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Evaluation of serum adipocytokine and interleukin-18 levels in patients with epilepsy

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Abstract

Objective: Epilepsy is a neurological disease characterized by recurrent seizures. The underlying pathophysiological mechanisms in epilepsy are not fully known. Our aim is to investigate the relationship between serum adipocytokine and interleukin (IL)-18 levels in epilepsy patients receiving and not receiving antiepileptic therapy.

Method: Our study was established as three groups. I: Epilepsy patients receiving antiepileptic therapy (n=30), II: Newly diagnosed epilepsy patients (n=30) and III: Control group (n=30). Serum adipocytokine and IL-18 levels were measured by enzyme-linked immunoassorbent assay method.

Results: It was determined that serum adipocytokine and IL-18 levels were increased in epilepsy patients who received topiramate treatment and did not receive antiepileptic therapy compared to the control group. Serum glucose, total protein, cholesterol and albumin concentrations of patients who received antiepileptic treatment were decreased compared to the control group ($p<0.001$). It was found that serum adipocytokine and IL-18 concentration in epilepsy patients who received topiramate treatment decreased compared to patients who did not receive treatment, but it was not significant ($p>0.05$). It was found that the body mass index (BMI) ratio of epilepsy patients who received antiepileptic treatment decreased and was significant compared to the control group and the group that did not receive treatment ($p<0.01$).

Conclusion: In our study, it was shown that serum adipocytokine and IL-18 levels were increased in epilepsy patients who received and did not receive antiepileptic therapy. Findings from this study suggest that adipocytokine and IL-18 may be useful markers for the inflammatory process of epileptogenesis.

Keywords: Topiramate, Interleukin-18, Adipocytokine, Epilepsy

INTRODUCTION

Epilepsy, which affects millions of people around the world, is a neurological disease characterized by recurrent seizures. The underlying pathophysiological mechanisms in epilepsy have not been fully elucidated. Neurological injuries such as stroke, central nervous system (CNS) infections, inflammation, traumatic brain injury, cerebrovascular injuries play an important role in the pathophysiology of epilepsy (1-3). The process is activated when the blood-brain barrier function is impaired. In this process, it is thought that inflammatory mediators leaking into the CNS may cause neuroinflammation (4, 5).

Vaspin, isolated from white adipose tissue and visceral tissue, is a biomarker belonging to the adipokine family. Some studies have suggested that active mRNA expression of vaspin in human adipose tissue may be a compensatory mechanism for obesity and insulin resistance (6, 7).

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Visfatin is an adipokine with different functions and synthesized from different cells. Adipocytes, neutrophils, monocytes, lymphocytes, hepatocytes and pneumocytes are the main sources of visfatin. It has been stated that visfatin level is high in acute and chronic inflammatory diseases (8, 9).

Chemerin is a protein that is synthesized from the inactive form of prochemerin and is cleaved by serine proteases and activated via its C terminals (10). It has been stated that the chemerin molecule, which is involved in the maturation and differentiation of adipocytes, is associated with paracrine/autocrine signals (11).

Interleukin (IL)-18 is a pro-inflammatory cytokine, and IL-18, a molecule that belongs to the IL-1 family and was initially shown as an interferon gamma (IFN-γ) inducing factor, has been reported to be associated with a number of inflammatory and autoimmune diseases (12).

A limited number of studies were found related to epilepsy with and without topiramate treatment with the mentioned biomarkers (13). Hence the aim of the present study was to investigate the relationship between serum adipocytokine and IL-18 levels in epilepsy patients.

