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Association of Serum C- Reactive protein (CRP) With Migraine

HOSSAIN MA[1], BHATTACHARJEE M[2], ISLAM MR[3], HOSSAIN MI[4], KHAN PA[5]

Abstract

Background: *Migraine is a highly prevalent and frequently disabling neurovascular disorder. The aim of the present study was to compare the serum level of CRP between migraine patients and others headache patient without migraine to see whether CRP is abnormally increased in patients with migraine.* ***Methods****: This comparative cross-sectional study was conducted at the department of Neurology, Mymensingh Medical College & Hospital. Total 150 patients with headache were selected according to selection criteria following informed written consent. They were divided into two groups, one group included patients who had headache with migraine and another group who had headache without migraine. Detailed clinical examination, proper history taking was done and serum level of CRP was measured of all patients. After collection of all the required data, final analysis was carried out by using the SPSS 23.0.* ***Results:*** *Among 150 patients, mean age of patients with migraine was 31.08 ± 11.29 years and without migraine was 31.37 ±11.53 years. Both groups were similar in terms of demographic profile (p>0.05). Serum CRP levels were significantly higher in patients with migraine than the patients without migraine (12.36±7.34 Vs 7.54±4.28, p<.001).* ***Conclusion:*** *This study observed that CRP level was significantly higher among migraine patients than in the patients with non-migraine headache. However, more comprehensive studies are required to validate this finding.*

Key words: *Headache, Migraine, Serum CRP.*

Introduction:

Migraine is the second most common cause of headache. It is a unilateral, pulsatile episodic headache associated with nausea, vomiting, visual and olfactory disturbances and sensitivity to light, sound or movement. Studies have revealed that 6% of men, 15% of women are affected with migraine worldwide over a 1-year period[1]. Migraine is a risk factor of stroke between and during attacks[2]. C-reactive protein (CRP) has been identified as a sensitive indicator of active systemic inflammation[3]. A small, uncontrolled retrospective review found abnormal CRP levels in migraineurs with complex clinical features referred to secondary or tertiary clinics[2]. C-reactive protein (CRP) is a protein found in the blood, the levels of which rise in response to inflammation (an acute-phase protein). CRP is synthesized by the liver[4]. As normal concentration of CRP in healthy human serum is usually lower than 6 mg/L, any cut-off value > 6 is considered pathognomic and is considered as a marker of inflammation. In migraine, different pattern of inflammatory markers has been observed in the systemic circulation, including increased levels of C-reactive proteins (CRP)[2and] interleukins (e.g. IL-4 and IL-5)[5], which are markers for inflammation, oxidative stress, disturbed agreeability of the blood cells and thrombosis. The aim of the present study was to compare the serum level of CRP between migraine

1. Dr. Md. Akmol Hossain, MD (Neurology), Phase B Student, Mymensingh Medical College, Mymensingh, Bangladesh.
2. Dr. Manabendra Bhattacharjee, Associate Professor and Head, Department of Neurology, Mymensingh, Medical College & Hospital, Mymensingh, Bangladesh.
3. Prof. Md. Rafiqul Islam, Professor and Chairman, Department of Neurology, BSMMU, Dhaka, Bangladesh
4. Dr. Md. Imran Hossain, Assistant Register, Department of Neurology, Mymensingh, Medical College & Hospital, Mymensingh, Bangladesh.
5. Dr. Md. Peyel Ahmmad Khan, Student of MD (Neurology), Phase-B, Mymensingh Medical College & Hospital, Mymensingh, Bangladesh.

patients and other headache patients without migraine to see whether CRP is abnormally increased in patients with migraine.

Materials and methods:

This cross-sectional comparative study was performed in Mymensingh Medical College Hospital, Mymensingh, Bangladesh. Seventy five patients in Neurology outpatient department of this hospital who had a diagnosis of Migraine fulfilling the International headache criteria were included in the study. Patient of acute or chronic inflammatory condition, malignancy, pregnancy, history of recent surgery, trauma, burn and who were getting oral contraceptives (OCP) were excluded. Another Seventy five age and sex matched headache without migraine individuals were taken as a comparison group.

The clinical features, investigation findings and relevant data were collected in a preformed data sheet from each patient. Severity of headache was assessed by visual analogue scale. Co morbid conditions were assessed by relevant history and investigations. Depression was diagnosed on the basis of DSM-V criteria.

Following interviewing the subjects of both Group blood samples of about 5.0 ml were collected from them by venepuncture under all aseptic precautions for estimation of CRP level. The serum CRP levels of all patients were measured by the LAT method.

Quantitative variables were expressed as mean ± standard deviation (SD) and qualitative variables were presented as percentages or proportions. Student's t-test was used to analyze quantitative variables while qualitative variables were compared by means of Chi-square test between two groups. $p < 0.05$ was considered statistically significant. Statistical analysis was performed using SPSS version 23.0.

