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Association of Metabolic Syndrome with Migraine: A Case-Control Study

REFAYET CNH[1], ALAM SM[2], RAHMAN HZ[3], ISLAM MR[4], BHUIYAN MM[5], HANNAN MA[6], RIZVI AN[7], YUSUF MA[8], KAWSAR MK[9], RAHMAN MH[10], MAHMOOD RH[11], HASAN M[12], SARKER I[13]

Abstract:

Background: *Migraine is a disabling primary headache disorder and metabolic syndrome is a major escalating public-health challenge worldwide. They share some common pathophysiology. But till date, their relationship is obscure.* ***Methods:*** *This study was conducted in headache clinic and inpatient-outpatient department of Neurology and Biochemistry laboratory of BSMMU, from June 2017 to February 2019. In these age-sex matched case control study, 30 migraine patient and equal number non migraine volunteer were taken according to inclusion exclusion criteria. Waist circumference (WC), blood pressure (BP), fasting plasma glucose (FPG), serum triglyceride (TG) and high density lipoprotein cholesterol (HDL-C) were measured among all.* ***Results:*** *In this case control study, 24 women and 6 men were taken in both case and control groups, with mean age (±SD) of 32 (±7.77) and 30 (±8.46) years respectively. Metabolic syndrome was significantly higher among migraineurs (36.7% in case and 13.3% in control group respectively, p=0.037). Patient with metabolic syndrome had 3.763 times more chance of having migraine then person without metabolic syndrome [p=0.037, OR=3.763, 95% C.I. (1.038-13.646)].* ***Conclusion:*** *There is an association between metabolic syndrome and migraine.*

Keywords: *Migraine, Metabolic syndrome, oxidative stress etc.*

Introduction:

Migraine is a common disabling primary headache disorder with high socio-economic and personal impacts. In the Global Burden of Disease Survey 2010, it was ranked as the 3rd most prevalent disorder and 7th highest specific cause of disability world-wide[1]. Migraine has two major sub types; migraine without aura (common migraine) and migraine with aura (Classical migraine). Migraine without aura, a clinical syndrome characterized by headache with specific features and associated symptoms.There are recurrent headache attacks, lasting 4-72 hour. Headache typically unilateral, pulsating quality, moderate to severe intensity, headache aggravated by routine physical activity and associated with symptom like nausea and/or photophobia and phonophobia[1]. Migraine with aura is primarily characterized by the transient appearance of focal neurological symptoms which usually precede or sometimes may accompany

1. Dr. Chowdhury Neamul Hassan Refayet, Resident Neurology, Department of Neurology, BSMMU, Dhaka, Bangladesh.
2. Dr. Sheikh Mahbub Alam, Associate Professor, Department of Neurology, BSMMU, Dhaka, Bangladesh.
3. Prof. (Dr). Hasan Zahidur Rahman, Professor, Department of Neurology, BSMMU, Dhaka, Bangladesh.
4. Prof. (Dr). Md. Rafiqul Islam, Professor and Chairman, Department of Neurology, BSMMU, Dhaka, Bangladesh.
5. Prof. (Dr). Md. Moniruzzama Bhuiyan, Professor, Department of Neurology, BSMMU, Dhaka, Bangladesh.
6. Prof. (Dr). MA Hannan, Professor, Department of Neurology, BSMMU, Dhaka, Bangladesh.
7. Prof. (Dr). Abu Nasir Rizvi, Professor, Department of Neurology, BSMMU, Dhaka, Bangladesh.
8. Dr. Md. Abdullah Yusuf, Assistant Professor, Department of Microbiology, NINS&H, Dhaka, Bangladesh.
9. Dr. Md. Jafrul Kawsar, Resident Neurology, Department of Neurology, BSMMU, Dhaka, Bangladesh.
10. Dr. Md. Habibur Rahaman, Resident Neurology, Department of Neurology, BSMMU, Dhaka, Bangladesh.
11. Dr. Md. Rakib Hasan Mahmood, Final Part Student, MD (Neurology), Department of Neurology, BSMMU, Dhaka, Bangladesh.
12. Dr. Mehedi Hasan, Resident Neurology, Department of Neurology, BSMMU, Dhaka, Bangladesh.
13. Dr. Imran Sarker, Registrar (Clinical Neurology), NINS&H, Dhaka, Bangladesh.

