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Serum YKL-40 (chitinase 3-like protein 1) levels in migraine patients during an attack

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Abstract

Objectives: The aim of this study was to investigate YKL-40 in migraine patients during migraine attacks. *Methods:* In this prospective study, 30 migraine patients with aura (MWA) and 30 migraine patients without aura (MWOA) who presented to the Neurological Outpatient Department of Konya City Hospital during a migraine episode as well as 28 healthy controls were included. According to the manufacturer's recommendations, serum YKL-40 levels were determined using an ELISA kit (FineTest). Statistical analysis of the data was performed with the IBM SPSS version 20.0 program. *Results:* The mean gender and age were similar between groups ($p>0.05$). The serum YKL-40 level was 3575 ± 604.975 pg/ml in the MWA group, 3339 ± 492.689 pg/ml in the MWOA group and 3190 ± 544.018 pg/ml in the control group. YKL-40 levels were significantly higher in MWA than in the control group ($p=0.028$). YKL-40 levels were similar in the MWA and MWOA groups ($p=0.302$). No significant difference was found between the group with MWOA and the control group ($p=0.915$). *Conclusion:* Although YKL-40 levels are increased in patients with migraine with aura during an attack, comprehensive studies with a larger sample are needed to clarify the relationship between YKL-40 and migraine.

Keywords: Migraine, migraine attack, aura, YKL-40, inflammation.

INTRODUCTION

Migraine is a neurovascular disorder characterized by unilateral, severe, throbbing headache attacks that are aggravated by physical activity and accompanied by photophobia, phonophobia, nausea and vomiting.[1,2] Migraine affects approximately 10-20 percent of the world's population and is the second most common cause of disease-related disability.[2,3] In addition to affecting the quality of life, migraine also imposes a substantial economic burden on society through treatment costs, reduced employment and lower labor productivity.[4]

Currently, migraine is diagnosed based on medical history, physical examination, and clinical criteria.[5] About 15-20% migraine patients have an aura, which is characterized by transient neurological disturbances 15-60 minutes before the onset of the headache.[6,7]

Although different mechanisms for migraine such as vascular dysfunction, neurogenic inflammation and activation of the trigeminovascular pathway have been suggested, the pathophysiology of migraine is still incompletely understood.[8-10]

Activation of the trigeminal nerve releases vasoactive peptides such as calcitonin gene-related peptide (CGRP) and pro-inflammatory mediators in the meninges, causing vasodilatation of the meningeal vessels and endothelial dysfunction leading to neurogenic inflammation.[11,12]

Migraine with aura is thought to be particularly associated with inflammation. Biomarkers of inflammation and endothelial damage such as C-reactive protein, CGRP, vascular endothelial growth factor and stable nitric oxide metabolites have been detected in migraine patients with aura.[12,13] The possible association between

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migraine and stroke as well as some non-atherosclerotic vascular diseases supports the role of the endothelium in migraine pathogenesis.[14]

However, due to the clinical heterogeneity of migraine symptoms, the variability of response to treatment and the lack of understanding of the pathophysiological mechanisms, reliable biomarkers are desirable for the diagnosis of migraine.[15,16]

Over the years, various neurotransmitters, neuropeptides, gliotransmitters and hormones have been proposed as potential biomarkers of migraine, including cytokines, homocysteine, serotonin, hypocretin-1, CGRP and glutamate. Despite a considerable amount of research, there is currently no widely accepted and validated biomarker for migraine.[17]

YKL-40, also known as chitinase 3-like-1 or human cartilage glycoprotein-39, is a member of the chitinase-like glycoprotein family.[18] YKL-40 is expressed by various cell types, including macrophages, chondrocytes, neutrophils, and synovial fibroblasts, as well as cancer cells. It acts by regulating vascular endothelial growth factor levels (VEGF).[19,20] YKL-40 has been reported to be involved in inflammation, endothelial dysfunction, extracellular matrix remodeling and differentiation, as well as angiogenic processes mediating macrophage maturation.[21-23]

Recent studies show that YKL-40 is a new marker for inflammation and endothelial dysfunction.[23] It also helps differentiate Alzheimer's disease from other types of dementia.[21,24]

There are a limited number of studies investigating YKL-40 levels in migraine patients. In this study, we investigated YKL-40 concentrations during an attack in patients diagnosed with migraine with and without aura.