Informed consent was obtained from competent patients before enrollment. In patients who were unable to give fully informed consent, assent was obtained from legal relatives. The study protocol was approved by the Ethical Review Committee of Mymensingh Medical College (Memo number: MMC/IRB/2019/126) on january 28, 2019.

Results:

Table-I

Distribution of respondents by socio-demographic characteristics (n=150)

Demographics	Migraine No(%)	Non-Migraine	p value No(%)
Age (years)			
< 30	45(60)	43(57.3)	
31-40	12(16)	14(18.7)	0.861
41-50	14(18.7)	12(16)	
51-60	04(5.3)	06(08)	
Total	75(100)	75(100)	
Mean ± SD	31.08±11.29	31.37±11.53	0.725
Gender			
Male	16(21.3)	21(28)	
Female	59(78.7)	54(72)	0.344
Total	75(100)	75(100)	
Socio– Economic Status			
Lower class	40(53.3)	46(61.3)	
Middle class	35(46.7)	29(38.7)	0.322
Upper class	0(00)	0(00)	
Total	75(100)	75(100)	
Occupation			
Housewife	51(68)	48(64)	
Student	12(16)	16 (21.3)	0.797
Business	5(6.7)	3(4)	
Service holder	3(4)	2(2.7)	
Farmer	1(1.3)	3(4)	
Others	3(4)		
3(3)			
Total	75(100)	75(100)	

*P value was determined by chi-square Test (c^2) and unpaired student t-test

Table I shows an equal number (n = 75) of migraine and non migraine headache patient were taken. The mean age was 31.08 ± 11.08 years in migraine group and 31.37 ± 11.53 years in non migraine group. Both group were similar in terms of age, sex and socio-economic status. In migraine 78% were female and in non migraine group female were 72%. 53.3% of migraine and 61.3% of non-migraine patients were from lower socio-economic class. Others were from middle class group. In migraine group, 68% were house wives and 16% were students. On the other hand, in non-migraine group it was 64% were house wives and 21.3% were student respectively.

Table-II

Distribution of respondents by characteristics of headache (n=150)

Characteristics Of headache	Migraine No(%)	Non-Migraine No(%)	Pvalue
Family history			
Present	31(41.3)	14(18.7)	
Absent	44(58.7)	61(81.3)	0.002
Total	75(100)	75(100)	
Severity of headache			
Mild	8(10.7)	42(56)	
Moderate	26(34.7)	24(32)	<0.0001
Severe	41(54.7)	09(12)	
Total	75(100)	75(100)	
Presence of aura			
With aura	24(32)		
Without aura	51(68)		
Total	75(100)		

*P value was determined by chi-square Test (c^2)

Table II shows in migraine group 41.3% had positive family history of headache and in non migraine group it was 18.7% and it was statistically significant (P= 0.002). In migraine group, 54.7% had severe headache, 34.7% had moderate headache and 10.7% had mild headache. In non-migraine group 12% had severe headache, 32% had moderate headache and 56% had mild headache. In term of severity it was statistically significant (P= <.001) 32% of migraine patients had aura and 68% of patient presented with headache without aura symptoms.

Table-III

Distribution of study subjects by associated conditions (Co-morbidity) (n=150).

Associated conditions (Co-morbidity)		Migraine No (%)	Non Migraine No (%)	P value
Hypertension	Present	02 (2.7)	03 (04)	0.649
	Absent	73 (97.3)	72 (96)	
IHD	Present	04 (5.3)	00 (00)	0.041
	Absent	71 (94.7)	75 (100)	
Stroke(Ischemic)	Present	06 (08)	01 (1.3)	0.043
	Absent	69 (92)	74 (98.7)	
Epilepsy	Present	01 (1.3)	00 (00)	0.316
	Absent	74 (98.7)	(75)	
Depression	Present	18 (24)	03 (04)	<0.001
	Absent	57 (76)	72 (96)	

P value was determined by chi- square test(X^2)

There was no association found in hypertension (p=0.649) and epilepsy (p=0.316) in both groups. In migraine group IHD was present in 5.3%, depression in 24% and stroke was present in 08% of patients (Table III)

Table-IV

Distribution of serum CRP level in migraine patients with or without aura (n=75)

Serum CRP level mg/L	Migraine with aura (Mean±SD)	Migraine without aura (Mean±SD)	P value
	12.72±7.6	10.7±10.43	0.379

*P value was determined by paired t test

Table IV shows mean CRP of migraine with aura is 12.72±7.6 and migraine without aura is 10.7±10.43. It was not statistically significant (P=0.379). The difference between the serum CRP level of migraine patients by age group was not statistically significant (p=0.256). The difference between the serum CRP level of male or female migraine patients was not statistically significant (p=0.125).