headache. Among different types of aura visual aura is the most common (90%) type[1]. Several theories have been put forward regarding the complex pathophysiology of migraine-the vascular theory, migraine generator theory, the cortical spreading depression theory and the trigeminovascular theory[2]. Activation of the trigeminovascular system plays a central role in the pathophysiology of migraine and linked to the pain of migraine[3]. Activated trigeminovascular system leads to release of inflammatory vasoactive neuropeptides (CGRP, substance-P, NO) from sensory afferents that innervate the major intracranial arteries, results in vasodilation, plasma protein extravasation, inflammation (termed as "neurogenic inûammation")[3]. More and more evidence indicates a primary role for CGRP as a mediator of migraine[2]. Cortical spreading depression (CSD) is hypothesized to cause the aura of migraine, activate trigeminal nerve afferents and alter blood-brain barrier permeability[2]. In migraine, special pattern of inflammatory and oxidative stress markers has been observed in the systemic circulation including increased levels of C-reactive proteins (CRP), interleukins (IL-1, IL-6), TNF-α[4,5]. Increased level of Leptin (activates IL and TNF-α, increase pain sensitivity) [5], Homocysteine (induces neurogenic inflammation, oxidative stress, inhibition of GABA-A receptor in migraine attack)[6] and decreased magnesium level in serum and brain (Mg in the brain triggers release of 5-HT- a vasoconstrictor)[2],have been observed among migraineurs. Migraine is associated with some major vascular diseases including- stroke, subclinical brain matter lesions, coronary artery disease and HTN[7]. The metabolic syndrome is a major escalating public-health problem and clinical challenge worldwide in the wake of urbanization, surplus energy intake, increasing obesity, and sedentary life habits[8]. Metabolic syndrome is present if $\geq$3 of the following five criteria are met: waist circumference >90 cm (men) or >8o cm (women) (adjusted for Asian population), blood pressure Systolic >130 or Diastolic >85 mmHg or on drug treatment for HTN is an alternate indicator, fasting triglyceride (TG) level >150 mg/dl or on drug treatment for elevated TG, fasting high-density lipoprotein (HDL) cholesterol level <40 mg/dl (men) or <50 mg/dl (women) or on drug treatment for reduced HDL-C and fasting blood sugar >100 mg/dl or On drug treatment for elevated glucose[8]. Metabolic syndrome confers a 5-fold increased risk of type 2 DM and 2-4 fold the risk of developing cardiovascular disease and stroke[9].

Though exact pathogenesis of metabolic syndrome is not clear, but abdominal adiposity and insulin resistance thought to be at the core of the pathophysiology of the metabolic syndrome and its individual components[10,11].Free fatty acid (FFA) are released in abundance from an expanded adipose tissue mass, which result in increased hepatic production glucose and triglycerides, leads to the lipid/lipoprotein abnormalities include reductions in HDL-C, reduce insulin sensitivity in muscle & increase pancreatic insulin secretion, resulting in hyperinsulinemia[10,11]. Insulin resistance in the liver, muscle, and adipose tissue is also associated with the abundance of proinflammatory cytokines[10,11]. In obese person elevated calcitonin gene related peptide (CGRP) and Leptin and decreased Adiponectin (an anti-inflammatory substance) have been observed in different studies[12]. Metabolic syndrome is found to be associated with hyperhomocysteinemia[13] and low serum magnesium levels[14].

The relationship between metabolic syndrome and migraine is still obscure and only few studies done regarding this topics[15], which have found positive[15-20] and negative associations[21]. Among previous studies conducted in BSMMU found migraine is associated with dyslipidemia[22], decreased level of serum Magnesium[23], hyperhomocysteinemia[24] all of them is also associated with metabolic syndrome. Another study in Bangladesh found migraine more severe in patients with comorbidities like DM, HTN and obesity[25].

