

A CROSS-SECTIONAL STUDY TO DETECT THE PREVALENCE OF HYPERHOMOCYSTEINEMIA IN PATIENTS OF MIGRAINE

Nidhi Kharb¹, Praveen Kumar Malik², Archana Ran³

¹Postgraduate Student, Department of Internal Medicine, ESIC Medical College and Hospital, Faridabad, (Haryana).

²Assistant Professor, Department of Internal Medicine, ESIC Medical College and Hospital, Faridabad, (Haryana).

³Assistant Professor, Department of Anaesthesiology, Hamdard Institute of Medical Sciences and Research, Jamia Hamdard.

ABSTRACT

BACKGROUND

Migraine is a common, disabling primary headache disorder. It is a constellation of symptoms like headache, nausea, vomiting, photophobia and other similar neurological dysfunction in varying admixtures. Since, migraine is a neurovascular disease, the highly reactive amino acid, homocysteine has been postulated to play a role in migraine pathophysiology.

MATERIALS AND METHODS

A total of 30 migraine patients participated in the present study including 22 females and 8 males. The study was directed towards the aim of finding out the prevalence of hyperhomocysteinemia in migraine patients, which came out to be 13.3% and other aim is to show association if any between homocysteine level and severity of migraine in which we found no direct relationship between serum homocysteine level and severity of migraine.

RESULTS

The study was carried out from May to June, 2017, among consecutive patient attending the OPD of Medicine and Psychiatry Department. In all, 30 migraine patients and 30 controls were interviewed during this phase. The result of the present study has been analysed and tabulated.

CONCLUSION

Prevalence of hyperhomocysteinemia in migraine was found to be 13.3% and there was no significant relation found between serum homocysteine levels and severity of migraine. Mean serum homocysteine level was found to be higher in migraine patient as compared to control, but the association did not come out to be statistically significant.

KEYWORDS

Migraine, Hyperhomocysteinemia.

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BACKGROUND

Homocysteine was discovered 70 years ago by Butz and du Vigneaud at the University of Illinois.¹ Homocysteine occupies central role in the metabolism of central amino acid, methionine. It is at the junction point of transsulfuration pathway and the formation of cysteine and excretion of sulfur on the one hand and remethylation of homocysteine to methionine with conservation of carbon skeleton on other.² Homocysteine is perhaps less well known because it is normally found in relatively less concentration within the cell ($\leq 1 \mu\text{mol/L}$) and in the circulation (5-15 $\mu\text{mol/L}$). Genetic defects in 5-MTHF reductase can consequently lead to hyperhomocysteinemia. The most

common polymorphisms are known as MTHFR C677T and MTR A2756G.^{3,4} These polymorphisms occur in about 10% of the world's population. Elevations of homocysteine can also occur in the rare hereditary disease homocystinuria. However, in recent times, elevated plasma Total Homocysteine (tHcy) has got the reputation as the "not so good thiol" because of its association with cardiovascular disease, end-stage renal disease, hypothyroidism, neural tube defects and cognitive dysfunction including Alzheimer's disease. Several studies reported that plasma tHcy levels increase with age depending on nutritional and metabolic factors and on changes in vitamin B12 absorption and renal excretion. Folic acid and vitamin B12 deficiency or MTHFR polymorphism is considered the essential cause of high tHcy concentration.^{5,6} Moreover, vegetarianism and sedentary lifestyle are important aetiological factors. Vegetarianism in India is multigenerational, lifelong and based on religious and cultural beliefs. In India, striking hyperhomocysteinemia has been commonly observed in markedly decreased intakes of folic acid and vitamin B12 in the vegetarians and urban middle class residents.^{7,8}

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Corresponding Author:

Dr. Praveen Kumar Malik,

Assistant Professor, Department of Internal Medicine,

ESIC Medical College and Hospital,

N.H. 3, NIT, Faridabad, Haryana- 121001.

E-mail: drpraveenmalik@gmail.com

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Many studies have revealed that supplementation of folic acid lowers homocysteine levels in most people with cobalamin having a small, but much significant effect, but with no such additional effect with vitamin B₆.⁹

Migraine is a common, disabling primary headache disorder. It is a constellation of symptoms like headache, nausea, vomiting, photophobia and other similar neurological dysfunction in varying admixtures. Typically, the headaches affect one half of the head are pulsating in nature and may last from 2 to 72 hours. The pain is generally made worse by physical activity. Up to one-third of people have an aura- typically a short period of visual disturbance, which signals that the headache will occur soon?