Table-V

Distribution of migraine patients by age group, gender, severity of attacks, and serum CRP level in migraine patients (n=75)

(Mean±SD)	Serum CRP level	p value
Age group		
< 30	13.12±11.6	
31-40	15.34±5.42	0.256
41-50	8.42±4.56	
51-60	11.23±2.34	
Gender		
Male	10.87±9.23	0.125
Female	12.72±10.7	
Severity of Headache		
Mild to moderate	8.87±8.72	<0.001
Severe	14.92±9.47	

*P value was determined by unpaired t test

Table-VI

Distribution of study subjects by serum CRP level (n=150).

Serum CRP level mg/L	Migraine No(%)	Non Migraine No(%)	P value
<6 21(28)	54(72)	< 0.001	
6-12 42(56)	18(24)		
13-24	09(12)	03(04)	
25-48	03(04)	00(00)	
Total 75(100)	75(100)		
Mean±SD	12.36±7.34	7.54±4.28	< 0.001

*P value was determined by chi-square Test (c^2) and unpaired student t- test

Difference between serum CRP level of migraine patients with mild to moderate headache and severe headache was statistically significant (p=<0.001). Difference between serum CRP level of migraine and non-migraine group was statistically significant (p Â 0.001). The serum CRP levels were significantly higher in migraine than non-migraine group. Mean CRP of migraine patients is 12.36±7.34 and non migraine group is 7.54±4.28 (Table V and VI).

Discussion

This cross-sectional comparative study was done on patients attending in outpatient department of Neurology, Mymensingh Medical College Hospital, Mymensingh with migraine fulfilling the criteria of international headache society and headache other than migraine to find out the relationship between serum CRP level.

In this study, the mean age difference between migraine and non-migraine was found statistically not significant (p= 0.861). Most of migraine Patient were in <30 years (60 %) group. Mean age of Migraine was 31.08 ± 11.29 years and non-migraine was 31.37 ±11.53 years. In a study Avci et al. also found that there was no significant difference between age group of patients with migraine and other type of headache[6].

According to the study, regarding distribution of study subjects by gender, between migraine and non-migraine a female dominance was found in both groups. However the difference was statistically not significant (p= 0.344). In migraine, 78.7% were female and in non-Migraine group

female were 72%. In Kruit et al study, they also found in both groups female patients were common with headache[7].

In this study, the difference of socio-economic status, occupation, between the migraine and non-migraine group was not statistically significant. Among them 53.3% of migraine and 61.3% of non-migraine patients were from lower socio-economic class. Others were from middle class group. Moreover, in migraine group, 68% were housewives and 16% were students. On the other hand, in non-migraine group it was 64% were house wives and 21.3% were student respectively. In Stewart et al study they also found that migraine prevalence was substantially higher in lower income groups[8].

According to this study result, presence of family history of headache difference between migraine and non-migraine group was statistically significant (p= 0.002). 41.3% of migraine patients had positive family history of headache. Whereas non migraine has 18.7%. In Rasmussen and Olesen study, stronger family history of migraine was also associated with migraine[9] which was similar with my study.

In this study result, there were statistically significant difference between migraine and non-migraine group were found in severity of headache. In migraine group 54.7% had severe headache, 34.7% had moderate headache and 10.7% had mild headache. In non-migraine group 12% had severe headache, 32% had moderate headache and 56% had mild headache. In stewart et al. study, they found that migraine has more attacks of headache than other type of headache [8].

This study result showed that, among them 32% of migraine patients had aura and 68% of patient presented with headache without aura symptoms. Ramasamy et al. also found that migraine without aura is most common type of migraine which corresponds with my study[10].

According to our study, among migraine and non-migraine group the associated co-morbidity conditions like ischemic heart disease (IHD) (p=0.041), depression (p=<0.001) and stroke (p=0.043) were significantly higher in patients of migraine than patients of non-migraine. There was no association found in hypertension (p=0.649) and epilepsy (p=0.316) in both groups. In migraine group IHD was present in 5.3%, depression in 24% and stroke was present in 08% of patients. In Buse et al study, they also found people with migraine were significantly (P < 0.001) more likely to report insomnia (OR 3.79 [3.6, 4.0]), depression (OR 3.18 [3.0, 3.3]), anxiety (OR 3.18 [3.0 3.3], angina or IHD (OR 2.64 [2.4, 3.0]) which corresponds with my study result[11]. Androulakis et al. also found that ischemic stroke incidents that occurred in mid to late life was significantly higher in patients of migraine than patients of non-migraine[12].

