

The value of highly specific C-reactive protein HS-CRP in migraine headache

Hussein Khalil*

* Neurologist at neurology Unit, Al-Diwaniyah teaching hospital, Al-Diwaniyah province, Iraq

Abstract

Background: Migraine is a well known neurologic disease, ordinarily portrayed by intermittent assaults of incapacitating headache and manifestations of autonomic nervous system disturbances. In about 33% patients, headache attacks are joined by transient “focal neurologic aura manifestations”. Migraine is a neurovascular disease accompanied by cranial vascular contractile dysfunction, neurogenic inflammation and cortical spreading depression. Brain tissue activation results in the production of peptides by the perivascular trigeminal areas which lead to an inflammatory response with dilation of extraparenchymal blood vessels. Inflammatory vasculopathy accompany repeated assaults of migraine attacks. A number of studies showed the elevation of certain inflammatory markers in association with migraine such as adhesion molecules, interleukins and C-reactive protein (CRP).

Aim of the study: To evaluate the role of HS-CRP in patients with migraine

Patients and methods: Current case control study included 100 patients with migraine headache and 100 apparently healthy subjects. Variables included in the present study are: age, gender and the level of highly specific C-reactive protein (HS-CRP). The study was conducted at the neurology unit, Al-Dewaniyah teaching hospital, Al-dewaniyah province, Iraq. The study started on January 2018 and ended at June 2018.

Results: Current study included 100 migraine patients with a mean age of 31.46 ± 5.75 years and 100 control subjects with a mean age of 30.55 ± 5.54 years and there was no significant difference in mean age between the two groups ($P=0.255$). Patients group included 23 men (23%) and 77 women (77%) whereas, control group included 24 men (24%) and 76 women (76%); no significant difference was encountered between the two groups with respect to gender ($P=0.868$). The level of Hs CRP in terms of median and inter-quartile range (IQR) in patients group was significantly higher than that of control group, 4.6 (4.9) versus 1.5 (2) $\mu\text{g/dl}$ ($P<0.001$). There was no significant difference in the level of Hs CRP between men and women in patients group, 5.3 (5.7) versus 4.6 (4.8) $\mu\text{g/dl}$ ($P=0.680$), as shown in figure 2. There was no significant correlation between age and level of Hs CRP in patients group ($r = -0.056$, $P = 0.581$).

Conclusion: The present study showed that Hs CRP is significantly higher in patients with migraine headache and this may explain the inflammatory role in the pathogenesis and prognosis of migraine headache.

Key words: Hs CRP, Migraine, Headache

Introduction

Migraine is a well known neurologic disease, ordinarily portrayed by intermittent assaults of incapacitating headache and manifestations of autonomic nervous system disturbances. In about 33% patients, headache attacks are joined by transient “focal

neurologic aura manifestations”. Migraine is more frequent in women than men with a male to female ratio of about 1:3 (1). The prevalence of migraine is about 13.2 % in the United States; in women it is about 17.5 % and in men it is about 8.6% (2). In women, the risk of acquiring migraine headache is greater at an age of less than 45, a fact that may be related

to some hormonal factors (3). Migraine is a neurovascular disease accompanied by cranial vascular contractile dysfunction, neurogenic inflammation and cortical spreading depression. Brain tissue activation results in the production of peptides by the perivascular trigeminal areas which lead to an inflammatory response with dilation of extraparenchymal blood vessels. Inflammatory vasculopathy accompany repeated assaults of migraine attacks (4, 5). A number of studies showed the elevation of certain inflammatory markers in association with migraine such as adhesion molecules, interleukins and C-reactive protein (CRP) (5-7). One of the inflammatory markers is the "High sensitivity C-reactive protein (hs-CRP)" which has been shown to be elevated in a number of vascular disorders such as cerebrovascular accidents (CVA) and ischemic heart disease (IHD) (8). The prognostic value of the hs-CRP levels has been reported and clinically applied in the evaluation of the severity of metabolic syndrome, the Framingham coronary risk score, subclinical atherosclerosis and the severity of hypertension (8, 9). The association of migraine with high CRP level has been observed in a large sample cohort study of females older than 45 and in a number of small sample case-control studies (7, 10-12). On the other hand the association between CRP (hs-CRP) and migraine was evaluated in 5906 patients with a mean age of 55.0 ± 8.5 years in the Reykjavik Study and 1345 patients with a mean age of 27.7 ± 5.5 years from the Reykjavik Study for the Young and the conclusion was that there is no significant difference in CRP levels ng migraine sufferers and nonmigraineurs (13).