Materials and methods:

This age-sex matched case control study was conducted in headache clinic and inpatient-outpatient department of Neurology and Biochemistry laboratory of BSMMU. Patients with migraine headache (according to ICHD-3 beta criteria)[1], age more than 18 years, who were willing to participate in this study and who had given informed written consent, were enrolled as case group. Age and sex matched non-migraineur volunteers, age more than 18 years were selected as control group. Both case and control were enrolled by purposive consecutive sampling technique. Participants had pregnancy or lactating, who were smoker, alcoholic, on active pain (during examination or sample collection), with acute illness (e.g. fever, acute myocardial infarction, acute stroke). had following conditions or diseases: Diabetes mellitus, hypothyroidism, Cushing's syndrome, acromegaly, polycystic ovarian syndrome, chronic kidney disease, nephrotic syndrome, chronic liver disease, who took following drugs: Glucocorticoid, Oral contraceptives, Amitriptyline, Valproic acid, Pizotifen, Beta blocker, Thiazide diuretics, Mirtazapine, Quetiapine, Olanzapine, Retinoids were excluded from this study. Secondary causes of metabolic syndrome along with its individual components were excluded among person whom was suffering from metabolic syndrome. Anthropometric measurements including height, weight, waist circumference (WC) were taken with participants following the standard protocol (participants wearing light clothes and without shoes). Body mass index (BMI) was calculated as the weight (kg) divided by square of the height (m^2). To measure waist circumference (WC), top of right iliac crest were located (WC-IC method). A measuring tape ((standard metered flexible measuring tape) was placed in a horizontal plane around abdomen (tape was snug but non compressive. Measurement (cm) was made at the end of a normal expiration. Blood pressure were measured in the both arms by auscultatory method using standard metered Mercury Sphygmomanometer (Model: ALPK-2), following the AHA, (2005)[26] guideline of blood pressure measurement. Participants were fasted at least 12 hour overnight before blood sample collection.Withall aseptic precaution measures 10 ml of venous blood were collected from each of the participants (using sterile 10 cc disposable plastic syringes). 2 ml of blood were collected in a gray cap test tube (containing EDTA) for measuring fasting plasma glucose and 5ml ofblood were collected in a red cap test tube for measuring fasting lipid profile. Coulter auto-analyzer machine (Model-AU680, USA) was used along with proper reagent to measure fasting plasma glucose and serum lipid profile.Metabolic syndrome was diagnosed according AHA/NHLBI, 2005 criteria[8].

Statistical analysis:

Demographic, anthropometric, clinical and laboratory characteristics (Data) were expressed as mean ± SD (standard deviation) for continuous variables or as percentages for categorical variables. Data were compared by using Student's t-test for continuous variables. For categorical variables, differences were assessed by the Chi-square test. To assess the relative significance of etiological variable, binary logistic regression was used. Results for the binary logistic regression were presented as odds ratios (OR) with a 95% confidence interval (CI). Data were analyzed by using statistics software SPSS v-25. In all cases, P values <0.05 were considered as statistically significant.

Results:

A total number of 60 participants were recruited for this study of which 30 migraineurs were in case group and the 30 respondents were in control group after fulfilling the inclusion and exclusion criteria.

Table-I

Distribution of the Study Groups by Age

Age Group (years)	Groups		P value
	Case	Control	
18 to 25	9 (30%)	11 (36.7%)	0.583 ð ns
26 to 30	7 (23.3%)	7 (23.3%)	1.000 ð ns
31 to 35	6 (20%)	4 (13.3%)	0.488 ð ns
36 to 40	5 (16.7%)	4 (13.3%)	0.717 ð ns
Above 40	3 (10%)	4 (13.3%)	0.687 ð ns
Total	30 (100%)	30 (100%)	0.919 ð ns
Mean ±SD (Years)	32 ± 7.77	30 ± 8.46	0.962 ð ð ns

*p- value was derived from Chi-Squire test, **p- value was derived from unpaired t-test, p-value < 0.05 was considered as significant, ns= not significant, s= significant

Table I shows that, the mean age (±SD) was 32 (±7.77) years in case group. The mean age (±SD) was 30 (±8.46) years in control group. Most of the study patients'ages were 18 to 25 years in case group (30%) and 18 to 25 years in control group (36.7%).