METHODS

This study was carried out in Dicle University Faculty of Medicine, Department of Neurology. The study was approved by the Dicle University Clinical Research Ethics Committee (ethic approval no:18/05/2018-176). The study was evaluated by two expert neurologists. Classification of epileptic seizures was carried out according to the epilepsy classification of the International League against Epilepsy, which was published in 2017 (14). Magnetic resonance imaging and electroencephalography (EEG) of the patients were taken. Patients with pathological EEG findings and patients with psychogenic seizures were not included in the study. Three groups were established: (I) The patient diagnosed with epilepsy (n=30): Patients who came one week after the seizure were included in the study. (II) Patients in this group included 30 epilepsy patients who received topiramate therapy as monotherapy for at least one year. (III) Healthy individuals who did not use any medication were selected as the control group (n=30). Conditions such as hypertension, acute and chronic infection, diabetes mellitus, autoimmune disease, fever, traumatic brain injury, psychiatric diseases, gastrointestinal disease, and obese individuals in all three groups were determined as the exclusion criteria of our study. An information form was signed by the volunteers in the patient and control groups in our study. It was conducted in accordance with the Declaration of Helsinki.

Biochemical Analyses

Blood samples were withdrawn from the epilepsy patient and from the control groups. Serum was obtained by centrifuging venous blood at 5000 rpm for 10 minutes. These serum samples were transferred to eppendorf tubes and kept at -80 degrees until the study day. Vaspin, visfatin, chemerin and IL-18 levels in the obtained serum were determined by enzyme-linked immunosorbent assay kits (Vaspin catalog no:YLB3664HU, the assay range for kit:1ng/mL→30ng/mL, sensitivity:0.48ng/mL, intra-interassay coefficients of variance <9%-<11%; visfatin catalog no:YLB3665HU, the assay rangefor kit: 1µg/L→20µg/L sensitivity:0.51µg/L, intra-interassay coefficients of variance: <9%-<11%, chemerin catalog no: YLB0782HU, the assay range for kit:2ng/L→40ng/L, sensitivity:0.96ng intra-interassay coefficients of variance <9%-<11%, IL-18:catalog no:YLB1955HU, the assay range for kit:5ng/L→100ng/L, sensitivity:2.35ng/L, intra-interassay coefficients of variance <9%-<11%, YL Biont, China) method. Serum triglyceride, albumin, globulin, total protein, cholesterol and glucose levels were studied by colorimetric method (Roche Modular Autoanalyzer; Roche, Tokyo, Japan).

Statistical Analysis

Statistical analyses were performed using SPSS 18.0 program (SPSS Inc., USA). The categorical variables were expressed as numbers and percentages. The conformity of the data to the normal distribution was checked with Kolmogorov-Smirnov and Shapiro-Wilk tests. 2-group student–T test for parameters with normal distribution. Three-group One Way ANOVA and Mann Whitney-U test were used to compare pairwise groups in parameters that were not normally distributed. Kruskal Wallis Test was used to compare more than two groups. Paired comparisons were made with Tukey HSD as a pot-hoc test in test by making bonferroni correction to understand which group caused the statistical difference. The cutoff values and corresponding sensitivity and specificity values for the prediction between the epilepsy group and the control group based on serum adipocytokine and IL-18 were estimated by receiver operating characteristic (ROC) curve analysis. Spearman correlation analysis was used to determine the relationship between the data. A result was accepted as statistically significant with a p-value < 0.05.

RESULTS

The mean age of the control group was 23.46±6.94 years, the mean age of the group that did not receive antiepileptic treatment was 27.83±13.20 years, and the mean age of the group that received topiramate therapy was 31.23±10.71 years, and there was no statistical difference between the three groups in terms of age. It was found that BMI ratio was lower in patients who received topiramate therapy compared to the control group and patients who did not receive treatment ($p<0.01$). There was no statistical difference between the genders in all three groups ($p>0.05$) (Table 1).

