Bangladesh Journal of Neuroscience 2015; Vol. 31 (1): 1-8

ORIGINAL ARTICLES

Association Between Serum C- Reactive Protein With Migraine: A Case Control Study

MD. ABDUL ALIM[1], M A HANNAN[2], SK ABDUL KADER[3], ABU JAFOR MD. SALAUDDIN[4], KABIRUZZAMAN[4], MASUD RANA[5], KHAIRUL KABIR PATWARY[4], NURUDDIN MOHAMMAD EUSUF[6], RASHED IMMAM JAHID[7], SAYED HASAN[4],HUMAYUN KABIR[8], A K M GOLAM KABIR[9]

Abstract:

Objective: *The present case-control study was undertaken to find the association between serum level of CRP and attack of migraine.* ***Methods:*** *The study was carried out at the Headache Clinic and Outpatient Department of Neurology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka over a period of 2 years from January 2010 to December 2011. Migraine patients attending at the above mentioned places were enrolled as cases, while apparently healthy attendants of cases and other healthy persons, who did not have any history of migraine, were included as control. Based on predefined enrollment criteria, a total of 163 subjects were included in the study. Of them 87 were cases and 76 were controls. The serum levels of CRP of both cases and controls were measured and a serum level of > 6 mg/L was considered as raised/ elevated CRP. Levels of CRP were compared between groups (case and control) using appropriate statistical tests.* ***Result:*** *The findings of the study showed that the age and sex distribution of case and control groups were almost comparable. The behavioral factors like food or smoking habit and tobacco leaf chewing had no difference between the groups. Over 20% of migraine patients had abnormally high CRP as compared to 7.9% in the control group (p = 0.021). The migraine patients were 3(95% CI = 1.1 - 8.1) times more likely to be associated with raised CRP (> 6 mg/L) than their healthy counterparts. There were 7 migraine patients with aura and 80 without aura. The level of CRP was not found to be associated with type of migraine (with or without aura) (p = 0.960).****Conclusion:*** *Every one in five patients exhibits abnormally high CRP. The level of CRP does not vary whether the migraine is being associated with or without aura. The migraineurs carry higher risk of developing elevated CRP than their normal counterparts.*

Key words: *Migraine, C-reactive protein, acute attack etc.*

Introduction:

Migraine is a disorder characterized by recurrent attacks of headache, widely variable in intensity, frequency and duration. Attacks are commonly unilateral and are usually accompanied by anorexia, nausea and vomiting. According to International Headache Society (IHS), migraine constitutes 16% of the primary headaches and it affects 10-20% of general population. About 15-20% women and 10-15% men suffer from migraine[1]. Over two-thirds of migraine sufferers either have never consulted a

1. Assistant Professor, Department of Neurology, Shatkhira Medical College, Shatkhira.
2. Professor, Department of Neurology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka.
3. Associate Professor, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka.
4. Assistant Professor, National Institutions of Neurosciences & Hospital, Dhaka.
5. Medical Officer, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka.
6. Assistant Professor, AD-DIN Medical College Hospital, 2 Baro-Magbazar, Dhaka
7. Medical Officer, National Institutions of Neurosciences & Hospital, Dhaka.
8. Neurologist. CMH Dhaka.
9. Asstt. Professor Radiology. National Institutions of Neurosciences & Hospital, Dhaka.

doctor or stopped doing so, which greatly affects quality of life (causing disability). Of the Bangladeshi patients suffering from headache 16.05% had migraine and 12.27% had co-existing migraine and THA[2].