In this study, there was statistical significant difference found in serum CRP level between migraine and non-migraine group. The serum CRP levels were significantly higher in migraine than non-migraine group. In Avcu et al., they found mean CRP was significantly greater in migraine patients than control, p<0.0001[6]. In Vanmolkot and Hoon study, they also found that serum CRP levels were increased in patients with migraine compared with control subjects which corresponds with my study[13]. In our study, difference between serum CRP level of migraine patients with aura and without aura was not statistically significant (p=0. 0.379). In Welch et al., they also found that serum CRP level was increased in migraine patients with aura and without aura[2].

In this study, difference between serum CRP level of migraine patients with mild to moderate headache and severe headache was statistically significant (p=<0.001). In Welch et al. they found CRP may be abnormal in patients of migraine who present with atypical, severe or complex clinical features[2].

In this study result, the difference between serum CRP level of migraine patients by age group was not significant (p= 0.256). Khalil, 2018 also found no significant difference of age group and CRP level[14].

In our study, the difference between serum CRP level of migraine patients of male and female was not significant (p= 0.125). Khalil, 2018 also found no significant difference in the level of CRP between

men and women[14]. There were some limitations like sample size was less than calculated values and it was purposive .The presence of high level of CRP in migraine patients may be due to other causes which were not excluded by relevant investigations. Highly sensitive CRP measurement could be more helpful, but lack of this facility is a limitation of this study. This study observed that CRP level was significantly higher among migraine patients than the patients with non-migraine headache and also higher CRP level was observed with severe headache than mild to moderate headache in migraine patients.

Conclusion

As migraine is a inflammatory disease and a risk factor for ischemic stroke, it is recommended to treat migraine patients at its earliest with proper and adequate antimigraine medications. Further case-control study with larger sample size is recommended.

References:

1. Hauser SL, Josephson SA. Harrison's neurology in clinical medicine, 3rd ed. McGraw-Hill Medical,; 2010 Jun 21.
2. Welch KM, Brandes AW, Salerno L, Brandes JL. C reactive protein may be increased in migraine patients who present with complex clinical features. Headache: The Journal of Head and Face Pain. 2006 Feb;46(2):197-9.
3. Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. Jama. 2001 Jul 18;286(3):327-34.
4. Lau DC, Dhillon B, Yan H, Szmitko PE, Verma S. Adipokines: molecular links between obesity and atheroslcerosis. American Journal of Physiology-Heart and Circulatory Physiology. 2005 May;288(5):H2031-41.
5. Munno I, Centonze V, Marinaro M, Bassi A, Lacedra G, Causarano V, Nardelli P, Cassiano MA, Albano O. Cytokines and migraine: Increase of IL 5 and IL 4 plasma levels. Headache: The Journal of Head and Face Pain. 1998 Jun;38(6):465-7.
6. 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 Dec;16(1):1-0.
7. Kruit MC, van Buchem MA, Hofman PA, Bakkers JT, Terwindt GM, Ferrari MD, Launer LJ. Migraine as a risk factor for subclinical brain lesions. Jama. 2004 Jan 28;291(4):427-34.
8. Stewart WF, Lipton RB, Celentano DD, Reed ML. Prevalence of migraine headache in the United States: relation to age, income, race, and other sociodemographic factors. Jama. 1992 Jan 1;267(1):64-9.
9. Rasmussen BK, Olesen J. Migraine with aura and migraine without aura: an epidemiological study. Cephalalgia. 1992 Aug;12(4):221-8.
10. Ramasamy B, Karri M, Venkat S, Andhuvan G. Clinical profile and triggers of migraine: an Indian perspective. Int J Res Med Sci. 2019 Apr;7(4):1050.
11. Buse DC, Reed ML, Fanning KM, Bostic R, Dodick DW, Schwedt TJ, Munjal S, Singh P, Lipton RB. Comorbid and co-occurring conditions in migraine and associated risk of increasing headache pain intensity and headache frequency: results of the migraine in America symptoms and treatment (MAST) study. The journal of headache and pain. 2020 Dec;21(1):1-6.
12. Androulakis XM, Sen S, Kodumuri N, Zhang T, Grego J, Rosamond W, Gottesman RF, Shahar E, Peterlin BL. Migraine age of onset and association with ischemic stroke in late life: 20 years follow up in ARIC. Headache: The Journal of Head and Face Pain. 2019 Apr;59(4):556-66.
13. Vanmolkot FH, Hoon JD. Increased C-reactive protein in young adult patients with migraine. Cephalalgia. 2007 Jul;27(7):843-6.
14. Khalil H. The value of highly specific C-reactive protein HS-CRP in migraine headache. Al-Qadisiyah Medical Journal. 2018 Dec 13;14(26):1-5.