Annals of Medical Research
DOI: 10.5455/annalsmedres.2018.12.300 2019;26(6):973-5

Original Article

Is migraine an inflammatory event? Which inflammatory markers can we use for migraine?

Buket Tugan Yildiz[1], Tulay Tuba Koca[2]

[1]Kahramanmaras Sutcu Imam University Faculty of Medicine Department of Neurology, Kahramanmaras, Turkey
[2]Kahramanmaras Sutcu Imam University Faculty of Medicine Department of Physical Medicine and Rehabilitation, Kahramanmaras, Turkey

Abstract

Aim: It is considered that a relationship exist between migraine and neurogenic inflammation. High levels of tumor necrosis factor, interleukin-6 and C-reactive protein were determined in the studies. The cytoprotective and antioxidant effect of bilirubin has been shown. Lower serum bilirubin levels have been shown some diseases. For all that, there is no consensus in the results. Our purpose in this study is to determine the relationship between migraine and inflammation markers like erythrocyte sedimentation rate, C-reactive protein , bilirubin.

Material and Methods: The study included 50 migraine patients and 40 healthy individuals as a control group. Erythrocyte sedimentation rate and C-reactive protein, bilirubin parameters, aspartate aminotransferase, alanine aminotransferase were recorded.

Results: Erythrocyte sedimentation rate and C-reactive protein were significantly higher in migraine group. Bilirubin parameters and aspartate aminotransferase , alanine aminotransferase values were similar.

Conclusion: Higher serum inflammatory markers support the role of inflammation in migraine pathogenesis. For bilirubin levels larger cross- sectional studies are needed.

Keywords: Migraine; inflammation; C-reactive protein; erythrocyte sedimentation rate.

INTRODUCTION

Migraine is a common primary headache with unilateral, throbbing, episodic pain (1). In previous studies it was determined that there is an association with migraine and neurogenic inflammation (1,2).

Increased levels of tumor necrosis factor (TNF) and interleukin-6 (IL-6) have, however, been recently reported in migraine patients compared with healthy controls (1,3). High C- reactive protein (CRP) values was found in migraine patients in some studies and have been considered to be a marker in assessing inflammation of migraine patients (1,4,5).

The cytoprotective, potent antioxidant effect of bilirubin, previously known as toxic waste, has been shown in recent studies (6-8).

It has been recently shown that serum total bilirubin level can be used to stratify arterial stiffness in patients with coronary artery disease (6,9).

Moreover, serum bilirubin is associated with glomerular filtration rate, and lower serum bilirubin is considered to be a potential risk factor to determine reduction of kidney function in the general population (10).

The aim of this study is to determine the relationship between migraine and inflammation markers like ESR, CRP and bilirubin.

MATERIAL and METHODS

The study was planned as a prospective case control. The study included 50 migraine patients and 40 healthy individuals. All patients had been diagnosed with migraine without aura according to the international headache society criteria, third edition (beta version) (11). Fasting blood was used to measure erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), bilirubin parameters, aspartate aminotransferase (AST), alanine aminotransferase (ALT). All these parameters were recorded. Patients with following diseases were

Received: 02.01.2019 **Accepted:** 02.04.2019 **Available online:** 08.04.2019
Corresponding Author: Buket Tugan Yildiz, Kahramanmaras Sutcu Imam University Faculty of Medicine Department of Neurology, Kahramanmaras, Turkey, **E-mail:** bukettugan@yahoo.com

not included: cardiovascular disease, cerebrovascular disease, hypertension, diabetes mellitus, presence of known hepatobiliary disease or surgery history, infectious disease, inflammatory disease that may influence the serum bilirubin concentrations.

Statistical Analysis

Continuous variables were shown as means ± standard deviation, and categorical variables were presented as percentages. We used the Kolmogorov-Smirnov test to identify data normality. The t test and Mann–Whitney U test were used to analyze data according to their distribution. The correlation between two continuous variables was analyzed using the Spearman approach. Statistical analysis was performed using SPSS 16.0 (SPSS Inc., Chicago, IL, USA); p<0.05 was designated as statistically significant.

