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INFLAMMATORY BIOMARKERS IN MIGRAINE- A PROSPECTIVE OBSERVATIONAL STUDY

Neurology

Rahul Mahajan* Senior Resident, Department Of Neurology, ABVIMS & Dr RML Hospital, New Delhi. *Corresponding Author

Kuljeet Singh Anand Professor & HOD , Department Of Neurology, ABVIMS & Dr RML Hospital, New Delhi.

Rakesh Kumar Mahajan Professor, Department Of Microbiology, ABVIMS & Dr RML Hospital, New Delhi.

Abhishek Juneja Senior Resident, Department Of Neurology, ABVIMS & Dr RML Hospital, New Delhi.

ABSTRACT

BACKGROUND-Neurogenic inflammation during migraine attacks may lead to raised serum inflammatory markers like hsCRP and procalcitonin.

OBJECTIVES- To determine the serum levels of hsCRP and procalcitonin in patients of migraine during attack and in between attacks as compared to healthy controls.

METHODS-This study was conducted on 50 consecutive patients of migraine fulfilling inclusion criteria and same number of healthy controls. The patients of migraine were diagnosed on the basis of International Classification of Headache Disorders 3rd Edition.

RESULTS- Mean serum hsCRP was significantly higher in migraine cases than in healthy controls, which was further raised during acute attack.Serum procalcitonin during acute attack of migraine was higher in significant proportion of cases when compared to interictal phase (p=0.025).

CONCLUSION-Migraine is a proinflammatory state which may have its implication in increased risk of stroke in migraine patients as reported by some past studies and these biomarkers may help in identifying patients at risk.

KEYWORDS

INTRODUCTION

Migraine is a complex disorder involving neural and vascular dysfunction characterized by recurrent episodic attacks of headache.[1] With an estimated global prevalence of 15%, it is a major public health problem with significant functional and socioeconomic impact. [2] Cortical spreading depression and trigeminovascular activation along with neurogenic inflammation are the main mechanisms suggested to be involved in the pathophysiology of migraine.[3,4] Because of neuroinflammation abnormalities in serum levels of inflammatory markers like C-reactive protein (CRP), interleukins and adhesion molecules have been observed in migraine.[5,6] Serum procalcitonin in recent times has been identified as a highly sensitive and specific marker of inflammation which was found to be raised in acute attacks of migraine in one study.[7] There has been evidence in the literature regarding serum CRP and procalcitonin as inflammatory risk marker for ischaemic stroke and coronary heart disease.[8,9] Migraine is a risk factor for stroke, especially in women who have migraine with aura.[10]The underlying mechanism of coexistence between migraine and cerebrovascular disease is unclear. Recurring episodes of perivascular inflammation in migraine patients as reflected by serum CRP along with serum procalcitonin can provide the missing link between migraine and cerebrovascular disease. There have been few studies in India that have evaluated inflammatory markers in migraine. This study was carried out to evaluate the serum levels of hsCRP and procalcitonin of migraine during attack and in between attacks as compared to healthy controls.

MATERIALS AND METHODS

This was a prospective observational study to evaluate the serum levels of hsCRP and procalcitonin in patients of migraine during attack and in between attacks as compared to healthy controls. This study was approved by Institutional Review Board and Ethics Committee. Study was conducted on 50 consecutive patients of migraine fulfilling inclusion criteria, presenting to the Department of Neurology and Casualty Department, ABVIMS & Dr. RML Hospital, New Delhi between February 2018 to August 2019. The patients of migraine were diagnosed on the basis of International Classification of Headache Disorders 3rd Edition, 2013(ICHD-III)[11] and classified into migraine with and without aura. Healthy controls were recruited consecutively from hospital staff, relatives of patients and general population. Written informed consent was taken from all the cases and controls before inclusion in the study.

Inclusion criteria- (a)Adult males and females of age 18-45 years diagnosed on the basis of ICHD-III criteria as migraine cases.(b)Age (±2 y), sex, body mass index matched healthy individuals as controls.

Exclusion criteria-Patients having non migranous headache, chronic migraine (headache ≥15 days/month) using NSAIDs frequently, who were on prophylactic therapy for migraine, known cases of diabetes mellitus, arterial hypertension, dyslipidemia, head injury, chronic renal disease,any inflammatory or infectious disease, thyroid disorders, history of epilepsy or stroke and cardiovascular disease, body mass index < 18 kg/m2 or > 35 kg/m2, any substance abuse and nicotine dependence,current pregnancy, lactation, or hormonal contraceptive use, drug use such as hormonal drugs, antiplatelet agents, anticoagulants, nitrates, statins.

