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A Comparative Study of Clinical Vascular Risk Factors and Serum Biomarkers of Endothelial Dysfunction in Patients of Episodic Migraine without Aura and Chronic Migraine

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ABSTRACT

Introduction: Migraine patients have increased prevalence of vascular risk factors. However, the vascular risk differs between the migraine subtypes. Differences in vascular risk factors and serum biomarkers of endothelial dysfunction between patients of migraine without aura and chronic migraine have been sparselystudied.

Aims and Objectives: The study aimed to assess the differences of vascular risk factors and biomarkers of endothelial dysfunction in episodic migraine without aura and chronic migraine patients.

Methods: The patients were recruited from Headache Clinic at a tertiary care hospital in Delhi, India. They were diagnosed as episodic migraine without aura and chronic migraine using International Classification of Headache Disorders-3 criteria. The patients were preventive drug-naïve and did not have medication overuse headache.Clinical vascular risk factors such as systolic blood pressure (SBP), diastolic blood pressure (DBP), ankle brachial index (ABI), body mass index (BMI), and waist hip ratio (WHr) were measured. A battery of biomarkers of endothelial functions was estimated, namely, serum levels of iCAM (intercellular adhesion molecule-1), myeloperoxidase (MPO), interleukin-6 (IL-6), tumour necrosis factor–alpha (TNF-alpha), asymmetric dimethyl arginine, fibrinogen (ADMA), von Willebrand's factor (vwF).

Results: Thirty-two patients each with episodic migraine without aura and chronic migraine were studied[(age28.8±7.9 years; 25 females and 7 males)vs.(30.6±8.8 years; 29 females and 3 malesrespectively)]. Patients with chronic migraine had significantly higher diastolic blood pressure (81.0±8.0 vs. 75.4±7.0mmHg; p=0.002), ABI (0.98±0.01 vs. 0.96±0.03; p<0.001), and lower WHr (0.91±0.03 vs. 0.95±0.03; p<0.001). Among the biomarkers of endothelial dysfunction, iCAM (180±290 vs.450±380ng/ml; p<0.001), MPO (155.2±1981.7 vs.415.4±266.0pg/ml; p<0.001), IL-6 (8.6±5.3 vs.10.8±4.9pg/ml; p=0.039), and ADMA levels (21.3±9.7 vs.32.6±28.3ng/ml; p=0.011) were significantly raised in patients with chronic migraine.

Conclusion: Our study shows that patients with chronic migraine have significantly higher vascular risk along with evidence of endothelial dysfunction compared to episodic migraine patients without aura. Chronic migraine patients therefore need to be evaluated for vascular risk in routine clinical practice.

Keywords: migraine, chronic migraine, vascular risk, biomarkers, endothelial dysfunction

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I. INTRODUCTION

Migraine is a common disabling disorder characterized by recurrent episodes of headache attacks. It is the third most prevalent medical condition and the second most disabling neurological disorder in the world.[1] It has been estimated that approximately 20% of the female population and 9% of the male population suffer from migraine in the Western world.[2,3]Increasing evidence suggests that migraine is associated with ischemic vascular events including myocardial infarction or even death due to cardiovascular disease.[4-6] The association of migraine and ischemic stroke is more robust in those with aura symptoms.[7]More recently, migraine with aura has been associated with other vascular diseases including intracerebral haemorrhage (ICH)[8], retinal vasculopathy[9]and vascular mortality.[10,11]Several studies also found incidental infarct like brain lesions in migraine patients.[12,13]Besides these above-mentioned disease associations, some studies have shown that migraine patients also have increased vascular risk profile namely obesity, hypertension, dyslipidemia, metabolic syndrome, and various markers of increased atherosclerosis as compared to the general population.[14]