Epidemiological studies have documented its high prevalence, high socioeconomic and personal impacts. In the Global Burden of Disease Survey 2010, it was ranked as the third most prevalent disorder and seventh-highest specific cause of disability worldwide.¹⁰ Migraine afflicts approximately 15% of women and 6% of men over a 1-year period. It is usually an episodic headache associated with certain features such as sensitivity to light, sound or movement; nausea and vomiting often accompany the headache. A useful description of migraine is a recurring syndrome of headache associated with other symptoms of neurologic dysfunction in varying admixtures.¹¹

Since migraine is a neurovascular disease, the highly reactive amino acid, homocysteine has been postulated to play a role in migraine pathophysiology.^{12,13,14,15} A few studies have investigated the relationship between homocysteine and migraine with conflicting results with some showing no association and other showing association between classical migraine and homocysteine only.¹⁶⁻¹⁷

So, in India where hyperhomocysteinemia is commoner as compared to western population due to prevalent food habits, it is imperative to know the relation between serum homocysteine levels and migraine and to evaluate the normal serum homocysteine level in Indian population. At present, there is little literature regarding the significance of the relationship between raised serum homocysteine level and migraine.

A cross-sectional study has been performed to find the prevalence of raised serum homocysteine in patients of migraine and has been compared with healthy controls with no complaints suggestive of migraine.

Rationale behind choosing this research topic was that many studies have tried to evaluate the relation between levels of homocysteine with conflicting results. Studies showed positive and negative relation, while some other equivocal and some concluding that reducing homocysteine levels could reduce the migraine attacks.

The magnitude of financial loss due to migraine as a health issue is immense. That is why, it is pertinent to find out the modifiable risk factor of migraine.

So, review of these studies was done from published literature-

A. Studies where homocysteine was raised in migraine patients.

A study performed by Bokhari Faraz A., Shakoori Tania A., Hassan Syed Ahmad A., Qureshi Hamid J., Qureshi Ghulam A. in a tertiary care hospital in Lahore, Pakistan, in 2010. Study concluded that plasma homocysteine levels to be significantly associated with MWOA. Additionally, plasma homocysteine levels were lower in MWA than in Migraine without Aura (MWOA).

A study published in 2008¹⁸ and performed to evaluate homocysteine plasma levels in 136 migraine with aura sufferers and in 117 sex- and age-matched controls. Mean homocysteine plasma levels as well as the proportion of subjects with hyperhomocysteinemia were significantly higher in patients with MA than in healthy controls.

A case-control study was performed by Gavganii Sima C., Hoseinian Mohammad M.¹⁹ in Tabriz, Shams Hospital and other clinics in Iran in 2012. Sixty five patients suffering from migraine were studied that 38.5% of them were male and 61.5% of them were females with an average age of 27.69 ± 9.50 (15-55) years and 65 normal people with 41.5% males and 58.5% females with an average age of 27.42 ± 8.25 (15-52) years (p>0.05). The mean level of serum in patient group is significantly higher than the control group (averagely, 14.49 ± 5.03 against 10.92 ± 4.68 micromole in litres; p<0.001). The difference was still remaining after sex control. Study concluded that serum homocysteine level in patients suffering from migraine is significantly high than in normal people.

B. Studies where homocysteine was not related/equivocal in migraine patients.

A study was performed by Hering-Hanit, R et al,²⁰ published on September 4, 2001, which evaluated total serum homocysteine with high-performance liquid chromatography in 78 patients with migraine and in 126 age- and sex-matched healthy volunteers. Only 1 man had significantly elevated blood homocysteine (38.6 µmol/L), while another had a borderline elevation (15.8 µmol/L) (reference value for both sexes in our laboratory is 4 to 14 µmol/L). Both patients suffered from migraine without aura and concluded that blood homocysteine is not elevated in migraine.