Table 1. Characteristics of control and patient groups

		Control group (n=30)		Epilepsy group not receiving antiepileptic therapy (n=30)		Epilepsy group receiving topiramate therapy (n=30)		p value
		n	%	n	%	n	%	
Gender	Female	16	53.3	16	53.3	15	50	
	Male	14	46.7	14	46.7	15	50	
Age (Year)		21.00(18.00-60.00) 23.46±6.94		20.50(18.00-60.00) 27.83±13.20		21.00(18.00-60.00) 31.23±10.71		0.093
BMI (kg/m²)		22.00 (14-36) 23.20±4.773		22.50(19-26) 22.23±2.063		20.50(18-24) * 20.90±1.517		0.020

Data are given as Mean±Standard deviation and median (minimum-maximum). p<0.001* The difference between the patient and control group is significant.
Abbreviations:BMI; Body mass index

Serum visfatin, vaspin, chemerin and IL-18 levels in patients who received and did not receive antiepileptic treatment were higher than the control group and were statistically significant. Serum total protein, albumin, glucose and cholesterol levels were found to be decreased and statistically significant compared to epilepsy patients who received and did not receive treatment (p<0.001). There was no statistically significant difference between the groups in terms of serum triglyceride, HDL and globulin values (p>0.05). (Table 2)

A positive correlation was observed between serum IL-18 levels and visfatin, chemerin in epilepsy patients receiving topiramate therapy (p<0.01). A positive correlation was observed between serum vaspin and visfatin and triglyceride levels (p<0.05). A positive correlation was observed between serum triglyceride level and BMI and visfatin (p<0.01). (Table 3)

Table 2. Comparison of epilepsy patients with and without antiepileptic treatment and the control group

Parameters	Control group (n=30)	Epilepsy group not receiving antiepileptic therapy (n=30)	Epilepsy group receiving topiramate therapy (n=30)	p value
Visfatin (ng/mL)	10.54 (4.75-14.64)	19.35 (12.88-68.95) *	15.10 (9.97-47.47) *	<0.001
IL-18 (µg/L)	12.23 (6.48-24.84)	16.08 (12.22-91.91) *	15.61 (11.11-44.58) *	0.007
Chemerin (ng/mL)	104.90 (73.86-165.40)	133.79 (95.46-958.67) *	122.93 (70.71-771.81) *	<0.001
Vaspin (ng/mL)	0.51 (0.16-0.96)	1.6703 (1.01-6.79) *	0.55 (0.23-1.32)*	<0.001
Glucose (mg/dL)	93.00 (59.00-104.00)	75.00 (55.00-95.00) *	74.00 (51.00-108.00) *	<0.001
Cholesterol (mg/dL)	149.00 (112.00-235.00)	162.00 (128.00-229.00)	144.00 (102.00-212.00) *	0.018
HDL (mg/dL)	45.55 (22.30-89.20)	49.10 (31.90-67.20)	47.80 (24.00-64.90)	0.992
Triglyceride (mg/dL)	95.00 (51.00-446.00)	117.00 (66.00-210.00)	119.00 (70.00-291.00)	0.394
Albumin (mg/dL)	5.18 (4.30-5.73)	5.03 (4.62-5.29) *	4.84 (4.42-5.22) *	<0.001
Globulin (mg/dL)	3.22 (2.77-3.76)	3.14 (2.64-3.43)	2.95 (2.75-4.06)	0.139
Total protein (mg/dL)	8.34 (7.20-9.24)	8.02 (7.62-8.61) *	7.8350 (7.17-8.67) *	0.001

Data are given as median (minimum-maximum). p<0.001* The difference between the patient and control group is significant.
Abbreviations: IL-18:Interleukin-18, HDL: High-density lipoprotein

Table 3. Correlation coefficients between parameters in the group receiving topiramate therapy

Parameters		BMI	Visfatin	IL-18	Chemerin	Vaspin
BMI		1				
Visfatin	r	0.323	1			
	p	0.082				
IL-18	r	-0.085	0.518**	1		
	p	0.656	0.003			
Chemerin	r	0.189	0.606**	0.728**	1	
	p	0,317	0.000	0.000		
Vaspin	r	0.311	0.444*	0.203	0.285	1
	p	0.094	0.014	0.283	0.127	
Triglyceride	r	0.413*	0.451*	0.223	0.218	0.043
	p	0.023	0.012	0.237	0.247	0.821