Table-II

Distribution of the Study Groups by Gender

Gender	Groups		p-value
	Case	Control	
Male	6 (20%)	6 (20%)	1.000 ns
Female	24 (80%)	24 (80%)	
Total	30 (100%)	30 (100%)	

Chi-square test was done as a test of significance and p-value < 0.05 was considered as significant, ns= not significant.

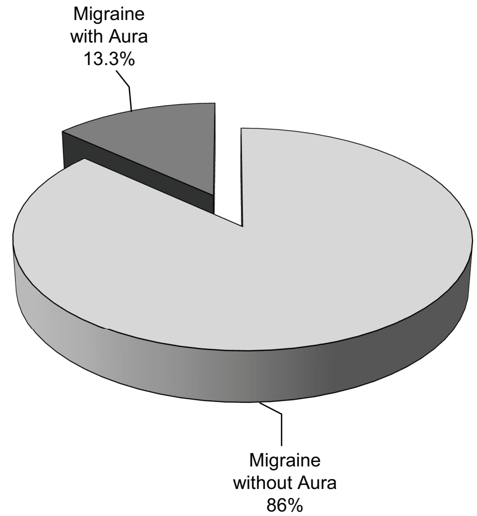

Fig.-1: *Pie Chart Showing Distribution of Migraineurs According to Presence of Aura*

Table-III

Distribution of the Study Groups by Metabolic Syndrome

Metabolic syndrome	Groups		Total	p-value
	Case	Control		
Yes	11 (36.7%)	4 (13.3%)	15 (25%)	0.037 s
No	19 (63.3%)	26 (86.7%)	45 (75%)	
Total	30(100%)	30(100%)	60(100%)	

Chi-square test was done as a test of significance and p-value < 0.05 was considered as significant, s = significant.

Table-IV

Distribution of the Study Groups by Different Variables

Variables	Groups		p-value
	Case (n=30) Mean ± SD	Control (n=30) Mean ± SD	
Height (cm)	154.81±6.39	155.54±7.12	0.676 ns
Weight (kg)	53.72±7.29	53.36±8.22	0.858 ns
BMI [Wt.(kg)/Height (m2)]	22.4±2.57	21.79±2.03	0.315 ns
Waist Circumference (WC) (cm)	86.98±6.55	81.77±4.51	0.001 s
Systolic blood Pressure (SBP)	123.00±11.19	114.17±13.14	0.007 s
Diastolic blood pressure (DBP)	76.50±6.84	73.17±6.23	0.053 ns
Fasting blood glucose (mmol/L)	5.44±0.66	5.20±0.52	0.117 ns
Total cholesterol (TC) (mg/dL)	199.7±40.08	194.53±38.83	0.614 ns
HDL Cholesterol (HDL-C)(mg/dL)	39.47±10.08	45.67±12.68	0.040 s
LDL Cholesterol (LDL-C) (mg/dL)	126.28±35.5	123.3±31.38	0.732 ns
Triglyceride (TG) (mg/dL)	170.13±85.1	126.8±60.87	0.027 s

Unpaired t test was done as a test of significance and p-value < 0.05 was considered as significant, ns= not significant, s= significant.

Table-V

Risk Assessment of Metabolic Syndrome as a Risk Factor of Migraine with Binary Logistic Regression Analysis

Variable	Groups				
	Case	Control	p-value	OR (95% CI)	
Patient with metabolic syndrome	11 (36.7%)	4 (13.3%)	0.037	3.763	(1.038-13.646)

CI=Confidence Interval; Odds Ratio=OR

Table II shows that male and female were equally distributed between case and control groups. Out of 30 participants, male were 6 (20%) and female 24 (80%) in each group.