A cross-sectional study performed in Isfahan City, Iran, in February 2013.²¹ Fasting serum levels of homocysteine were measured in 130 Migraine with Aura (MA) patients (31 males and 99 females) aged 15-60 years. Severity, frequency and duration of migraine attacks as well as HDR were determined in each patient according to international headache society criteria by a neurologist. Study concluded that there is no significant association between serum levels of homocysteine treatment studies with severity, frequency, duration and HDR.

C. Interventional studies.

Study performed in the Headache Center of the San Luca Hospital (Vallo della Lucania, SA) for two years (2003-2004).²² Study concluded that the administration of folates and vitamin B12 is able to produce a reduction of the migraine index and plasma levels of homocysteine.

D. Indian literature.

We are yet to find any publication relating homocysteine and migraines to the horizon of our knowledge.

Evaluating homocysteine level in India and to assess the relation of it with migraine is even more important as hyperhomocysteinemia is even more prevalent in India due to diet.

A review of the studies supporting this fact is as follows- A study performed by Diabetes Unit, King Edward Memorial Hospital and Research Centre, Pune, India included 441 middle-aged men (149 rural, 142 slum and 150 urban middle-class residents, mean age 39 years). Data on lifestyle, socioeconomic status, nutrition and medical history were obtained. Circulating concentrations of vitamin B12, folate, ferritin, Total Homocysteine (tHcy) and haematological indices and cardiovascular risk variables were measured. Median plasma B12 concentration was low (110 pmol/L). Overall, 67% of men had low vitamin B12 concentration (<150 pmol/L) and 58% had hyperhomocysteinemia (>15 micromol/L). Of the urban middle class, 81% had low vitamin B12 concentration and 79% had hyperhomocysteinemia.

A study performed in Department of Medicine, All India Institute of Medical Sciences, New Delhi, and published in 2002 concluded that low intakes of folic acid and vitamin B12 and hyperhomocysteinemia in both the healthy population living in urban slums and adjacent urban non-slum areas are important observations for the prevention of nutritional and cardiovascular diseases in the Indian subcontinent.

AIMS AND OBJECTIVES

Primary Objectives-

- To find the prevalence of hyperhomocysteinemia in migraine patients and to look for association, if any, between level of serum homocysteine and severity of migraine using migraine index.
- To evaluate level of serum homocysteine in normal population and to compare it with that in cases of migraine.

Secondary Objectives-

- To find the demographical characteristics of migraine patient in terms of age, gender, family history and to determine and quantify the loss of performance secondary to migraine either at work place or at home.
- To determine the mean duration of episode of headache, frequency (i.e. episodes per month).

MATERIALS AND METHODS

Study Design and Type of Study- The study was a hospital-based cross-sectional study.

Study Site- This study was conducted at tertiary care hospital study was performed mainly in Department of Medicine and Psychiatry, which has daily OPD attendance of around 250 as per hospital medical record.

Target Population- The study recruited new consecutive OPD patients in the Department of Medicine and Psychiatry with the chief complaint of headache and symptoms suggestive of migraine using the following inclusion and exclusion criteria.

Inclusion Criteria

- Those diagnosed to have migraine with or without aura as per the criteria laid by International Headache Society, 2013.
- Those who provided informed consent.

Exclusion Criteria

- Headache due to any other primary or secondary causes.
- Age less than 12 or more than 60 years.
- Patients suffering from cardiac, renal or nervous system disease other than migraine, which were known cause of hyperhomocysteinemia.
- Patients with macrocytic anaemia.
- Seriously ill and non-consenting patient.

METHODOLOGY

Total of 60 patients were recruited for the study, out of which, 30 patients were diagnosed as migraine and 30 patients were healthy controls. A valid written consent was obtained by the primary investigator from all the patients selected for the study as per inclusion and exclusion criteria. Control were selected in a way that none of them reported with any known cause of hyperhomocysteinemia.

All the necessary steps were taken to rule out any known cause of hyperhomocysteinemia or to validate the inclusion and exclusion criteria of study, which included a detailed history and general and systemic examination along with all necessary investigations (including blood homocysteine levels). A copy of case sheet will be uploaded showing all the investigations performed.