The presence of such controversy in the available published articles and the will toward searching for a diagnostic and prognostic inflammatory marker that is associated with migraine justified the conductance of the current study. The aim of this study is to compare the level of hs-CRP

between a sample of patients with migraine and apparently healthy control subjects and also between male patients and female patients and to disclose the relation of hs-CRP with the age of migraineurs.

Patients and Methods

Current cased control study included 100 patients with migraine headache and 100 apparently healthy subjects. Variables included in the present study are: age, gender and the level of highly specific C-reactive protein (HS-CRP). The study was conducted at the neurology unit, Al-Dewaniyah teaching hospital, Al-dewaniyah province, Iraq. The following patients were excluded from the two groups: patients with rheumatoid arthritis, women taking oral contraceptive pills, patients with infection and those patients on anti-hypertensive treatments as these may interfere with the level of Hs CRP. The study started on January 2018 and ended at June 2018. Data were collected, summarized, presented and analyzed using statistical package for social sciences (SPSS) version 23. Assessment of normality distribution was carried out using Kolmogorov-Smirnov test. Numeric variables were expressed as mean and standard deviation or median and inter-quartile range (IQR) according to type of distribution whether normal or not, whereas categorical data were expressed as number and percentage. Chi-square test was used to study association between categorical variables and student t-test or Mann Whitney U tests were used to compare mean between any two independent groups. The level of significance was chosen at *P*-value of equal or less than 0.05.

Results

Current study included 100 migraine patients with a mean age of 31.46 ± 5.75 years and 100 control subjects with a mean age of 30.55 ± 5.54 years and there was no significant difference in mean age between the two

groups ($P=0.255$). Patients group included 23 men (23%) and 77 women (77%) whereas, control group included 24 men (24%) and 76 women (76%); no significant difference was encountered between the two groups with respect to gender ($P=0.868$), as shown in table1. The level of Hs CRP in terms of median and inter-quartile range (IQR) in patients group was significantly higher than that of control group, 4.6 (4.9) versus 1.5 (2)

$\mu\text{g/dl}$ ($P<0.001$), as shown in figure 1. There was no significant difference in the level of Hs CRP between men and women in patients group, 5.3 (5.7) versus 4.6 (4.8) $\mu\text{g/dl}$ ($P=0.680$), as shown in figure 2. There was no significant correlation between age and level of Hs CRP in patients group ($r = -0.056$, $P = 0.581$), as shown in figure 3.

Table 1: Characteristics of patients and control groups

Characteristics	Control group	Patient group	<i>P</i>
Number of cases	100	100	---
Age (mean SD) years	30.55 $\pm$ 5.54	31.46 $\pm$ 5.75	0.255
Gender (M/F)	24/76	23/77	0.868