Methodology-A detailed history of migraine was obtained including disease duration (y), age at onset, average duration of current headache (h), onset to peak, presence of aura, trigger factors, accompanying symptoms, frequency along with location and severity of pain. Severity of headache was evaluated with visual analog scale score (range, 1 [minimum pain] to 100 [maximum pain]). All patients and control subjects received a complete physical and neurologic examination. Comorbidities (coronary artery disease, stroke, diabetes mellitus, or thyroid disease) and inter current illnesses such as respiratory or urinary infections were determined from the patient history, physical examination and laboratory tests (biochemical and hematologic tests). Blood pressure, body weight, height, smoking habits and education level were recorded for all migraine patients and control subjects.After obtaining informed voluntary consent, blood sample of migraineurs were taken during their headache attack (or within 24 hours after headache) and at least one week after their last headache attack (in between attacks after overnight fasting for at least 8 hours). Blood sample of controls were taken in the morning after overnight fasting of at least 8 hours. Samples were collected in plain vials and were centrifuged for 10 minutes at 2200-2500 rpm, the serum separated thereafter was collected in plastic screw cap vials which were sent to Microbiology department. Estimation of serum hsCRP and procalcitonin levels were done in the Microbiology department, ABVIMS, Dr. RML Hospital, New Delhi by ELISA kit manufactured by Calbiotech and immunochromatographic test kit (B.R.A.H.M.S PCT-Q) manufactured by Thermoscientific respectively.

Statistical analysis--Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± SD and median. Normality of data was tested by Kolmogorov-Smirnov test. If the normality was rejected then non parametric test was used. Quantitative variables were compared using unpaired t-test/Mann-Whitney Test (when the data sets were not normally distributed) between the two groups and paired t-test/ Wilcoxon test for comparing during attack and in between attacks.Qualitative variables were compared using Chi-Square test /Fisher's exact test. A p value of <0.05 was considered statistically significant.The data was entered in MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0.

RESULTS

There was no significant difference regarding age, sex and BMI distribution in the migraine and control group as shown in table I. Majority of study participants(68%) were females belonging to age group of <30 years having normal BMI.

Table I - General characteristics of the migraine cases and healthy controls

Characteristic	Migraine Cases	Controls	p-value
Mean Age (in years)	28.92± 5.92	28.52 ±5.57	p = 0.687
Females (%age)	68%	68%	p= 1
BMI (kg/m2)	22.29±1.83	22.37±1.66	p = 0.523

Among migraine cases 34 out of 50 did not have any aura, 33 out of 50 them had disease duration of less than 5 years as shown in table II. 60 % of migraine cases had acute attack frequency of less than 4/month.

Table II- Distribution of migraine cases according to disease duration, frequency of attacks,presence of aura, pain severity and associated symptoms

		Cases		Mean Value
		N	%	
Duration (years)	<5	33	66.0	4.4± 2.24
	≥5	17	34.0	
Frequency (attacks/month)	<4	30	60.0	3.26±1.71
	≥4	20	40.0	
Aura	Absent	34	68.0	
	Present	16	32.0	
Pain Severity (As per VAS Score)	Mild	02	04	
	Moderate	40	80	
	Severe	08	16	
Associated Symptoms	Photophobia	32	64	
	Phonophobia	42	84	
	Nausea	41	82	
	Vomiting	08	16	

Mean serum hsCRP was significantly higher in migraine cases than in healthy controls (2.318±1.518 vs 1.350±0.599, p<0.001), also mean serum hsCRP in migraine cases during attack was higher than in between attacks (2.532±1.453 vs 2.318±1.518, p=0.029),which on statistical analysis was significant.

Table III- Relation of serum hsCRP with various factors in migraine cases and controls

Factor		Cases (in between attacks)			Cases (during attacks)			Controls		
		Serum hsCRP (mg/L)		P value	Serum hsCRP (mg/L)		P value	Serum hsCRP (mg/L)		P value
		Mean	± SD		Mean	± SD		Mean	± SD	
Age (yrs)	<30	2.348	1.704	0.881	2.559	1.618	0.781	1.372	0.585	0.760
	≥30	2.283	1.303		2.443	1.242		1.319	0.632	
Sex	M	2.281	1.465	0.908	2.506	1.495	0.999	1.288	0.612	0.618
	F	2.335	1.563		2.505	1.442		1.379	0.600	
BMI	<22.9	2.397	1.549	0.579	2.597	1.453	0.501	1.416	0.671	0.307
	≥22.9	2.133	1.478		2.293	1.449		1.233	0.439	
Duration	<5	2.361	1.625	0.785	2.567	1.599	0.683			
	≥5	2.235	1.327		2.388	1.116				
Frequency	<4	2.227	1.434	0.607	2.400	1.298	0.530			
	≥4	2.455	1.664		2.665	1.662				
Aura	Absent	2.268	1.468	0.736	2.409	1.365	0.494			
	Present	2.425	1.663		2.712	1.627				

One-Way ANOVA: p > 0.05; Not significant; **p<0.001; Highly significant

There were no significant differences in serum hsCRP levels in relation to age, sex, BMI, duration of disease, frequency of attacks and presence or absence of aura.

Although no statistically significant difference regarding serum procalcitonin levels in migraine cases and healthy controls (p=0.307) was observed but the proportion of migraine cases having serum procalcitonin in the range of 0.5-2mcg/L during acute attack of migraine i.e. 16% was significantly higher than when measured in between attacks i.e. 6% (p=0.025). There were no significant differences in serum procalcitonin levels in relation to age, sex, BMI, duration of disease, frequency of attacks and presence or absence of aura.