Diagnosis of migraine is made by International Headache Society (IHS) criteria. Headache diary, migraine triggers, medical history, investigations like EEG, CT scan, 3D CT angiogram and MRA of brain (only to exclude secondary causes) are needed to diagnose the disease[3]. Migraine is a risk factor for ischemic stroke, in particular in young woman suffering from migraine with aura[4]. Migraine is also associated with silent brain infarcts and deep white matter lesions detected by magnetic resonance imaging[5]. Both types of brain lesion have been shown to increase stroke risk in the general population[6]. Although the mechanisms underlying the association between migraine and ischemic cerebrovascular disease are unknown, it is believed that inflammation within certain brain tissues resulting from neuronal activation and the subsequent release of proinflammatory neuropeptides from perivascular nerve endings occur during a migraine attack[7,8]. However,

C-reactive protein (CRP), an acute-phase reactant, synthesized by the liver in response to factors released by fat cells (adipocytes) and macrophages[9], has been identified as a sensitive indicator of active systemic inflammation and an independent risk marker for cardiovascular morbidity, including ischemic stroke[10]. A small, uncontrolled retrospective review found abnormal CRP levels in migraineurs[11]. CRP levels rise dramatically during inflammatory processes occurring in the body. It rises above normal limits within 6 hours and peaks at 48 hours depending of the severity of the disease and precipitating cause.

Therefore, CRP values can prove useful in determining disease progress or the effectiveness of treatment. Normal concentration in healthy human serum is usually lower than 6 mg/L, slightly increasing with ageing. Higher levels are found in late pregnant women, mild inflammation and viral infections (10-40 mg/L), active inflammation, bacterial infections (40-200 mg/L) and burns (> 200 mg/L)[12]. 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 as a marker of inflammation. In migraine, different inflammatory markers have been observed in the systemic circulation, including increased levels of C-reactive proteins (CRP)[11,13].

Repeated attacks of migraine have been suggested to carry the risk of inflammatory arteriopathy disrupt the vascular endothelial function and structure, ultimately leading to increased risk of atherosclerosis and ischemic stroke in migraine[14,15]. Stroke is the most disabling of all the neurological diseases and poses a huge burden both socially and economically. The treatment is often frustrating and rehabilitation is not readily available. As CRP has been identified as a sensitive indicator of active inflammation and is frequently associated with migraine, abnormally high

CRP in migraineurs could be detected early to prevent ischemic heart disease and stroke.

Materials & Methods:

This case-control study was conducted over a period of period of 2 years from January 2010 to December 2011 at the Headache Clinic and Out-patient Department of Neurology of Bangabandhu Sheikh Mujib Medical University, Dhaka. The study commenced after having ethical clearance from Institutional Review Board of the university. Migraine patients attending at the above mentioned places were enrolled as cases. Healthy attendants of case and other healthy adult persons visiting the OPD of BSMMU, who did not have a history of migraine, were included as control. A total of 87 cases and 76 controls were included in the study. Adult (18 – 50 years) migraine patients (diagnosis was based on International Headache Society criteria) of either sex who were not on prophylactic medications like pizotifen, propanolol, amitryptyline, pizotifen, topiramate, sodium valproate etc. were included in the study. Data were processed and analysed using software SPSS (Statistical Package for Social Sciences) version 11.5. Data presented on categorical scale were compared between groups using Chi-square (χ^2), Fisher's Exact Test, while data presented on continuous scale were compared between groups using Unpaired t-Test. The risk of having elevated CRP in migraineurs was computed with the help of Odds Ratio and its 95% confidence interval. Level of significance was set at 0.05 and $p < 0.05$ were considered significant.

Results:

The age and sex of the case and control groups were almost comparable between groups. Married population was significantly higher in the case group than that in the control group (0.039). Lower middle class people were much higher in the case group (25.3%) than that in the control group (6.6%) (p = 0.001). There was no significant difference between the groups with respect to BMI

(p = 0.089) (Table I). Very few subjects in the case and control groups had smoking and betel-nut chewing habit with no significant intergroup difference (p = 0.609 and p = 0.632). All the subjects in either group were accustomed to Bengali food (Table II).