Ethics statement

The ethics committee approval was obtained for this study. All participants gave written consent form.

RESULTS

The study included 50 migraine without aura patients with mean age of 36.8± 10 years, 40 healthy individuals with mean age of 38± 1.1 years. There was no significant difference between the two groups in terms of age (p = 0.06), gender (p = 0.42). The descriptive and comparative data for the study are summarized in Table 1. According to this, ESR (p = 0,015) and CRP (p = 0,005) were significantly higher in migraine group. Bilirubin parameters and AST, ALT values were similar. It was found that ESR was negative correlated with direct bilirubin (rho = - 0.286; p = 0.044) (Figure 1) and total bilirubin (rho = -0.368, p = 0.008).

Table 1. Descriptive and comparative analysis of the groups

	Migraine (N=50)	Control (N=50)	p
Age (year)	36.8±10	38.4±1.1	0.06
Gender (M/F)	3/47	2/38	0.42
ESR	16.2±11.2	14.6±10.2	0.015
CRP	8.1±17	0.39±0.40	0.005
DBb	0.17±0.11	0.20±0.071	0.09
InBb	0.52±0.97	0.38±0.20	0.37
TBb	0.69±1	0.59±0.26	0.52
AST	24.5±8.4	24.5±10.3	0.99
ALT	18.9±7.9	15.9±10.3	0.21

Abbreviations: TBb: total bilirubin; InBb: indirect bilirubin; DBb: Direct bilirubin; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; AST: aspartate aminotransferase; ALT: alanine aminotransferase

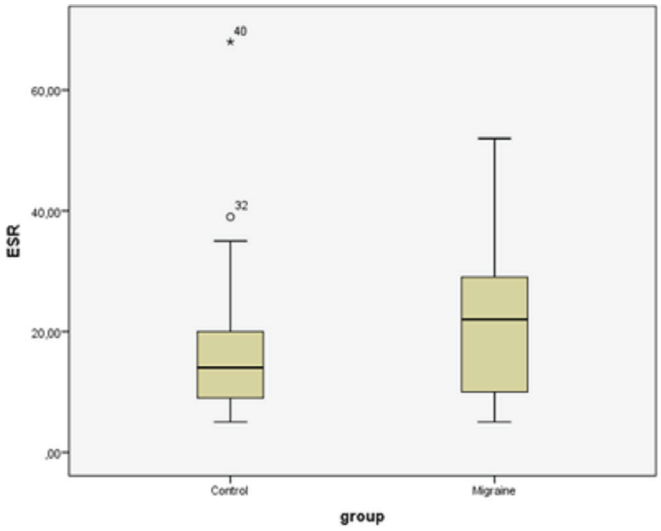

Figure 1. Boxplot of the ESR of the groups

DISCUSSION

Migraine is a common primary headache with unilateral, throbbing, episodic pain (1). Recent insights for the pathogenesis of migraine suggested that migraine should be considered a primary neurovascular disorder, where reduced cerebral blood flow, reactive arterial vasodilatation, neurogenic inflammation and decreased inhibition of central pain transmission coexist (2,4). Several large studies have shown that inflammation plays a significant role in the pathogenesis of migraine, wherein largely pro-inflammatory cytokines are released and involved in sensitization of nerve endings during migraine (12). Increased levels of TNF, IL-6 have been reported in migraine patients compared with healthy controls (1,3).

Recent studies have demonstrated that bilirubin has cytoprotective and strong antioxidant properties (6-8). Several studies showed that lower serum concentrations of bilirubin are associated with multiple sclerosis, systemic lupus erythematosus, diabetes mellitus (13-15).

You- Fan Peng at al. studied serum CRP and bilirubin levels in migraine patients. They found that significantly lower median direct bilirubin, total bilirubin, indirect bilirubin in migraine patients in comparison with healthy controls and CRP levels were higher in migraine patients (1).

Ling Cao at al. found that serum bilirubin concentration also were lower in migraine patients compared with healthy controls (6).