The mechanism underlying the association between migraine and cardio- and cerebrovascular disorders are currently unknown. Various mechanisms including endothelial dysfunction have postulated to account for such increased vascular disease associations in migraine patients.[15]Broadly speaking, endothelial dysfunction primarily results in impairment of endothelial-dependent vasodilatation. This is due to a decrease in the bioavailability of vasodilating factors and an increase in endothelium-derived vasoconstrictors.[16] In addition, induction of endothelial activation is characterized by a proinflammatory and procoagulatory environment, which enhances atherogenesis and vascular diseases. Endothelial dysfunction results in endothelial activation, which can be assessed with biomarkers and vascular reactivity studies. However, recent studies of biomarkers and vascular reactivity studies of endothelial dysfunctions in migraine patients found conflicting results.[17,18] Further, very few studies have combined the clinical vascular risk factors assessments and endothelial dysfunction assessments together in migraine patients to test the hypothesis as to whether these can be correlated. Only a handful of studies have been undertaken to differentiate these associations between patients of episodic migraine without aura and chronic migraine.

The present study aimed to study the differences, if any of vascular risk factors and biomarkers of endothelial dysfunction in episodic and chronic migraine patients using a battery of clinicaland biochemical measures.

Methods

This was a prospective observational study. The subjects were consecutive migraine patients attending Headache Clinic at G B Pant Institute of Post Graduate Medical Education and Research, (GIPMER), Delhi.The study was approved by Institutional Ethics Committee. Informed written consent for the participation was taken from all patients.

Inclusion criteria

1. Any patient aged 18 to 50 years of age who fulfilled the diagnostic criteria laid down by ICHD-3[19] for episodic migraine (EM) without aura (1.1), and chronic migraine (CM) (1.3).
2. Patients should be preventive drug-naive (no history of any previous preventive drug treatment).
3. Episodic migraine patients should have headache attacks of 4-14/month in the last month.
4. If the patient had multiple headaches at the time of presentation, migraine should be the most prominent headache at the time of presentation.

Exclusion criteria

1. Patients with other secondary headache including medication overuse headache.
2. Episodic migraine patients with aura
3. Patients who are pregnant, lactating.
4. Patients who are on chronic anti-inflammatory or immunomodulatory drugs, statins, antihypertensives, nitrates or antiepileptic drugs, and females who are using oral contraceptives.

Assessment

All patients were evaluated as per a detailed structured proforma covering all aspects of clinical characteristics of headache. These include disease onset duration, duration of attack, frequency, location, character, premonitory symptoms, systemic symptoms like nausea, vomiting, photophobia, phonophobia, clinical autonomic symptoms/signs, triggers, motor and psychological symptoms during headache and postdrome.Detailed family history for headache was taken. Relevant biochemical (hemogram, liver function tests, kidney function tests, thyroid function tests) and radiological tests were done to exclude secondary causes. Severity of pain was rated on visual analogue scale (VAS). Impact of headache was assessed by headache impact test

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(HIT 6) and headache related disability was assessed by migraine disability assessment test (MIDAS). A baseline screening headache diary for 1 month was used before inclusion in the study for all the migraine patients to classify them into EM, and CM.

Clinical Vascular risk factors

A battery of clinical vascular risk factors such as systolic blood pressure (SBP), diastolic blood pressure (DBP), ankle brachial index (ABI), body mass index (BMI), and waist hip ratio (WHr) were measured. The auscultatory method of blood pressure (BP) measurement with a properly calibrated and validated sphygmomanometer was used. Subjects were made to sit comfortably in a chair for at least 5 minutes with arm supported at heart level. The appropriate size cuff (bladder length 80% and width at least 40% of arm circumference) was use to ensure accuracy. The systolic BP was defined as appearance of the first sound (Korotkoff phase 1) and diastolic BP is defined as disappearance of the sound (Korotkoff phase 5)[20]. Also resting brachial and ankle blood pressures were measured in supine position on both extremities, 5 min apart and the mean pressure recorded and ABI wascalculated. Patients with ABI <0.9 was considered to have peripheral arterial disease (PAD)[21]. For BMI, height was measured in centimeters on wall mounted stadiometer and weight (kg) was determined using a weighing scale with 100gm as minimum measuring unit.The BMI was calculated as the weight in kilograms divided by the square of height inmeters. In the present study the cut off level for BMI≥ 25 was taken for obesity[22].Waist Circumference (WC) was measured midway between the inferior margin of the last rib and the crest of the ileum and hip circumference (HC) around the pelvis at the point of maximum protrusion of the buttocks, both in a horizontal plane, without compressing the soft tissues. Waist Circumference (WC) and HC were recorded to the nearest cm and WHrwas defined as a ratio of WC to HC.