Duration of Study- Study was performed within duration of 2 months from May 2017 to June 2017 between 9 a.m. to 12 p.m. daily by using questionnaire (prepared using international headache society guidelines, 2013 and MIDAS).

Study Tool- A headache questionnaire based on International Headache Society, 2013, along with detailed clinical history was used to assess the patient's headache and it was an open-ended questionnaire made in Hindi, which is the most legible language for patient visiting to ESIC. Both the original questionnaire, namely, the criteria lead by IHS, 2013, and MIDAS (migraine disability assessment score) questionnaire used for finding the severity of migraine were translated in vernacular language (Hindi) of the participant by the expert translator and furthermore both the original and translated version were validated by back translation and retranslation followed by piloting. Questionnaire also assesses the sociodemographic profile of the subjects, medical history and family history of migraine. MIDAS (Migraine Disability Assessment Score) was used to assess the severity of migraine and to evaluate the loss of performance secondary to migraine attacks. MIDAS consists of 5 questions to assess the severity, thus grading the migraine disability into minimal, mild, moderate and severe disability and the validity of MIDAS has already been proved.²³ It divides migraine into 4 grades with Grade I- With minimal or infrequent disability with score between 0-

5, Grade II- Mild or infrequent disability: 6-10, Grade III- Moderate disability: 11-20, Grade IV- Severe disability: >20. In our study comprising of 30 migraine patient has been divided into 4 groups on the basis of 4 grades of MIDAS.

Ethical Considerations- Prior to commencement of the study approval from Institutional Ethics Committee was obtained and written informed consent from each participant was taken before the interview. In case of minor less than 18 years, the consent is taken from both the patient and caregiver. The participants were assured that all information will be kept confidential.

Statistical Analysis- The data was entered into Microsoft Excel 2007 spreadsheet. To look for association between level of serum homocysteine and severity of migraine ANOVA test was applied and t-test was applied to compare the level of homocysteine between migraine patients and control.

RESULTS

The study was carried out from May to June, 2017, among consecutive patient attending the OPD of Medicine and Psychiatry Department. In all, 30 migraine patients and 30 controls were interviewed during this phase. The result of the present study has been analysed and tabulated.

In our study, number of migraine patients with hyperhomocysteinemia was 4 out of which 3 were females and 1 was male. Hence, the prevalence of hyperhomocysteinemia in patients with migraine was calculated using formulae-

Prevalence = Number of people with the disease (with hyperhomocysteinemia) at a given time × 100.

Number of people at risk = (4/30) × 100 = 13.3%.

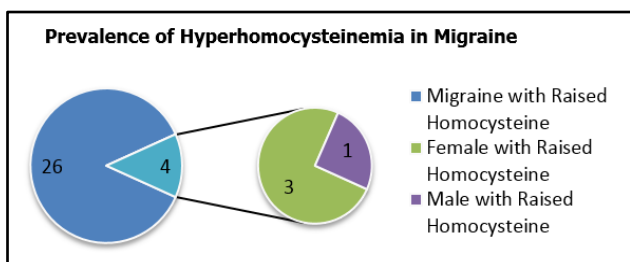


Figure 1. Pie of Pie to Show the Prevalence of Hyperhomocysteinemia in Patients with Migraine and Further Distribution of Those on the Basis of Gender

In our study, the age of presentation varied from 14-47 years for migraine patients with median age being 26.5 years.

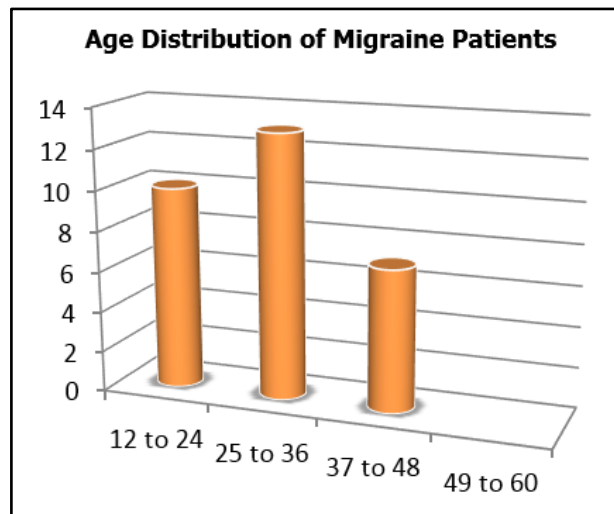


Figure 2. Bar Diagram to Show Age Distribution. X Axis Represents Range of Age (in Years) and Y Axis Represents Number of Patients