In our study we found higher serum CRP and ESR levels in migraine patients compared with same age and gender healthy controls (Figure 1). This result is consistent with the inflammatory pathogenesis of migraine; but serum bilirubin concentrations were same with healthy controls reverse other studies.

In this study our patients were not in migraine attack and they were not newly diagnosed and some of them were using various drugs. Serum bilirubin levels may be

associated with migraine duration, but we didnot record patients' migraine durations .

These findings were limited by small samples, the number of patients included in the study can be increased. These are limitations of this study.

In our study serum bilirubin concentrations were not different in migraine patients compared with healthy individuals. Our patients were not in migraine attack and we do not now patient's migraine duration. There may be no difference between bilirubin parameters due to these factors.

CONCLUSION

Serum ESR and CRP levels were higher in migraine patients than healthy controls. Higher serum inflammatory markers supports the role of inflammation in migraine pathogenesis. Larger cross- sectional studies are needed to establish whether serum bilirubin, ESR, CRP may be a marker for identifying the degree of inflammation in migraine patients and it may also be beneficial for treatment in the future.

Competing interests: The authors declare that they have no competing interest.
Financial Disclosure: There are no financial supports
Ethical approval: Institutional Review Board of Kahramanmaras Sutcu Imam University Faculty of Medicine Department (approval No. 29/29.08.2018).

Buket Tugan Yildiz RCID: 0000-0001-6783-2336
Tulay Tuba Koca ORCID: 0000-0002-4596-858X

REFERENCES

1. Peng YF, Xie LQ, Xiang Y, et al. Serum bilirubin and their association with c- reactive protein in patients with migraine. J Clin Laboratory Anal 2016;30:982-5.
2. Spierings EL. Pathogenesis of the migraine attack. Clin J Pain 2003;19:255- 62.
3. Sarchielli P, Alberti A, Baldi A, et al. Proinflammatory cytokines, adhesion molecules, and lymphocyte integrin expression in the internal jugular blood of migraine patients without aura assessed ictally. Headache 2006;46:200-7.
4. Lippi G, Mattiuzzi C, Cervellin G. C- reactive protein and migraine. Facts or speculations? Clin Chem Lab Med 2014;52:1265-72.
5. Peng YF, Wei Y, Qin YH, et al. A relationship between migraine undergoing no pharmacological therapy. Clin Chem Lab Med 2016;54:e249-51.
6. Cao L, Xue L, Luo DM. Lower serum bilirubin concentration in patients with migraine. Int J Clin Exp Med 2015;8:13398-402.
7. Stocker R, Yamamoto Y, McDonagh AF, et al. Bilirubin is an antioxidant of possible physiological importance. Sci 1987:235:1043-6.
8. Kapitulnik J. Bilirubin: An endogenous product of heme degradation with both cytotoxic and cytoprotective properties. Mol Pharmacol 2004;66:773-9.
9. Tanındı A, Erkan AF, Alhan A, et al. Arterial stiffness and central arterial wave reflection are associated with serum uric acid, total bilirubin and neutrophil-to- lymphocyte ratio in patients with coronary artery disease. Anadolu Kardiyol Derg 2015;15:396-403.
10. Kawamoto R, Ninomiya D, Hasegawa Y, et al. Association between serum bilirubin and estimated glomerular filtration rate among elderly persons. PLoS One 2014;9:115-294.
11. IHS. The international classification of headache disorders, third edition (beta version). Cephalalgia 2013;33:629-808.
12. Eising E, Datson NA, Maagdenberg AM, et al. Epigenetic mechanisms in migraine: a promising avenue? BMC Med 2013;11:26.
13. Peng F, Deng X, Yu Y, et al. Serum bilirubin concentrations and multipl sclerosis. J Clin Neurosci 2011;18:1355-9.
14. Dos Santos BH, de R Almeida CM, Skare TL. Systemic lupus erythematosus activity and serum bilirubins. Acta Reumatol Port 2013;38:242-6.
15. Fukui M, Tanaka M, Shiraishi E, et al. Relationship between serum bilirubin and albuminuria in patients with type 2 diabetes. Kidney Int 2008;74:1197-201.