Biomarkers of endothelial dysfunction

Venous blood, 10 ml was collected under aseptic condition by experienced laboratory technicians from the respondents after 8 hours fast. It was allowed to clot at 25^{o}C for 30 minutes followed by centrifugation at 800g for 10 minutes and subsequently the serum was separated and aliquots were prepared. A battery of biomarkers of endothelial functions was estimated, namely, serum levels of iCAM (Intercellular adhesion molecule), myeloperoxidase (MPO), interleukin -6 (IL-6), tumour necrosis factor–alpha (TNF-alpha), asymmetric dimethyl arginine (ADMA), fibrinogen (on Elitepro Instrumentation Laboratory), von Willebrand's factor (all by ELISA commercially available kits).

Statistical analysis

Sample size calculation

Using a previous study with prevalence and association estimates for various vascular risk factors[23]and assumed 80% power and 5% alpha error, 1:1 ratio of two groups, the sample sizewas estimated to be 32 patients in each group.

Statistical analysis was done using SPSS software package (version 25). Categorical data were summarized as frequencies and percentages. Continuous data were summarized as mean, andStudent t test was used to compare the means. Non-parametric analyses such as Mann-Whitney U test was used for the parameters that are not normally distributed. Post-hoc Bonferroni adjustments were made for multiplicity testing. X^2 test with Yates correction and Fisher's exact test was used to compare proportions between the groups. The level of significance was set at $p<0.05$.

II. RESULTS

Thirty-two patients each with episodic migraine without aura and chronic migraine were studied. Mean age at presentation was 28.8±7.9 years for patients with episodic migraine without aura (25 females and 7 males) and 30.6±8.8 years for the patients with chronic migraine (29 females and 3 males). The headache burden of the two groups is shown in Table 1.

Table1. Headache burden

Headache characteristics	**Episodic Migraine without Aura (n=32)**	**Chronic Migraine (n=32)**
Duration of illness (years) (mean ± SD)	5.7±5.2	6.7±4.5

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Attack duration if untreated (hours)(mean ± SD)	13.9±5.9	9.9±3.4
Attack duration if treated with acute medication (hours)(mean ± SD)	1.9±0.7	2.4±1.3
Migraine days per month(mean ± SD)	5.8±1.1	17.9±4.6
Headache days per month(mean ± SD)	--	23.4±4.7
Headache attack severity (by VAS)(mean ± SD)	6.7±0.6	6.5±0.6
HIT-6 Score(mean ± SD)	63.8±5.1	66.7±3.8
MIDAS Score(mean ± SD)	29.3±8.3	30.1±13.8

Clinical vascular risk factors

Patients with chronic migraine had significantly higher diastolic blood pressure (81.0±8.0 vs. 75.4±7.0; p=0.002), ABI (0.98±0.01 vs. 0.96±0.03; p<0.001), and lower WHr (0.91±0.03 vs. 0.95±0.03; p<0.001). Mean BMI of the patients with chronic migraine was also higher (27.2±2.3) compared to those with episodic migraine but did not reach statistical significance (Table 2).

Table 2: Comparison of clinical vascular risk factors in patients of episodic migraine without aura vs. episodic migraine with aura

Clinical vascular risk factors*	**Episodic migraine without aura**	**Chronic Migraine**	**p value**
Systolic blood pressure (SBP) (mmHg)	116.9±12.9	117.4±12.7	0.893
Diastolic blood pressure (DBP) (mmHg)	75.4±7.0	81.0±8.0	**0.002**
Ankle Brachial Index (ABI)	0.98±0.01	0.96±0.03	**<0.001**
Body Mass Index (BMI) (kg/m^2)	24.2±2.4	27.2±2.3	0.812
Waist Hip Ratio (WHr)	0.91±0.03	0.95±0.03	**<0.001**

***** All values are mean ± standard errors. Significant p values are shown in bold.

Biomarkers of endothelial dysfunction

Among the biomarkers of endothelial dysfunction, serum levels of iCAM (180±290 vs 450±380, p value<0.001), MPO (155.2±1981.7 vs 415.4±266.0, p value<0.001), IL-6 (8.6±5.3 vs 10.8±4.9, p value-0.039), and ADMA levels (21.3±9..7 vs 32.6±28.3, p value – 0.011) were significantly raised in patients with chronic migraine (Table 3).