**p<0.01, *p<0.05 Abbreviations: IL-18: Interleukin-18, BMI: Body mass index

A negative correlation was found between serum IL-18 and visfatin and chemerin (p<0.01) serum vaspin levels and BMI in the epilepsy group who did not receive antiepileptic therapy (p<0.05). (Table 4)

Table 4. Correlation coefficients between parameters in the group not taking antiepileptic drugs

Parameters		BMI	Visfatin	IL-18	Chemerin	Vaspin
BMI		1				
Visfatin	r	-0.062	1			
	p	0.744				
IL-18	r	0.091	0.625**	1		
	p	0.632	0.000			
Chemerin	r	-0.078	0.458*	0.667**	1	
	p	0.681	0.011	0.000		
Vaspin	r	-0.424*	0.081	0.044	0.366*	1
	p	0.020	0.670	0.816	0.047	
Triglyceride	r	-0.274	0.162	-0.135	-0.280	-0.106
	p	0.143	0.393	0.478	0.134	0.578

**p<0.01, *p<0.05 Abbreviations: IL-18: Interleukin-18, BMI: Body mass index

In the ROC curve analysis performed between epilepsy patients and the control group, the cut-off value of the visfatin molecule was 14.24, sensitivity 81.7% and specificity 96.7%. Cut-off value of IL-18 molecule was determined as 24.21 sensitivity, 20% and specificity as 96.7%. The cut-off value of the chemerin molecule was determined as 163.68, sensitivity 35% and specificity 96.7%. The cut-off value of the vaspin molecule was 0.96, sensitivity of 58% and specificity of 96.7%. (Figure 1)

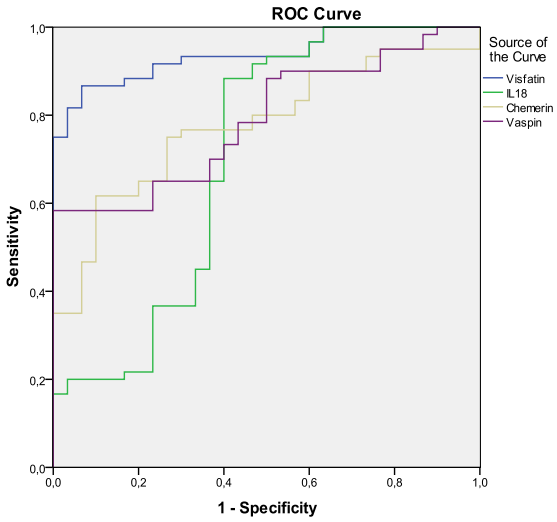

Figure 1. The ROC curve analysis of vaspin, visfatin, IL-18 and chemerin for prediction between the frequently control group between in patients with epilepsy. Abbreviations: IL-18: Interleukin-18, ROC, receiving operating characteristic.

DISCUSSION

Epilepsy is a disease characterized by recurrent seizures that cause behavioral, cognitive psychology and neurobiological disorders (15). The pathophysiology of epilepsy has not been fully explained. It has been observed that pro-inflammatory cytokines such as IL-1β, IL-2, and IL-6 increase after epileptic seizures (16).

In the study, it was determined that serum visfatin, vaspin, chemerin, and IL-18 serum levels increased in patients with epilepsy. It was observed that the levels of these biomarkers were decreased in patients receiving topiramate therapy, but not significantly. It was found that the BMI ratio of epilepsy patients who received topiramate therapy decreased compared to the control group and the group that did not receive antiepileptic treatment.

Studies in the literature on epilepsy patients and serum vaspin, visfatin, and chemerin levels were generally performed in pediatric patients. However, these studies are limited in number (13). This is the first clinical study in adult epilepsy patients.