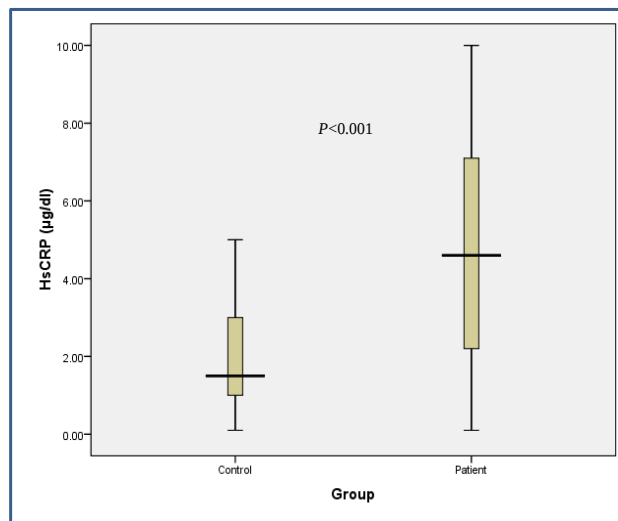


Figure 1: Level of Hs CRP in control and patient groups

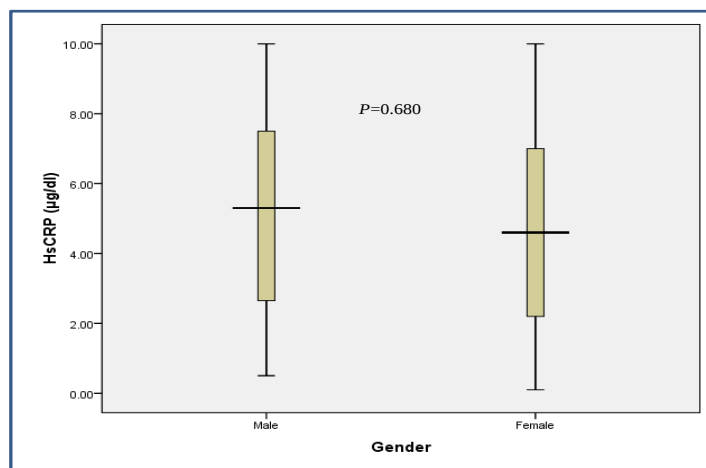


Figure 2: Level of Hs CRP in male and female patients

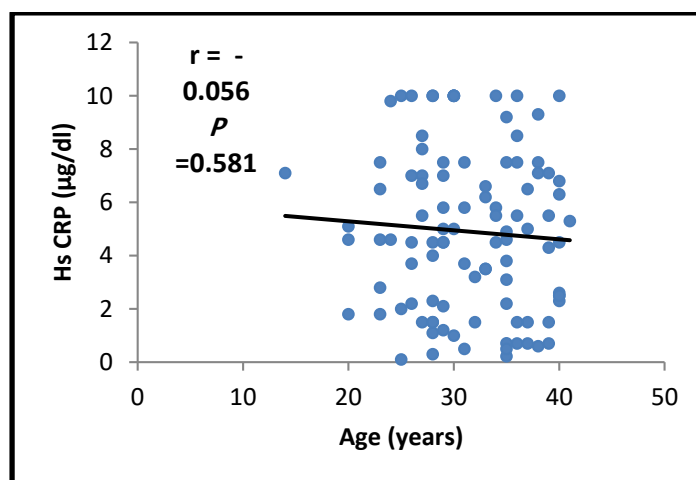


Figure 3: Correlation between age and Hs CRP level in patient group

Discussion

In our study, serum hs-CRP levels were significantly higher in patients with migraine in comparison with healthy control group. This result is similar to the finding of Avciet *al.* (14). In addition our findings are similar to the results obtained by a large prospective cohort study and a number of case control studies (7, 10-12). Moreover, our findings are supported by the finding of other studies that showed elevation of inflammatory markers in association with migraine (5-7). However, our findings disagree with the

findings of a number of studies that failed to show a relation between Hs-CRP and migraine (13, 15). It was stated previously in the section of introduction that Hs-CRP is a marker of inflammation and the high level of CRP in patients with migraine that has been shown in this study and several other studies is suggestive of an inflammatory role in the pathophysiology of migraine. The high level of Hs-CRP in patients with migraine may be attributed to the release of a number of inflammatory cytokines and oxidative stress (5-6). In the present study the correlation

between age of patients with migraine and the level of Hs-CRP was negative; however it was not significant. A moderate negative correlation between age of patients with migraine and the level of Hs-CRP was described by Gudmundsson *et al.* (13). There, was also no significant difference in the Hs-CRP level between male and female patients enrolled in the present study, suggesting lack of difference in the pathophysiology of inflammation contributing to migraine in men and women and that the same possible pathophysiologic mechanism works in both sexes.