Majority (97 .7%) of the migraine patients experienced throbbing nature of pain and only 2.3% had dull-aching pain. Nearly three-quarter (74.7%) of patients felt pain of moderate severity, 23% of mild severity and only 2.3% had severe pain. In more than three-quarters (78.1 %) of the cases the pain lasted for 4 - 72 hours and in 21.8% cases it persisted for up to 4 hours. Pain was mainly unilateral (74.7%) followed by bilateral (24.1%) and generalized (1.1%) ((Table III). Of the associated symptoms, over 95% complained of nausea, 77% vomiting, and 28.7% photophobia. Phonophobia, vertigo, insomnia, one-sided weakness and unconsciousness were rarely reported. Some 7(8%) cases have had aura during an attack with visual aura being predominant (85.7%) (Table IV). Comparison of blood pressure between case and control groups did not reveal any significant difference with mean systolic and diastolic blood pressures within normal physiological ranges (p = 0.767 and p = 0.756 respectively) (table V).

The mean C-reactive protein was significantly higher in the case group than that in the control group (p = 0.041). The mean ESR was also significantly higher in the case group than that in the control group (p < 0.001). The case and controls were almost alike with respect to total count of WBC and neutrophil (p = 0.776 and p = 0.190 respectively), but esinophils and lymphocytes were much lower in the case group (p = 0.003 and p = 0.072 respectively) (Table VI). Serum CRP was observed to bear a significantly linear correlation with ESR (r = 0.379, p < 0.001), but it was not found to be correlated with total count of WBC (r = 0.129, p = 0.101) (Fig. 1 & 2).

Table-I

Distribution of demographic characteristics between groups

Demographic characteristics	Groups		p-value
	Case(n = 87)	Control(n = 76)	
Age#	25.6 ± 6.7	25.1 ± 6.8	0.671
Sex*			
Male	25(28.7)	22(28.9)	0.976
Female	62(71.3)	54(71.1)	
Marital status*			
Married	53(60.9)	34(47.7)	0.039s
Unmarried	34(39.1)	42(55.3)	
Residence*			
Urban	50(57.7)	69(90.8)	<0.001s
Rural	37(42.5)	7(9.2)	
Social status*			
Upper-middle class	8(9.2)	17(22.4)	0.001s
Middle class	57(65.5)	54(71.1)	
Lower-middle class	22(25.3)	5(6.6)	
BMI*			
<25	55(63.2)	38(50.0)	0.089
≥25	32(36.8)	38(50.0)	

Figures in the parentheses indicate corresponding %;
*Chi-squared Test (c^2) was done to analyzed the data.

Data were analyzed using Unpaired t-Test and were presented as mean ± SD.

Table-II

Association between behavioral factors and migraine

Behavioral factors	Groups		P value
	Case(n = 87)	Control(n = 76)	
Smoking*	5(5.7)	3(4.0)	0.609
Betel-nut chewing with tobacco leaf**	2(2.3)	2(2.7)	0.632
Food habit (average Bengali food)*	87(100.0)	75(100.0)	——

Figures in the parentheses indicate corresponding %;
*Chi-squared Test (÷2) was done to analyze the data; **Fisher's Exact Test was done to analyze the data.

Table-III

Distribution of patients by detailed history of migraine (n = 87)

Symptoms	Frequency	Percentage
Throbbing	85	97.7
Dull-aching	02	2.3
Severity of pain		
Mild	20	23.0
Moderate	65	74.7
Severe	02	2.3
Duration of each episode		
Up to 4 hours	19	21.8
4-72 hours	68	78.1
Location		
Unilateral	65	74.7
Bilateral	21	24.1
Generalized	01	1.1
Family history of migraine	16	18.4
Antimigraine medications used		
Analgesics/Paracetamol	87	100

Table-IV

Distribution of patients by associated symptoms (n = 87)

Associated symptoms	Frequency	Percentage
Nausea	83	95.4
Vomiting	67	77.0
Photophobia	25	28.7
Phonophobia	3	3.4
Vertigo	2	2.3
Insomnia	01	1.1
Weakness (one-sided)	01	1.1
Unconsciousness	01	1.1
Aura	07	8.0
Type of aura (n = 7)		
Visual	06	85.7
Sensory	01	14.3

Table-V

Comparison of blood pressure between case and control groups

Blood pressure (mm Hg)#	Groups		P value
	Case(n = 87)	Control(n = 76)	
Systolic BP	120.1 ± 10.2	121 ± 10.9	0.767
Diastolic BP	75.0 ± 8.1	74.5 ± 8.5	0.756

Data were analyzed using Unpaired t-Test and were presented as mean ± SD.