Table III shows that, 36.7% patient in case group and 13.3% person in control group were suffering from metabolic syndrome. However 63.3% patient case group and 86.7% person in control group had no metabolic syndrome. P value=0.037, which was statistically significant.

Table IV shows that, waist circumference (WC) (p=0.001s), systolic blood pressure (SBP) (p=0.007), triglyceride (TG) level (p=0.0.027) were significantly higher among migraineurs (case group), while high density lipoprotein cholesterol (HDL-C) levels were significantly lower among were significantly (p=0.040). However, there were no statistically significant difference in height (p=0.676), weight (p=0.858), body mass index (BMI) (p=0.315), diastolic blood pressure (DBP) (p=0.053), total cholesterol (TC) (p=0.614), low density lipoprotein cholesterol (LDL-C) (p=0.732), fasting blood glucose (FBS) (p= 0.117) among case and control group.

Table V showed that, Patient with metabolic syndrome had 3.763 times more chance of having migraine then person without metabolic syndrome [p=0.037, OR=3.763, 95% C.I. (1.038-13.646)].

Discussion:

Metabolic syndrome and migraine both are common risk factor of ischemic stroke and cardiovascular disease. They share some common pathophysiology e. g. obesity, dyslipidemia, Insulin resistance, raised Interleukins (IL-1, IL-6), CRP, Leptin, Homocysteine, CGRP and decreased Adiponectin and serum magnesium. But there relationship is obscure[15].This age-sex matched case control study has found that, 36.7% patient in case group (migraineurs) and 13.3% person in control group (non-migraineurs) have been suffering from metabolic syndrome. This result is statistically significant (p=0.037). So migraine headache is associated with metabolic syndrome. Celikbilek et al., (2015)[15] in a study, conducted in Yozgat region (Central Anatolia), have found that, metabolic syndrome associated with migraine (p=0.001). In their study, 33% migraine patients have been suffering from metabolic syndrome. A recent study in Southeast Asia (Bhoi, et al., 2012)[16], has found that, 31.9% migraineurs (n=135) have metabolic syndrome. In both of these studies, number of migraineurs with metabolic syndrome is almost similar to this study. However, Rahim et al., (2007)[29] have found that, prevalence of metabolic syndrome among Bangladeshi population is 13.5% (a study involving 3981 subjects aged >20). This prevalence of metabolic syndrome is almost similar to the control group of this study. So it indicates that, participants of control are approximately representing general population of Bangladesh.

Anthropological measures among the population of this study- height (cm) is 154.81±6.39 and 155.54±7.12 (Mean ± SD) (p=0.676) in case and control group respectively. Weight is 53.72±7.29, 53.36±8.22 (Mean ± SD) (p=0.858) in case and control group respectively. BMI [Wt. (kg)/Height (m^2)] was 22.4±2.57 and 21.79±2.03 (Mean ± SD) (p=0.315) in case and control group respectively. None of which is statistically significant. But waist circumference (cm) 86.98±6.55 and 81.77±4.51 (p=0.001) in case and control group respectively, is significantly higher among migraineurs. Both Salmasi et al., (2012)[21] and Celikbilek et al., (2015)[15] have found that, migraineurs have significantly higher BMI and weight circumference then non- migraineurs. Measures commonly have been used for assessing obesity are BMI and waist circumference (WC). Unfortunately, BMI is not considered to be a good estimate of obesity in Asian Indians as they have a characteristic obesity phenotype, with relatively lower BMI but with central obesity[27]. It has been suggested that, fat distributed in the abdominal region, particularly visceral fat is more metabolically important than other fat depots[27]. Bhoi, et al., (2012)[16], in a study conducted in Southeast Asia, has found that, 31.9% migraineurs have metabolic syndrome but only 13 are obese. This indicates different pattern of obesity of people in this region. Increased waist circumference, a marker of central (visceral) obesity, is also a core component of metabolic syndrome. It is relevant to migraine pathophysiologylogy in various mechanisms like- increased interleukins (IL-1, IL-6), TNF-α, CRP, calcitonin gene-related peptide (CGRP), Leptin., homocysteine and decreased adipocetin and low serum magnesium Streel et al., (2016)[18] and Guldiken et al., (2009)[16] also have been found that, migraine is associated with increased abdominal obesity.