IL-18, a classical pro-inflammatory cytokine, is associated with the IL-1 family released from the NLR family pyrin domain containing 3 (NLRP3) inflammasome. It has been reported that IL-18 is produced in the CNS and its receptors are expressed in neurons (17-19). Liu et al. (20) stated that IL-18, caspase 1, and NLRP3 inflammasome expression increased in their experimental epilepsy model. In this sense, Mochol et al. (21) suggested that there is an increase in serum IL-18, and IL-18BP receptor levels in patients receiving carbamazepine. In our study, it was found that there was a significant increase in serum IL-18 levels in patients with epilepsy. The elevation

of serum IL-18 level in epilepsy patients suggests that it may increase pro-inflammatory cytokine release in glial cells and impair the permeability of the blood-brain barrier. Mochol et al. found no correlation with serum IL-18 and BMI ratio in their study. They found that the serum IL-18 level was high in patients with a BMI ratio of less than 30 kg/m² and did not correlate with the BMI (21). In our study, no correlation was found between BMI and serum IL-18 levels. Hung et al. (22) suggested that high serum IL-18 level may be a risk marker for metabolic risk, but this is independent of obesity and insulin resistance. This study showed similar results with previous studies. In addition, there was a positive correlation between serum IL-18 level and serum chemerin, visfatin levels. These results indicate that adipose tissue may contribute to inflammation.

It has been stated that the concentration of chemerin rises in response to pro-inflammatory molecules to induce migration of macrophages, natural killer cells, and dendritic cells to the site of inflammation (23). The CNS has also been suggested that elevated chemerin levels in other tissues may serve as a biomarker of chronic inflammation (24). In our study, it was found that there was a significant increase in serum chemerin levels in patients with epilepsy. Elhady et al. (25) found significantly higher serum chemerin levels in idiopathic pediatric epilepsy patients receiving treatment, especially in those with uncontrolled seizures. In our study, it was shown that there was a positive correlation between serum chemerin levels and IL-18, visfatin and vaspin levels in patients with epilepsy. The high serum chemerin concentrations and its correlation with IL-18 indicate that angiogenesis is induced in endothelial cells and may induce inflammation by activating pro-inflammatory cytokines.

Studies with the visfatin molecule have generally focused on metabolic and immune diseases, and its inflammatory mediator role has been defined in some studies. Visfatin can induce the expression of pro-inflammatory cytokines such as IL-1, IL-6 and TNF-α. NF-κB can also be increased by visfatin (26, 27). In our study, it was shown that serum visfatin levels were significantly increased in patients with epilepsy. It has been reported that the serum visfatin level is significantly increased in children treated with valproic acid (13). Sonmez et al. (28) stated that in pediatric patients receiving topiramate treatment, adiponectin levels increased in the 6th and 12th month, leptin levels decreased, and there was no statistical significance in visfatin levels. High serum visfatin concentrations in our study suggest that it may cause leukocyte infiltration by increasing adhesion molecules and pro-inflammatory cytokines, and may induce inflammation in microglial cells by increasing the release of cytokines in adipose tissue that functions as an endocrine organ. The positive correlation between serum visfatin and vaspin, chemerin and IL-18 concentrations in the epileptogenesis process in the correlation analyzes indicates that neuronal inflammation may contribute to the epilepsy process.

Vaspin has been shown to inhibit the expression of pro-inflammatory adipocytokines such as resistin, leptin and TNF-α in mesenteric and subdermal white adipose tissues (29). In our study, it was determined that there was a significant increase in serum vaspin levels in patients with epilepsy. Meral et al. (13) stated that serum vaspin concentration was increased in pediatric patients receiving valproic acid, but it was not significant. The high serum vaspin concentration suggests that it may increase free reactive oxygen radicals by increasing vascular adhesion molecules, and therefore, a molecular mechanism that can serve the metabolic pathway in the vascular inflammatory response of serum vaspin concentration will be used in physiopathology.

Uludag et al. (32) in their study on epilepsy patients receiving topiramate and valproic acid treatment, they reported that these values were higher in obese epilepsy patients, where serum leptin levels decreased significantly in non-obese patients. Generally, normal weight and overweight patients were selected in studies with adipocytokine biomarkers in epilepsy patients. Our patient group was selected from non-obese patients, so the fact that the biomarkers we studied were high in these patients makes our study valuable.