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Table 3. Comparison of biomarkers of endothelial dysfunction in patients of episodic migraine without aura vs. chronic migraine

Biomarkers of Endothelial dysfunction*	**Episodic Migraine without Aura**	**Chronic Migraine**	**p value**
iCAM (ng/ml)	180±290	450±380	**<0.001**
Myeloperoxidase (MPO) (pg/ml)	155.2±1981.7	415.4±266.0	**<0.001**
Interleukin-6 (IL-6) (pg/ml)	8.6±5.3	10.8±4.9	**0.039**
TNF-alpha (pg/ml)	17.7±16.6	13.5±5.9	0.142
Asymmetric Dimethyl Arginine (ADMA) (ng/ml)	21.3±9.7	32.6±28.3	**0.011**
Fibrinogen (mg/dl)	351.3±110.3	389.8±118.8	0.299
vWF (ng/ml)	4.4±2.2	4.4±2.9	0.203

*All values are mean ± standard errors. Significant p values are shown in bold.

III. DISCUSSION

We found that the patients with chronic migraine have significantly higher vascular risk along with evidence of endothelial dysfunction compared to episodic migraine patients without aura. Patients with chronic migraine had higher diastolic blood pressure andhigher waist hip ratio (suggesting abdominal obesity) and lower ABI scores suggesting peripheral vascular atherosclerosis. These vascular risk factors have been strongly associated with cardiovascular and cerebrovascular diseases.[4,5,7] Episodic migraine with aura patients are known to have significant vascular risk associations but such associations with chronic migraine patients were not studied in detail previously.[8-11]

Previously, Mathew et al[24], reported that patients with chronic daily headache, transformed originally from episodic migraine, had a higher possibility of hypertension. Bigal et al[25], carried out a randomised case–control study to identify the factors associated with induction and transformation from episodic to chronic migraine. They found a strong association between hypertension and chronic migraine with and without analgesic overuse, when the study group was compared with episodic migraine and chronic posttraumatic headache. Contrarily, Huang et al[26] found that the frequency of elevated blood pressure wasn't higher in CM patients than non-CM group. They suggested that analgesic overuses maybe the reason of higher frequency of elevated BP in patients with chronic daily headaches and its subtypes. However, we have excluded the patients of chronic migraine with analgesic overuse. It is interesting to note that many population-based studies have also found that diastolic blood pressure is higher in migraine patients than non-migraine controls.[27] However, a separate analysis comparing episodic and chronic migraine has not been performed. Further, in a recent studyby Ramusino[28] et al hypertension was postulated to have contributed to the chronic evolution of headache with mechanisms shared with migraine; i.e., vascular tone alteration and autonomic dysregulation.

Obesity including abdominal obesity has been strongly associated with chronic migraine and is a considered as an important predisposing factor for the chronification of migraine. Bigal and Lipton[29] found that increased BMI was associated with an increased prevalence of transformed migraine from 0.9% in normal weighted to 1.2% in overweight, 1.6% in obese and 2.5% in morbidly obese subjects but had no influence on chronic tension type headache. In a recent study, Kristoffersen et al[30]found that both total body obesity and abdominal obesity were associated with a higher prevalence of migraine when compared to headache-free controls, for individuals < 50 years of age.Thus, our finding of increased abdominal obesity in chronic migraine patients is consistent with the above results.