METHODS

In this prospective study, 60 patients aged 18-65 years with migraine presenting to the neurology outpatient department of Konya City Hospital between 01 December 2021 and 01 March 2022 and 28 healthy controls matched for age and sex were included. Patients were excluded if they had secondary headaches other than drug overuse headache diagnosed according to ICHD-3 diagnostic criteria, or when there was a history of malignancy, smoking, alcohol and drug use, pregnancy, and breastfeeding, acute or chronic infection, chronic systemic diseases, or hematological disease.

A detailed medical history was taken from the migraine patients and neurological and radiological examinations were performed. They were clinically examined by two neurologists in the Neurology Outpatient Clinic. The diagnosis of migraine was made according to the diagnostic criteria of the International Classification of Headache Disorders (ICHD)-III. The patients in the migraine group were divided into two subgroups: migraine with aura (MWA, n=30) and migraine without aura (MWOA, n=30). Healthy individuals who had no history of headache who had provided blood samples for a routine health examination were included in the study as a control group (n=28).

Sample collection

Blood samples were collected during the migraine attack from the migraine subjects. After the participants had rested for ≥15 minutes, a 10 ml blood sample was taken from the right antecubital vein. Samples were centrifuged at 1500 rpm for 15 minutes within 30 minutes of collection and the sera obtained were transferred to two Eppendorf tubes and stored at -80°C until analysis.

Measuring the YKL-40 level

Serum YKL-40/Citinase-3-like protein 1 levels were determined using the Human CHI3L1 (Chitinase-3-like protein 1) Enzyme Linked Immunosorbent Assay (ELISA) Kit (Fine Test, Wuhan, China, catalogue number: EH0093) according to the manufacturer's recommendations.

The sensitivity of the ELISA kit was 37.5 pg/mL and the range of the standard curve was 62.5-4000 pg/mL. The estimated inter- and intra-test precision was <10% and ≤8% coefficient of variation, respectively. The absorbance of the standards and samples was measured at 450 nm with a Multiskan Sky Micro-plate Reader (Thermo Scientific, Waltham, MA, USA). To determine the YKL-40 serum level, a standard curve was constructed with the standard concentration on the x-axis and the absorbance on the y-axis. Each sample was run in duplicate.

Statistical analysis

The IBM SPSS 20 program was used to analyze the data. Descriptive statistics for categorical variables were presented as numbers and percentages, and continuous variables were presented as means and standard deviations. The chi-square test was used for the analysis of categorical data. The conformity of the continuous

variables to a normal distribution was determined with the Kolmogorov-Smirnov test. If the variables were normally distributed, a one-way test ANOVA was used to compare the groups, and in cases where the assumption of normality was not established, the Kruskal-Wallis test was used. Since the variances in the groups were homogeneous, the Bonferroni test was used as a post hoc test for group comparisons after ANOVA. The homogeneity of variances was checked with Levene's test. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 88 participants comprising 30 MWA patients, 30 MWOA patients and 28 control subjects were enrolled in the study. 45 patients met the exclusion criteria and were excluded from analysis. The mean age of the MWA patients (21 females and 9 males) was 46.18 ± 11.7 years, while the mean age of the MWOA patients (20 females and 10 males) was 44.23 ± 12.54 years. The mean age of the control group (19 females and 9 males) was 41.07 ± 11.7 years. The patient and control groups were statistically similar in terms of gender and age (p>0.05).

The YKL-40 serum level was 3575 ± 604.975 pg/ml in the MWA group, 3339 ± 492,689 pg/ml in the MWOA and 3190 ± 544,018 pg/ml in the control group. A statistically significant difference was found in the YKL-40 levels between in the groups (p=0.031). The YKL-40 level was significantly higher in MWA than in controls (p=0.028). YKL-40 levels were similar in the MWA and MWOA groups (p=0.302). Similarly, no significant difference was found between the MWOA group and the control group (p=0.915) (Figure 1).