Variable		N (%)
Gender	Male	8 (26.7)
	Female	22 (73.3)
Family history of migraine	Present	11 (36.7)
	Absent	19 (63.3)
BMI (kg/m ²)	Underweight (<18.5)	10 (33.3)
	Normal weight (18.5-24.9)	12 (40)
	Overweight (25-29.9)	8 (26.7)
	Obese (>30)	0 (0)

Table 1. Demographical Characteristics of Patients

Result revealed that out of 30 migraine patients included in study, 22 (73.3%) were females and 8 (26.7%) were male. Significant history of migraine was present in one or more family members in case of 11 (36.7%) patients in migraine group as compared to 19 (63.3%) who did not have any such history. 10 patients were underweight in contrast to 8 being in overweight category. 12 patients had normal BMI.

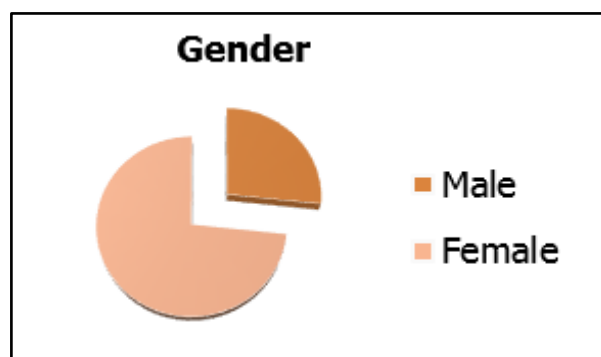


Figure 3. Explode Pie in 3D Showing the Percentage Wise Gender Distribution of Migraine Patients Included in the Study

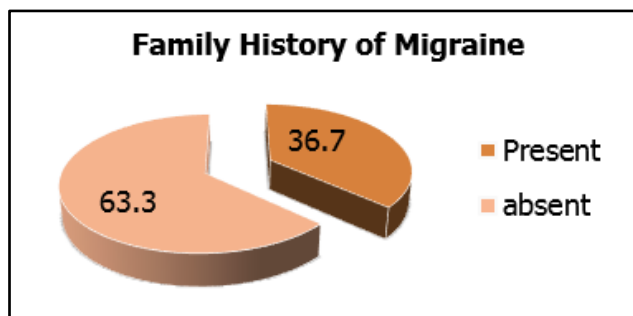


Figure 4. Exploded Pie in 3D Chart Representing the Percentage of Patient Having Family History of Migraine

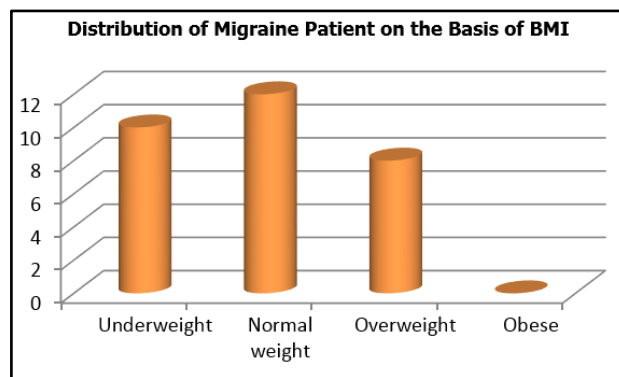


Figure 5. Bar diagram to Show the Distribution of Migraine Patient on the Basis of BMI Established by WHO in 1997 and Published in 2000. X Axis Represents Classification of BMI and Y Axis Represents Number of Patients

Variable	Group 1 (n=0)	Group 2 (n=2)	Group 3 (n=9)	Group 4 (n=19)	dF	F	p value
Mean S Hcy level		12 ± 3.39	9.6 ± 3	11.45 ± 3.53	2	1.417	0.260

Table 2. Mean Serum Homocysteine Level in Groups Divided on the Basis of Severity of Migraine Using MIDAS Questionnaire

30 migraine patients were divided into 4 groups using grading criteria of MIDAS questionnaire. In our study, no migraine patient fell into group 1 (minimal disability), whereas maximum number of migraine patient (63.3%) came into group 4, i.e. most severe disability with score of more than 20. Group 2 (6.6%) and 3 (30%) had subjects with mild and moderate disability, respectively.

