significant for the migraine subgroups, in comparison with the control group. The fact that visfatin is released from adipocytes indicates that it stimulates the neuroimmune mechanism by activating receptors within the pathophysiology of the neurons. Moreover, this causes migraine headaches through inducing Nf-K B molecules in the vascular endothelium.

The concentration of serum chemerin in the blood is related to diabetes, metabolic syndrome and obesity[23,24]. Chemerin plays a significant role in the development of insulin resistance and in the differentiation of human adipocytes[25,26]. It was first known as a chemoattractant for immune cells, including macrophages and dendritic cells[27]. In the present study, it was determined that serum chemerin levels were higher in migraine patients than in the control group and that this difference was statistically significant. A positive correlation was found between serum chemerin levels and serum vaspin, visfatin and IL-18 levels, both in the migraine with aura group and in the migraine without aura group. The high level of serum chemerin in the migraine group indicates that it most probably plays a role in the inflammatory response within the neuroimmune mechanism. This creates migraine pathophysiology through increasing nitric oxide production in the metabolic pathway of the endothelial nitric oxide synthase cascade.

Vaspin plays a local endocrine role as an adipocytokine by enhancing the onset and progression of atherosclerosis in obese patients. This affects the endothelium, vascular smooth muscle, macrophages and vascular hemostasis[28,29]. It inhibits the expression of proinflammatory adipocytokines, including leptin, resistin and TNF-α, in mesenteric and subdermal white adipose tissues[30]. In the present study, it was observed that the serum vaspin levels were higher in the migraine patients than in the control group and that this difference was statistically significant. This rise in levels was also found to be significant in the migraine subgroups, in comparison with the control group. In the light of this information, the higher serum vaspin levels in the migraine patients suggest that vaspin plays an inhibitory role in the vascular inflammatory response.

Cytokines bind afferent neuron receptors and directly generate pain, while proinflammatory cytokines increase the sensitivity of pain through directly activating nonreceptive neurons and producing an action potential[31,32]. IL-18 is encoded by the IL-18 gene, which induces inflammatory reactions, and it is a proinflammatory cytokine that induces

IFN-γ[33,34]. In the present study, serum IL-18, which is a proinflammatory cytokine in migraine patients, was found to present statistically higher levels in the migraine patients than in the control group. It has been reported that interferon beta, which is often used to treat multiple sclerosis, reduces IL-18 expression[35]. The high levels of serum IL-18 in the migraine patients suggest that it causes inflammatory mediators to be released into the circulation, and that these inflammatory mediators stimulate receptors in neurons and cause migraines.

Many studies have been conducted to explain the pathogenesis of migraines. In one such study, Silva et al.[36] investigated endothelial function in migraine patients during the interictal period and found that there were no statistically significant differences in terms of forearm flow-mediated vasodilation, fasting nitrates and nitrites, glucose and lipid profiles. Nevertheless, in the present study, the serum glucose levels in the migraine patients were found to be lower than in the control group, and this difference was statistically significant. This lower serum glucose concentration in the migraine patients was most likely due to increased glucose intake through stimulation of the appetite center due to increased serum visfatin levels. This conclusion was reached because a previous study demonstrated that plasma glucose levels decreased in mice that were given visfatin[37]. Conversely, there was no statistical relationship between serum glucose and serum visfatin in the present study.

In an experimental study conducted by Bozakoğlu et al.[38], it was stated that serum chemerin levels were related to triglyceride expression in the group with normal glucose tolerance[38]. In the present study, the serum triglyceride levels were determined to be higher in the migraine patients, and this difference was statistically significant. The higher serum triglyceride concentration may have resulted from the serum chemerin level. However, there was no correlation between serum chemerin and serum triglycerides.

In conclusion, the serum vaspin, visfatin, chemerin and IL-18 levels were found to be higher in migraine patients. Another point worth mentioning is that these findings may be related to migraine pathogenesis. The increased levels of proinflammatory molecules seen in the migraine patients and the lack of difference between migraine patients with aura and without aura make our study valuable. We consider that inflammation is very important in the pathophysiology of migraine with aura. Nonetheless, we believe that more comprehensive studies are needed in order to further understand the role of serum vaspin, visfatin, chemerin and IL-18 levels in the pathophysiology of migraine headaches.

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