Table-VI

Association of inflammatory markers and haematological variables with migraine

Inflammatory markers & haematological variables#	Groups		p-value
	Case(n = 87)	Control(n = 76)	
Serum CRP (mg/L)	5.7 ± 6.1	4.2 ± 6.0	0.041
ESR (mm in 1st hour)	20.3 ± 16.1	11.3 ± 7.5	<0.001
Total count of WBC (/cu-mm)	8700 ± 240	8410 ± 790	0.776
Neutrophil(%)	57 ± 15	64 ± 6	0.190
Lymphocyte(%)	34 ± 8	32 ± 15	0.164
Esinophil (%)	3.6 ± 1.5	2.1 ± 1.0	0.003
Monocyte(%)	3.6 ± 1.5	1.9 ± 1.2	0.072
Basophil(%)	0.8 ± 0.4	0.0 ± 0.0	0.186
Hb (g/dl)	13.0 ± 2.0	14.1 ± 1.0	< 0.001

Data were analyzed using Unpaired t-Test and were presented as mean ± SD.

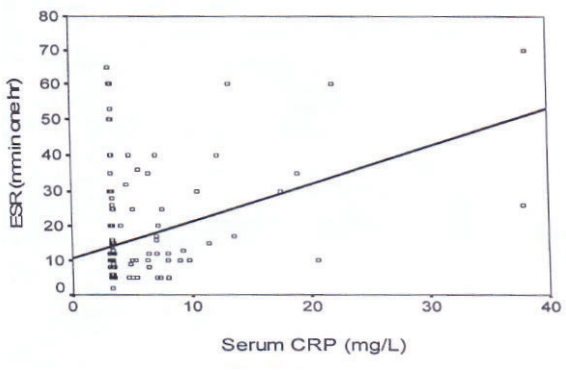

Fig. 1: *Correlation between serum CRP and ESR*

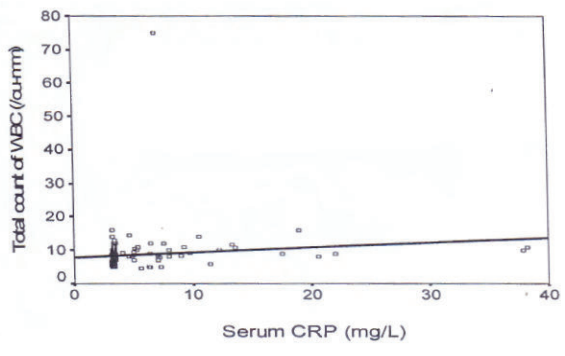

Fig.-2: *Correlation between serum CRP and total count of WBC*

Table VII

Association of CRP with migraine

Serum CRP (mg/L)	Groups		p-value	Odds Ratio
	Case(n = 87)	Control(n = 76)		(95% CI of OR)
> 6 (Raised)	18(20.7)	6(7.9)	0.021	3.1(1.1- 8.1)
≤6 (Normal or low)	69(79.3)	70(92.1)		

Figures in the parentheses indicate corresponding %;
Data were analyzed using Unpaired t-Test and were presented as mean ± SD.

Table-VIII

Association between CRP and migraine with or without aura

Serum CRP (mg/L)**	Migraine		p-value
	With aura(n = 7)	Without aura(n = 80)	
Raised	2(28.6)	16(20.0)	0.960
Normal or low	5(71.4)	64(80.0)	

Figures in the parentheses indicate corresponding %;
**Fisher's Exact Test was done to analyze the data.