On one-way ANOVA, no statistically significant difference was found between the four groups (defined on the basis of severity of migraine) and mean homocysteine level ($F(2, 27) = 1.417, p = 0.26$).

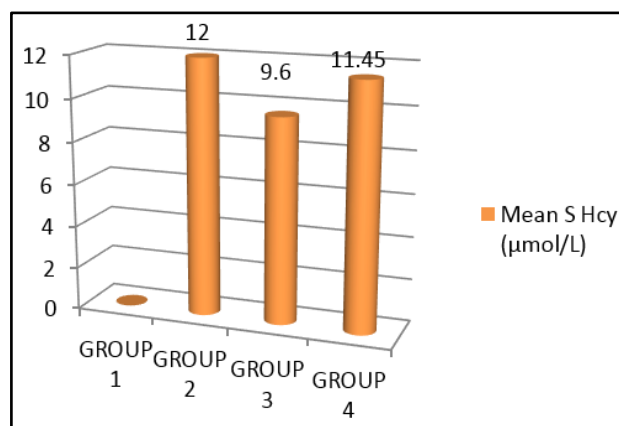


Figure 7. Bar Diagram to Show the Mean Serum Homocysteine Level in Various Groups Based on Severity of Migraine

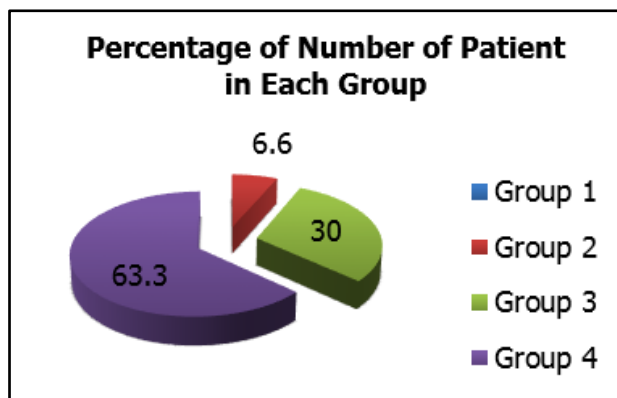


Figure 6. Exploded Pie in 3D Representing Number of Patient in Each of 4 Groups

Berksonian Bias, usually noted in hospital-based study where people with severe disease report to hospital usually, while with mild disease report lesser to hospital. Further sample size was less to find out association. Total 120 sample size in total is needed.

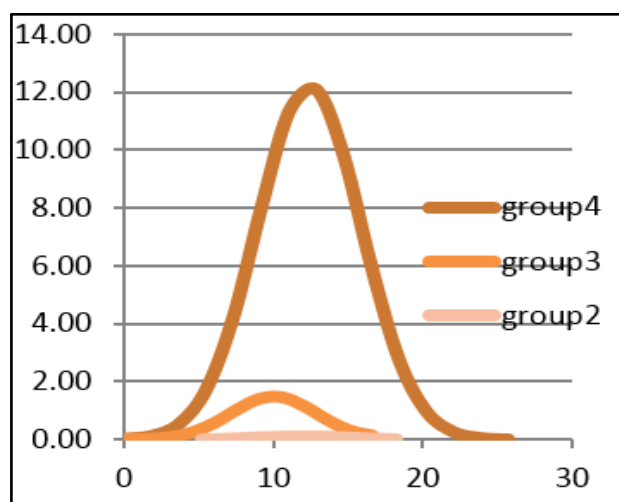


Figure 8. Bell Diagram to Represent the Normal Distribution of Serum Homocysteine Level in Various Groups Based on Severity of Migraine. X Axis Represents Serum Homocysteine Level in µmol/L