Topiramate, a new generation antiepileptic drug, has been reported to adversely affect body weight (30). The mechanism of topiramate-related weight loss has not been fully elucidated. It has been stated that topiramate treatment can reduce body weight by inhibiting the white adipose tissue deposits affected by the activity of lipoprotein lipase in brown adipose tissue. It has also been reported that topiramate stimulates the activation of lipoprotein lipase in skeletal muscles and therefore supports substrate oxidation (33). Li et al. (31) a study of 6.8-year-old children with epilepsy treated with topiramate showed a reduction in BMI. It has been stated that the increase in adiponectin biomarker levels in those receiving topiramate therapy may be an important factor in topiramate-related weight loss. In our study, it was shown that the BMI ratio decreased significantly in the group receiving topiramate therapy. In addition, a positive correlation was observed between serum triglyceride and visfatin concentration and BMI ratio in the group receiving topiramate therapy. It has been reported that glucose concentration decreased and glucose tolerance was impaired in the rat who received topiramate therapy (34). In our study, it was observed that the serum glucose concentration was significantly decreased in the treated and untreated group compared to the control group. Topiramate therapy has been reported to decrease serum triglycerides and cholesterol concentrations (35). In the study of Uludağ et al. (32) no

change was observed in serum triglyceride level. In our study, there was no significant decrease in serum cholesterol level and no significant difference in serum triglyceride and HDL concentrations in patients receiving topiramate therapy. In addition, it was determined that there was a significant decrease in serum cholesterol, total protein and albumin concentrations in the group receiving topiramate therapy. It is thought that the concentration of serum glucose, cholesterol, total protein and albumin in those receiving topiramate therapy may have suppressed the appetite center with the effect of topiramate, and thus their concentrations may have decreased. Ben-Menachem et al. (35) stated in their study that weight loss occurred and calorie intake decreased in the 3th month of topiramate treatment. In the same study, it was shown that leptin levels decreased as weight loss increased, and there was an improvement in glucose, cholesterol and insulin levels.

The high specificity and probability ratios of serum visfatin, chemerin, vaspin and IL-18 values in ROC analyzes suggest that these biomarkers may be a reliable biomarker in the evaluation of epilepsy disease. It can be evaluated as a biomarker in the diagnosis of epilepsy with large-scale studies.

Limitations of this Study

The small number of patients in the study is among the main limitations of the study. Another limitation of our study is that the relationship between the duration of treatment and serum adipocytokine and IL-18 levels in patients receiving topiramate treatment was not evaluated.

CONCLUSION

İn this study, it was found that serum adipocytokine and IL-18 levels were increased in epilepsy patients who received and did not receive topiramate therapy, and BMI rate decreased in patients who received topiramate therapy. The fact that these cytokines were higher than the control group with the decrease in BMI in topiramate treatment may indicate that these cytokines play a role in the pathophysiology of the disease. Therefore, we think that neuronal inflammation is very important in the pathophysiology of epilepsy.

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Conflict of Interest

The authors declare that they have no conflict of interests regarding content of this article.

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Ethical Declaration

This study was done in Mardin Artuklu University Graduate Education Institute and is the product of the thesis study registered with the number 698205 in the national thesis center.

Is Previously Presented?

Some part of this study was previously presented as oral presentation on 21st International Eastern Mediterranean Family Medicine Congress held in 12-15 May, 2022 Adana, entitled as Evaluation of serum adipocytokine and interleukin-18 levels in patients with epilepsy

Author Contributions

Concept: AD, DK, VJ, Design: AY, OA, MUÇ, AD, DK, Supervising: AD, DK, HA, Financing and equipment: AD, DK, HA, AY, VJ, OA, Data collection and entry: AY, OA, MUÇ, AD, DK, VJ, Analysis and interpretation: AD, VJ, OA, HA, DK, Literature search: DK, AY, VJ, AD, Writing: AD, OA, MUÇ, DK, Critical review: VJ, MUÇ, HA, AD, DK.

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