



## RESEARCH ARTICLE

## Serum Apelin-36 Levels in Migraine Patients with Aura and without Aura

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### Abstract

Migraine is a chronic disease which affects approximately 12-18% of the society, can be accompanied by neurologic and systemic symptoms, and is characterised by mild or severe recurring headache attacks. The aim of this study is to determine serum apelin-36 level in the patients with migraine with aura and without aura and to compare the obtained data with the data of the healthy control group. The migren study group consisted of 44 women patients, suffering from migraine with (n = 16) and without (n = 28) aura were assessed during the migraine attack, immediately after, and during the headache-free period. The apelin-36 levels of the individuals in the patient and control groups were determined by ELISA method. In all migraine groups with aura ( $1.86 \pm 0.67$ ) and without aura ( $1.85 \pm 0.77$ ), serum apelin-36 levels were significantly higher as compared to the control ( $0.44 \pm 0.07$ ) ( $p < 0.001$ ). Our findings support the relationship between migraine and the apelin-36 levels.

### Keywords

Apelin-36, Aura, Cytokines, Migraine

### Introduction

Migraine is a chronic disease which affects approximately 12-18% of the society, can be accompanied by neurologic and systemic symptoms, and is characterised by mild or severe recurring headache attacks [1]. The aetiology and pathophysiology of the migraine

which causes an important workforce loss to have not been clearly illuminated yet. Genetic factors due to the familial frequency, and environmental factors due to the triggering factors, such as cigarette smoke, perfume scent, and open air, are considered to play a role in its aetiology [2]. Migraine is usually divided into two subtypes being with aura and without aura. Aura is a phase which either emerges before the headache period or accompanies it, usually lasts less than an hour, and is accompanied by visual, sensory and motor impairments [3,4]. Today, studies on understanding the pathophysiology of migraine continue. It is approached as a multifactorial disease in the genetic aspect and its pathophysiology is being attempted to be explained with various neuronal and vascular theories [5].

While Apelin is an adipocytokine, it is also a neuropeptide and a cardiovascular peptide. The apelin G protein which undertakes various physiologic roles is an endogenous ligand of apelin receptor (APJ) which is a linked receptor [6]. It is widely expressed in various organs such as the heart, lung, kidney, liver, adipose tissue, gastrointestinal tract, brain, adrenal glands, endothelium, and human plasma [7]. Apelin turns into various isoforms such as apelin-12, apelin-13, apelin-17 and apelin-36 by separating from preproapelin, the

77-amino-acid precursor, with an enzymatic reaction. The effects of apelin vary depending on its form. It was reported that the apelin with 13 and 17 amino acids had a stronger biologic activity than the apelin form containing 36 amino acids [8,9]. Although experimental apelin studies focused on the cardiovascular system in the beginning, in the studies performed later, it was reported that apelin played a role in various processes such as regulating the food intake [10], regulation of liquid metabolism [11], experimental pain models [12], bone metabolism [13], and preventing the oxidative stress occurring in the human adipocytes [14].

The objective of this study is to determine serum apelin-36 level in the patients with migraine with aura and without aura and to compare the obtained data with the data of the healthy control group. It is also aimed to scrutinise the probability of any relation between migraine disease, the certain treatment and aetiology of which have not been determined yet, and apelin.

## Patients and Methods

This study consisted of 80 female cases. The migren study group consisted of 44 women patients, suffering from migraine with (n = 16) and without (n = 28) aura were assessed during the migraine attack, immediately after, and during the headache-free period. Mean duration of migraine attack was  $16 \pm 12$  h. Migraine with or without aura was diagnosed according to the criteria of the Headache Classification Committee of the International Headache Society [15]. The patients were at the age of 18-45 years (mean  $\pm$  standard deviation:  $29.6 \pm 7.7$  years). The control group included 36 healthy women, aged 18-45 years (mean age  $30.4 \pm 10.1$ ). All subjects were non-smokers, non-alcoholic, free of any cardiovascular, metabolic, neurological, psychiatric, and coagulation disease and none of them was under any preventive headache treatment before the testing session.

In the cases included in the study, serum samples were taken from the antecubital vein after at least 12 hours of hunger during the period between the attacks in the patient group. Blood samples were centrifuged at  $+4^\circ\text{C}$  4000 rpm for 10 minutes. The obtained serums were stored in the Eppendorf tubes at  $-80^\circ\text{C}$ . The apelin-36 levels of the individuals in the patient and control groups were determined by ELISA (Enzyme-linked immunosorbent assay) method by using Phoenix Pharmaceuticals, INC. brand ELISA kit (antibody coated 96-well plate human Apelin-36).