Among other components of metabolic syndrome, systolic blood Pressure (SBP) is significantly higher among migraine population than control group (Mean ± SD) (123.00±11.19 and 114.17±13.14 respectively. p=0.007) but there is no significant difference in diastolic blood pressure (DBP) in between migraine and non-migrainure (76.50±6.84 and 73.17±6.23 respectively, p=0.053). Celikbilek et al., (2015)[15] and Salmasi et al., (2012)[21] have found that, migraineurs have significantly increased systolic diastolic blood pressure, then non-migrainure. Now, both mean systolic and diastolic blood pressure among control group is within optimal level (< 120/80mmof Hg) (EHS/ECC, 2018), but systolic blood Pressure (SBP) among migraineurs not optimal (<130/85 mm of Hg) (EHS/ECC, 2018). This might be an indication of endothelial dysfunction and sympathetic over activity- pathology relevant to these disease process.

Among biochemical components of metabolic Syndrome, Triglyceride (mg/dL) [170.13±85.1 and 126.8±60.87 (Mean ± SD) in case and control group respectively, p=0.027] is significantly higher among migraineurs and HDL cholesterol (mg/dL) is significantly lower among migraineurs [39.47±10.08 and 45.67±12.68 (Mean ± SD) in case and control group respectively, p=0.040]. Among other component of lipid profile total cholesterol (TC) [199.7±40.08 and 194.53±38.83 (Mean ± SD) in case and control group respectively, p=0.614] and LDL Cholesterol (mg/dL) [126.28±35.5 and 123.3±31.38 (Mean ± SD) in case and control group respectively, p=0.732] have no significant difference in between case and control group. However, both Salmasi et al., (2012)[21] and Streel et al, (2016)[18], have found that, HDL-C is significantly lower among migraineurs. Celikbilek et al., (2015)[15] have found that, migraineurs have significantly higher triglyceride level in comparison to control group. High triglyceride and low HDL is indistinguishably related to metabolic syndrome and several previous studies have established that, migraine is associated with dyslipidemia. A study previously done in BSMMU (Saleheen et al., 2016)[22] has found that, migraine is associated with dyslipidemia. That study has found, triglyceride is significantly higher among migraineurs [173.67±61.39 and 128.68±46.31 (Mean ± SD) in case and control group respectively, p=0.000]. This result is approximate to the result of this study. This pattern of dyslipidemia (high triglyceride and low HDL) and elevated blood pressure is relevant with cardiovascular and cerebrovascular adverse events.

This study has not found any significant difference of fasting blood glucose (mmol/L) level between case and control group [5.44±0.66 and 5.20±0.52 (Mean ± SD) in case and control group respectively, p=0.117]. Insulin resistance (IR) (a prior stage, in which a person may go through years before developing pre-diabetes followed by type 2 DM) is related to metabolic syndrome and migraine. Fava et al., (2013)[28] have found that, migraine is associated with insulin resistance.So direct measuring of IR could have given us better idea. This is included in WHO diagnostic criteria of metabolic syndrome (1998). However, in this study, AHA/NHLB, (2005) criteria is used, for which measuring of insulin resistance is not required.

Conclusion:
The study suggests that, the metabolic syndrome is associated with migraine. Though body mass index is higher among migraineurs then non-migraine but it is not statistically significant. But waist circumference (a core component of metabolic syndrome) is significantly higher among migraineurs. Among other different components of metabolic syndrome systolic blood pressure, triglycerides are significantly higher and HDL-C significantly lower among migraineurs in contrast to non-migraineur.

Recommendation:
Though the study was conducted on small sample size, it may be recommended that, metabolic syndrome along with its components should be searched in migraineur, as some commonly prescribed anti-migraine drugs are associated with weight gain, dyslipidemia and insulin resistance.

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