Over 20% of the case group had abnormally high CRP (> 6 mg/L) as compared to 7.9% of the control group. The likelihood of having raised CRP in patients with migraine was more than three-fold (95% of CI = 1.1- 8.1) higher than that of their healthy control (p = 0.021) (Table VII). There were 7 migraine patients with aura and 80 without aura. Level of CRP did not differ between migraine with and without aura (p = 0.960) (table VIII).

Discussion:

In the present study, the major demographic characteristics (age and sex) and behavioral factors (food habits, smoking and tobacco leaf chewing) were almost comparable between migraineurs and healthy controls. The mean age of the patients was 25 years with a female preponderance (71%). Smoking habit was very less (5.7%) and betel-nut chewing with tobacco leaf was even less (2.3%). The body mass index (BMI) also did not differ between the groups with mean BMI in case and control groups were 23.8 and 24.8 kg/m^2 respectively. The mean age of the migraineurs were 24.6 years and mean BMI 21.6 kg/m^2 with a female predominance (78 %) and was consistent with other findings[13] but smoking habit was, however, somewhat higher (14%).

In our study, CRP level parallelly increased with ESR as it happens in most of the inflammatory process and as migraine attacks are associated with sterile inflammation[16] and as WBC count did not show any linear increase along with CRP, we can say that this increased level of CRP is not due to infection. But we did not find any similar study which shows the association between ESR and serum CRP level. The age and sex distribution were almost comparable between migraineurs and control subjects and no behavioral factors like food habit or smoking habit, tobacco leaf chewing were any different between the case and control groups, it can be conceived that the raised CRP in the case group is associated with migraine, unless otherwise proved.

It was found that over 20% of migraine patients (cases) exhibited abnormally high CRP (> 6 mg/L) which was almost 3 times more than that found in control group (7.9%) and this raise was not associated with presence or absence of aura (p = 0.934)[11] and found raised CRP in 43% of migraine patients, which compares well with our findings but they found raised CRP level more in without aura group (55.1%) than that of aura group (32.2%), which is not similar with these study. After adjustment for

confounding variables, the relationship between serum CRP and migraine remained significant.

As migraine attacks are accompanied by repeated vascular inflammation of the cranial blood vessels and CRP is a marker of inflammation, repeated attacks of migraine have been suggested to carry the risk of inflammatory arteriopathy of the cranial vessels[16] and consequent thrombosis. Inflammatory processes within the vasculature are well-recognized to play a central part in the pathogenesis of ischemic stroke[17,18]. Repeated episodes of perivascular inflammation during migraine attacks might, therefore, contribute to the increased risk of stroke in migraine[19,20]. The exact mechanisms underlying the association between migraine and ischemic cerebrovascular disease are still elusive. However, it is believed that inflammation within certain brain tissues resulting from neuronal activation and the subsequent release of proinflammatory neuropeptides from perivascular nerve endings occur during a migraine attack[8]. A retrospective review on a small sample found abnormal CRP levels in migraine patients with complex clinical features referred to secondary or tertiary clinics indicating that this protein might play a significant role in the pathogenesis of migraine[11].

The inflammatory process in migraine carries the potential disruption of the vascular endothelial function and structure. This increases the risk of atherosclerosis and vascular diseases. Repeated episodes of perivascular inflammation during migraine attacks might therefore contribute to the increase risk of ischemic stroke in migraine[15]. Stroke is one of the most disabling of all the neurological diseases and in the context of our country it poses a huge social burden. The treatment cost-benefit is frustrating and rehabilitation is not expectedly available. So we should concentrate more on prevention of stroke. As CRP is a marker of inflammation and a risk factor for ischemic stroke[16] , migraine patients should be treated appropriately as early as possible otherwise it will go a long way in controlling migraine and reducing the incidence of ischemic stroke.