Role of inflammation have been considered in last 10 years and gain attention in the “neurogenic inflammation theory” hypothesized by Moskowitz and co-workers (5). This hypothesis takes into consideration the clinical advantage of non-steroidal anti-inflammatory drugs (NSAID's) and other anti-inflammatory agents in relieving migraine assaults. Moreover, inflammation plays a significant role in atherogenesis and atherothrombosis which are well known for their association with migraine. This hypothesis become more acceptable because of the finding those Hs-CRP levels are higher among migraineurs than healthy control subjects (10-12).

In conclusion, the present study showed that Hs CRP is significantly higher in patients with migraine headache and this may explain the inflammatory role in the pathogenesis and prognosis of migraine headache.

References

1 Headache Classification Subcommittee of the International Headache Society The international
14 Avci AY, Lakadamyali H, Arikan S, Benli US, Kilinc M. High sensitivity C-reactive protein and cerebral white matter hyperintensities on magnetic resonance imaging in migraine patients. *The Journal of Headache and Pain*. 2015;16:9.

classification of headache disorders: 2nd edition. *Cephalalgia*. 2004;24(suppl 1):9–160.

2 Victor TW, Hu X, Campbell JC, Buse DC, Lipton RB. Migraine prevalence by age and sex in the United States: a life-span study. *Cephalalgia*. 2010;30:1065–1072.

3 Schürks M, Rist PM, Bigal ME, Buring JE, Lipton RB, Kurth T. Migraine and cardiovascular disease: systemic review and meta-analysis. *BMJ*. 2009;339:b3914.

4 Bolay H, Reuter U, Dunn AK, Huang Z, Boas DA, Moskowitz MA. Intrinsic brain activity triggers trigeminal meningeal afferents in migraine model. *Nat Med*. 2002;8:136–142. doi: 10.1038/nm0202-136

5 Waeber C, Moskowitz MA. Migraine as an inflammatory disorder. *Neurology*. 2005;64(10 suppl 2):S9–S15. doi: 10.1212/WNL.64.10_suppl_2.S9.

6 Sarchielli P, Alberti A, Baldi A, Coppola F, Rossi C, Pierguidi L, Floridi A, Calabresi P. Proinflammatory cytokines, adhesion molecules, and lymphocyte integrin expression in the internal jugular blood of migraine patients without aura assessed ictally. *Headache*. 2006;46:200–207.

7 Tietjen GE, Herial NA, White L, Utley C, Kosmyna JM, Khuder SA. Migraine and biomarkers of endothelial activation in young women. *Stroke*. 2009;40:2977–2982.

8 Bassuk SS, Rifai N, Ridker PM. High-sensitivity C-reactive protein: clinical importance. *CurrProblCardiol*. 2004;29:439–493.

9 Ridker PM, Cook N. Clinical usefulness of very high and very low levels of C-reactive protein across the full range of Framingham risk scores. *Circulation*. 2004;109:1955–1959.

10 Kurth T, Ridker PM, Buring JE. Migraine and biomarkers of cardiovascular disease in women. *Cephalalgia*. 2007;28:49–56.

11 Welch KM, Brandes AW, Salerno L, Brandes JL. C-reactive protein may be increased in migraine patients who present with complex clinical features. *Headache*. 2006;46:197–199.

12 Vanmolkot FH, de Hoon JN. Increased C-reactive protein in young adult patients with migraine. *Cephalalgia*. 2007;27:843–846.

13 Gudmundsson LS, Aspelund T, Scher AI, et al. C-reactive protein in migraine sufferers similar to that of nonmigraineurs: The Reykjavik Study. *Cephalalgia: an international journal of headache*. 2009;29(12):1301–1310.

15 Guldiken B, Guldiken S, Demir M, Turgut N, Kabayel L, Ozkan H, Ozcelik E, Tugrul A. Insulin resistance and high sensitivity C-reactive protein in migraine. *Can J Neurol Sci*. 2008;35:448–451.