## Statistical analysis

SPSS 18.0 for Windows (SPSS, Inc, Chicago, Illinois, USA) package software was used for the statistical analysis of the data. The comparison between the groups was carried out with the Student's t-test. The statistical limit of significance was taken as  $p < 0.05$ .

## Results

In all migraine groups with aura ( $1.86 \pm 0.67$ ) and without aura ( $1.85 \pm 0.77$ ), serum apelin-36 levels were significantly higher as compared to the control ( $0.44 \pm 0.07$ ) ( $p < 0.001$ ) (Table 1). No statistically significant difference between the levels of apelin-36 in serum of migrain group with aura and without aura was observed (Table 2). Table 3 shows the ages and age ranges of migraine patients and healthy controls. No significant difference in the mean ages were observed between the groups ( $p > 0.05$ ).

## Discussion

Migraine type of a headache is one of the most frequent headache types that affect the society negatively. Due to its high prevalence, penetration, age and geographical distribution, significant functional and socio-economic effects, it is defined by the World Health Organisation as a high priority public health issue [16,17]. However, the feeling of pain is a complex phenomenon, and its pathogenesis and association with aura are still controversial issues. There are a number of hypotheses and many attempts have been made to combine them all into one theory that would assume the involvement of brain vessels and trigeminal nevre [18,19]. Recent studies have confirmed that apelin is a powerful vasodilator and positive inotropethat has some physiological effects [20]. Therefore, we designed the present study to investigate the possible relationship between apelin-36 and migraine with aura or without aura. In this study, the apelin-36 levels in the patients with migraine with aura and without aura were found to be statistically significantly higher when compared to the control group. Along with this, when the patients with migraine with aura and without aura were evaluated among themselves, a statistically significant difference in terms of the apelin-36 levels was not determined between the migraine patient groups with aura and without aura.

**Table 1:** Serum Apelin-36 levels in groups of control and migraine.

Groups	n	Apelin-36 Levels (ng/ml)		P value
		Mean	Std. Deviation	
Migraine patients	44	1.85	0.73	< 0.001
Control	36	0.44	0.07	

**Table 2:** Serum Apelin-36 levels of migraine patients.

Groups	n	Apelin-36 levels (ng/ml)		P value
		Mean	Std. Deviation	
With aura	16	1.86	0.67	> 0.05
Without Aura	28	1.85	0.77	

**Table 3:** The Demographic Results of Patients and Controls Groups.

	Control (n = 36)	Migraine with aura (n = 16)	Migraine without aura (n = 28)
Age (Year)	$30.4 \pm 10.1$	$29.6 \pm 7.7$	$29.3 \pm 7.7$
Age ranges	18-58	18-58	21-56

n.s,  $p > 0.05$

Apelin-13 plays a significant role in the modulation of pain response at the supraspinal level in mice and the analgesic effect of apelin-13 was mediated by the activation of the APJ receptor and endogenous opioid system [21]. The studies carried out recently on the pathophysiology of migraine with aura and without aura revealed many mechanisms which were not known before [22]. The presence of APJ receptor mRNA in the parts of the brain such as hypothalamus amygdala and dorsal raphe nucleus which ensure the pain control at the central level indicates the probable role of apelin in nociception [10]. Lv, et al. reported that icv injections of apelin-13 at different doses in the acetic acid-induced visceral organ pain models in rats showed an antinociceptive effect. This effect is interpreted as it is a result of strengthening the analgesic effect of morphine by apelin-13 [12]. Similarly, in an experimental study in which Xu, et al. [21] examined the effect of apelin-13 on the pain modulation at the supraspinal level, while the presence of dose and time dependent antinociceptive effect of apelin-13 on rats was demonstrated, it was determined that antinociceptive activity of apelin-13 emerged through the activation of the endogenous opioid system. The antinociceptive effect that emerged in the same study was antagonised by APJ receptor antagonist apelin-13 [21]. These results gave rise to the thought that apelin could provide an insight into new pharmacological approaches in pain control with APJ and opioid system mediated analgesic effect. Our study may be important, because it reports that the apelin-36 levels increased in migraine patients compared with healthy volunteers. There have not been studies on apelin-36 levels in migraine patient in the literature.

Knowing migraine pathophysiology is necessary for its prophylaxis and attack treatment. Apelin which shows anti-inflammatory and neuroprotective effects also has strong vasodilator effects. According to the findings obtained from the results of this study, we must ask two important questions. Is the serum apelin-36 concentration being high in patients with migraine a defence mechanism which the body creates to enhance the patients' pain-tolerance-duration and threshold? Can the fact that apelin creates strong vasoconstriction in smooth muscles have any effect in the migraine formation mechanisms? To obtain the answers to these questions, many new studies should be carried out in the future.

## Conflict of Interest

The Authors declare that there are no conflicts of interest.

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