Conclusion:

The study concluded that, C-reactive protein is a marker of migraine and migraine is an inflammatory process. More than one-fifth of the patients of migraine possess abnormally high CRP and the level of CRP does not vary whether the migraineurs being associated with or without aura. The migraineurs carry significantly higher risk of developing elevated CRP than their normal counterparts.

References:

1. Goadsby PJ, Lipton RB, Ferrari MD. Migraine:current understanding and treatment. N Engl J Med 2002;3(46):257-70.
2. Hannan MA, Haque A, Ullah AKM, Khan MRK, Islam MR 2007, 'Epidemiologic features of primary headache patients in tertiary centre in Bangladesh', Bangladesh J Neuroscience 2007;23(I):11-22.
3. Headache Classification Sub-committee. The International Classification of Headache Disorders. Cephalalgia 2004;24 (suppl. 1):9-160.
4. Bouser MG, Welch KM. Relation between migraine and stroke. Lancet Neurol 2005;4:533-42.
5. Kruit MC, van Buchem MA, Hofman PA, Bakkers JT, Terwint GM, Ferrari MD et al. 'Migraine as a risk factor for subclinical brain lesions. JAMA 2004;291:427-34.
6. Vermeer SE, Hollander M, van Dijk EJ , Hofman A, Koudstaal PJ, Breteler MM. Silent brain infarcts and white matter lesions increased stroke risk in general population: the Rotterdan1 Scan Study. Stroke 2003;34:1126-9.
7. Carolei A, Marini C, De Matteis G. Italian National Research Council Study Group on Stroke in the Young. History of migraine and risk of cerebral ischaemia in young adults. Lancet 1996;347:1503-6.
8. Waeber C, Moskowitz MA. Migraine as an inflammatory disorder. Neurology 2005;64(10): S9-S15.
9. Lau DC, Dhillon B, Yar H, Szmitko PE, Verma S. Adipokines: molecular links between obesity and athcroslcerosis', Am J Physiol Heart Circ Physiol 2005;288(5):2031-41.

10. 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;286(3):327-34.

11. Welch KM, Brandes AW, Salerno L, Brandes JL. C-rcactivc protein may be increased in migraine patients who present with complex clinical features. Headache 2006;46:197-9.

12. Clyne B, Olshaker JS. The C-reactive protein. J Emerg Med 1999;l7(6):1019-25.

13. Vanmolkot FH, de Hoon JN. Increased C-reactive protein in young adult patients with migraine. Cephalalgia 2007;27(7):843-6.

14. Bonetti PO, Lerman LO, Lerman A. Endothelial dysfunction: a marker of atherosclerotic risk. Arterioscler Thromb Vase Biol 2003;23: 168-75.

15. Buring JE, Hebert P, Romero J. Migraine and subsequent risk of stroke in the Physicians Health Study. Arch Neurol 1995;52:129-34.

16. Bolay H, Reuter U, Dunn AK, Huang Z, Boas DA, Moskowitz MA. Intrinsic brain activity triggers trigeminal meningeal afferents in a migraine model. Nat Med 2002;8(2):136-42.

17. Lindsberg PJ, Grau AJ. Inflammation and infection as risk factors for ischemic stroke. Stroke 2003;34:2518-32.

18. Tatemichi TK, Mohr JP. 1989.'Migraine and stroke. In: Barnett HJM, Mohr JP, SteinBM, editors. Stroke: Pathophysiology diagnosis and management. vol. 2. NewYork: Churchill Livingstone; 1989. p. 845-68.

19. DiNapoli M, Cappelli R, Ceccarelli E, DiGianfilippo G, Donati C et al. Evaluation of Creactiveprotein measurement for assessing the risk and prognosis in ischemic stroke: a statement for health care professionals from the CRP pooling project members. Stroke 2005;36:1316-29.

20. Tzourio C, Tehindrazanarivelo A, Iglesias S. Case-control study of migraine and risk of ischemic stroke in young women. Br Med J 1995;310:830-33.