DISCUSSION

Neuroinflammation is a process involving mainly microglia and astrocytes that is essential for healthy brain function.[20] However, in many neurological diseases such as Alzheimer's disease, increased microglial and astroglial activation, increased inflammatory cytokines, oxidative stress, vascular dysfunction as well as impaired integrity of the blood-brain barrier integrity result in decreased neurogenesis.[20,25]

Although its physiological role is not fully understood, elevated serum levels of YKL-40 have been found in various inflammatory diseases and malignancies.[23] In addition, increased YKL-40 in the brain and cerebrospinal fluid (CSF) has been found in various neurological and neurodegenerative diseases associated with inflammatory processes.[26] Increased gene expression of YKL-40 in the brain has been reported in various neurological diseases such as stroke, traumatic brain injury, amyotrophic lateral sclerosis, multiple sclerosis (MS) and Alzheimer's disease.[27]

In addition, the expression of YKL-40 by astrocytes has been observed in amyloid plaques and in the immediate vicinity of neurofibrillary tangles in both acute and chronic neurological disorders as well as in Alzheimer's disease.[23,28] In a recent study investigating the

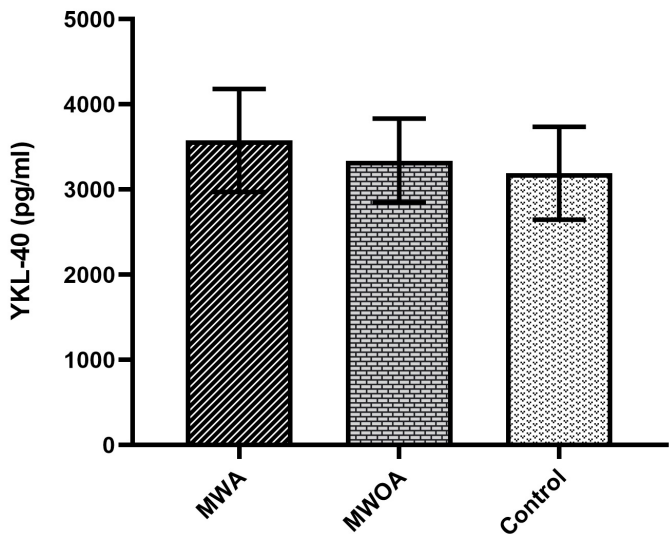

Figure 1. Comparison of the YKL-40 levels between the MWA, MWOA and control groups.

mechanisms regulating the expression of YKL-40 in astrocytes in vitro, it was shown that under neuroinflammatory conditions, abundant expression of YKL-40 is present in astrocytes and cultured macrophages. Furthermore, it has been reported that transcription of YKL-40 in astrocytes is induced by cytokines released by macrophages, leading to morphological changes, and altered motility of astrocytes.[28]

CSF levels of YKL-40 have been shown to be different in patients with Alzheimer's disease and mild cognitive impairment. It has been suggested that this inflammatory marker may predict the conversion of mild cognitive impairment in Alzheimer's disease, especially in the presence of the APOE ε4 allele.[21]

In addition, an association between YKL40 and MS accompanied by neuroinflammation has been shown. Serum YKL-40 levels are higher in the clinically isolated syndrome patients (CIS) and in relapsing-remitting patients MS (RMMS) group than in controls. YKL-40 levels were higher in the CIS group than in the RRMS group. Since serum levels of YKL-40 are elevated in the disease, it has been suggested that YKL-40 may be a useful marker of the inflammatory process in MS.[29]

In this study, we aimed to evaluate the association of YKL-40 with the inflammatory response during a migraine attack. To date, there is only one study investigating serum YKL-40 levels in patients with migraine. Dundar *et al*.[30] investigated YKL-40 levels in their study of 50 MWA, 50 MWOA and 50 healthy control subjects. The mean serum YKL-40 levels of migraine patients and healthy subjects were 36.40 ± 28.73 ng/ml and 18.45 ± 10.23 ng/ml, respectively. Serum YKL-40 levels were significantly higher in MWA and MWOA patients compared to controls ($p<0.001$). No significant difference was found between the MWA and MWOA groups ($p>0.05$). The results of our study are consistent with this previous study. However, in contrast to our study, serum samples were taken from migraine patients during a migraine attack.

In conclusion, this is the first study to investigate serum levels of YKL-40 during an attack in migraine patients with and without aura. Our study finds that the overlap in YKL-40 ranges between control and migraine patients is such that it has limited clinical value in distinguishing migraine from non-migraine headaches. Large-scale studies should be conducted with a larger number of patients.

DISCLOSURE

Ethics: The study design was approved by the Medicines and Non-Medical Devices Ethics Committee of KTO Karatay University by decision dated 19/11/2021 and number 2021/019. Data availability: The data of this manuscript can be obtained from the corresponding author upon reasonable request.

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Conflict of interest: None.

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