Association of increased ABI with migraine had shown inclusive results although in one study, patients with long landing migraine (more than 10 years) had significantly higher ABI scores compared to healthy controls suggesting peripheral atherosclerosis risk for the migraineurs.[31]

The mechanism underlying the association between migraine and cardio- and cerebrovascular disorders are currently unknown. Various mechanisms including endothelial dysfunction have postulated to account for such increased vascular disease associations in migraine patients.[15]Broadly speaking, endothelial dysfunction primarily results in impairment of endothelial-dependent vasodilatation. This is due to a decrease in the bioavailability of vasodilating

factors and an increase in endothelium-derived vasoconstrictors.[16] In addition, induction of endothelial activation is characterized by a proinflammatory and procoagulatory environment, which enhances atherogenesis and vascular diseases. Endothelial dysfunction results in endothelial activation, which can be assessed with serum biomarkers and vascular reactivity studies. However, recent studies of biomarkers of endothelial dysfunctions in migraine patients found conflicting results.[17,18]

In our study, among the biomarkers of endothelial dysfunction, iCAM, MPO, IL-6and ADMA levels were significantly elevated in CM patients compared to episodic migraine patients. iCAM is a cell surface glycoprotein expressed on endothelial, immune, and epithelial cells and belongs to Ig superfamily.[32] It plays role in leucocyte trans-endothelial migration, in innate and adaptive responses to inflammation, regulates many essential cellular functions, and drives inflammatory responses. MPO is found in the aniline blue granules of myeloid cells (neutrophils and monocytes).[33] It plays a role in phagocytosis and microorganism killing. Reactive oxygen species derived from MPO promote development of host tissue damage and disease. MPO plays a role in atherosclerosis and cardiovascular and cerebrovascular diseases. IL-6 is released by macrophages, B & T-cells, eosinophils and basophils and plays a role in induction and control of acute phase protein synthesis, stimulationof haematopoiesis, stimulation of antibody production by B-cells and neutrophil activation, macrophage maturation and increased expression of IL-1 and TNFα.[34]Methylated residues of arginine undergo proteolysis to form ADMA.[35] It causes endothelial dysfunction due to low levels of NO. High plasma ADMA levels have a strong positive correlation with cardiovascular and cerebrovascular events. These biomarkers of endothelial dysfunction have been found to be elevated in migraine patients in general but not many studies were done specifically to seek differences between episodic migraine and chronic migraine.A recent study by Togha et al[23] showed that the serum levels of IL-6, CRP and TNF-α were significantly higher among subjects with CM than the EM and controls.

We used a battery of tests for biomarkers of endothelial dysfunction and found significantly elevated multiple biomarkers of endothelial dysfunction in CM patients in 4 out of 7 measures. The findings of our study therefore raises the possibility of their role for vascular risk in these patients. Endothelium modulates vascular function and structure, mainly by production of nitric oxide which protects the vasculature against the development of atherosclerosis and thrombosis. Endothelial dysfunction occurs in association hypertension, contributing to inflammation in the vascular wall, of resistance arteries as well as to increased lipoprotein oxidation, smooth muscle cell proliferation, extracellular matrix deposition, cell adhesion, and thrombus formation in conducting arteries.[36] Similarly, abdominal obesity is associated with vascular endothelial dysfunction, caused by a reduced nitric oxide availability secondary to an enhanced oxidative stress production.[37] Endothelial dysfunction in peripheral arterial disease has also been found to be related to increase in plasma markers of inflammation.[38]

Limitation of the present study include small sample size. Further the absolute values of various parameters that were estimated were found to be mostly within normalcut-off and hence, though the comparisons of the two groups showed statistical significance, their clinical significance remains uncertain.

Despite these limitations, our study by directly comparing two groups of migraine clearly demonstrated differences in terms of vascular risk factors and biomarkers of endothelial dysfunction. Although the exact pathophysiology of CM is uncertain, the role of atypical pain processing, central sensitization, cortical hyperexcitability, and neurogenic inflammation has been implicated in its pathogenesis.[39] When viewed in this context, the findings of our study showing significantly elevated biomarkers of endothelial dysfunction possibly related to persistent neurogenic inflammation in CM assumes importance and needs further exploration by larger studies.

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