Table IV- Relation of serum procalcitonin with various factors in migraine cases and controls

Factor		Cases (in between attacks)			Cases (during attacks)			Controls		
		Serum Procalcitonin (mcg/L)		P-value	Serum Procalcitonin (mcg/L)		P value	Serum Procalcitonin (mcg/L)		P value
		<0.5	0.5-2.0		<0.5	0.5-2.0		<0.5	0.5-2.0	
Age (yrs)	<30	25 (92.6%)	2 (7.4%)	0.650	23 (85.2%)	4 (14.8%)	0.804	28 (96.6%)	1 (3.4%)	0.390
	≥30	22 (95.7%)	1 (4.3%)		19 (82.6%)	4 (17.4%)		21 (100%)	-	
Sex	M	15 (93.8%)	1 (6.3%)	0.959	13 (81.3%)	3 (18.8%)	0.716	16 (100%)	-	0.488
	F	32 (94.1%)	2 (5.9%)		29 (85.3%)	5 (14.7%)		33 (97.1%)	1 (2.9%)	
BMI	<22.9	33 (94.3%)	2 (5.7%)	0.897	29 (82.9%)	6 (17.1%)	0.736	32 (100%)	-	0.178
	≥22.9	14 (93.3%)	1 (6.7%)		13 (86.7%)	2 (13.3%)		17 (94.4%)	1 (5.6%)	
Duration	<5	31 (93.9%)	2 (6.1%)	0.980	28 (84.8%)	5 (15.2%)	0.820			
	≥5	16 (94.1%)	1 (5.9%)		14 (82.4%)	3 (17.6%)				
Frequency	<4	28 (93.3%)	2 (6.7%)	0.808	25 (83.3%)	5 (16.7%)	0.875			
	≥4	19 (95.0%)	1 (5.0%)		17 (85%)	3 (15%)				
Aura	Absent	32 (94.1%)	2 (5.9%)	0.959	29 (85.3%)	5 (14.7%)	0.716			
	Present	15 (93.8%)	1 (6.3%)		13 (81.3%)	3 (18.8%)				

Chi-Square Test : p > 0.05; Not significant

DISCUSSION

Many of the studies in past had reported that serum levels of hs-CRP were elevated in migraine cases during interictal period as compared to healthy controls which is consistent with the findings of present study,[12,13] thus supporting the fact that neurogenic sterile inflammation plays a role in pathogenesis of migraine as suggested by Moskowitz and colleagues.[14] Gudmundsson et al found no difference between migraine patients and healthy controls in terms of the CRP level.[15] The difference is possibly due to racial and ethnic characteristic of population studied along with inclusion-exclusion criteria applied in their study. To our knowledge, there is no study in the literature which has compared the serum hsCRP levels during attack phase and in between attacks in the same migraine patient but the results of present study are in concurrence with the theory of neurogenic sterile inflammation during migraine attack. Vanmolkot et al[12] and Welch et al[16] noted that CRP levels tend to be higher in patients with migraine without aura than with aura whereas Salehi et al[13] and Tietjen et al[5] reported higher CRP levels in migraine with aura than without aura . Present study did not find any significant difference between mean serum hsCRP values of migraine cases with or without aura which is in concurrence with the results reported by Gurger et al[17] and thus supporting the hypothesis that pathophysiologic mechanisms for migraine with or without aura are similar. Procalcitonin (PCT) is a highly sensitive and specific marker of inflammation, the production of which is governed by Calc-1 gene. Alternative splicing of the mRNA from Calc-1 leads to the generation of calcitonin gene-related peptide (CGRP), which is thought to act at multiple sites along the trigeminovascular pathway in pathogenesis of migraine resulting in sterile inflammation.[18] In addition to PCT being a possible marker of proinflammatory state in migraine it is also a partial agonist of the CGRP1 receptor, thus possibly have a direct role in the pathogenesis of migraine.[19] In the present study there was no significant difference regarding serum procalcitonin levels in migraine cases and healthy controls which was in contrast to the findings of study conducted by Leira et al.[20] The difference is probably due to inclusion of chronic migraine cases in the study by Leira et al which were excluded in our study. In present study the proportion of migraine cases having serum procalcitonin in the range of 0.5-2mcg/L during attack phase i.e 16% was significantly higher than when measured in between attacks i.e 6%. Similar findings were reported by Turan et al but predominantly in cases of migraine without aura.[7] This was probably because proportion of migraine with aura cases in study by Turan et al was lower than present study, also in present study serum procalcitonin was measured in same migraine case during attack phase and in between attack. Based on evidence from the previous studies along with present study it can be concluded that migraine is a proinflammatory state which may have its implication in increased risk of stroke in migraine patients as reported by some past studies. The limitations of present study were (a) being carried out at tertiary level centre, study sample may not be true representative of community distribution and (b) use of semi quantitative method for serum procalcitonin estimation. In future well planned studies are warranted in order to explore the potential of serum inflammatory biomarkers like hsCRP and procalcitonin as a diagnostic biomarker for migraine.

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