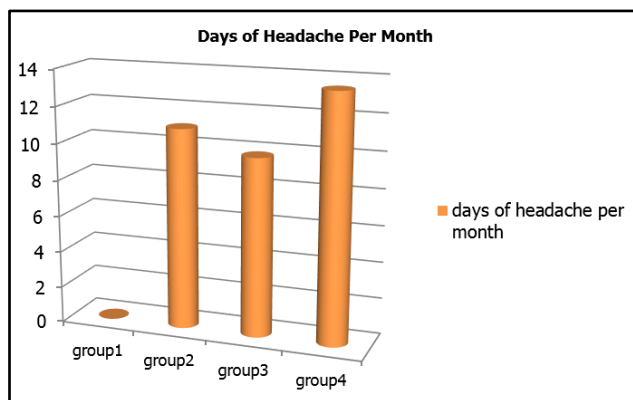


Figure 9. Clustered Columns to Show the Duration of Headache (in hours) per Episode and Number of Days with Headache per Month in Various Groups Based on Severity of Migraine

Median duration of headache was found to be 12-24 hours. Days of headache per month varied from 5-25 days with median duration per month being 11 days.

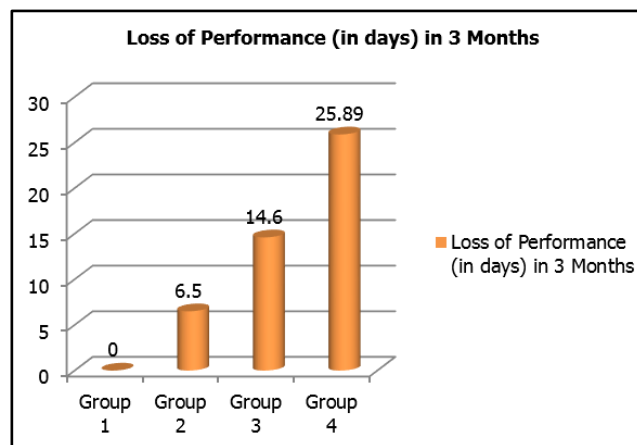


Figure 10. Bar Diagram to Illustrate the Loss of Performance (in days) in Various Groups Based on Severity of Migraine

Medial loss of performance secondary to migraine either at work place or at home accessed using MIDAS was 24 days in 3 months (range = 6-40 days).

Variable		Mean ± S.D.	t Statistic	Confidence Interval		P Value
				Lower Limit	Upper Limit	
Homocysteine level	Control	9.3 ± 2.65	-1.92	-3.11	0.058	0.059
	Migraine	10.8 ± 3.4				

Table 3. Representing Mean Serum Homocysteine Level in Control and Migraine Patients

Homocysteine levels were found to be higher among patients with migraine as compared to normal population. However, this population was not found to be statistically significant (p = 0.059).

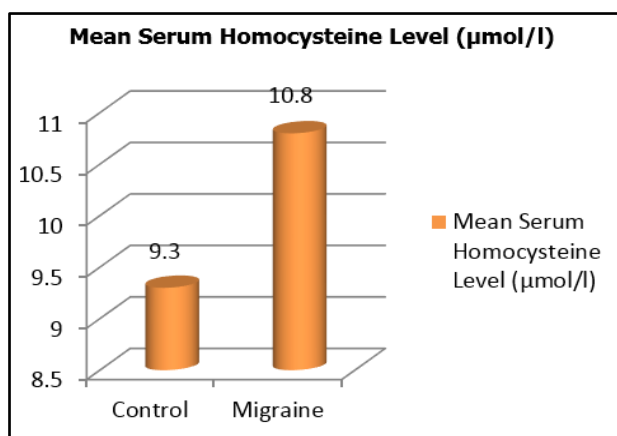


Figure 11. Bar Charts Showing Mean Serum Homocysteine Level in Control and Migraine Patient

DISCUSSION

The literature was thoroughly searched for the related research works. In our study, the total number of patients with migraine was 30 with median age being 26.9 years (range 14-47 years). The mean age in male and female patients was found to be 25.1 ± 6.9 years and 30.9 ± 9.7 years, respectively. A similar study showed the average age of migraine patient was 27.69 ± 9.50 (15-55) years. Another study observed the mean age to be 34.01 ± 0.9 years. The mean age in male and female patient was found to be 33.8 ± 2.0 years and 34.2 ± 1.05 years, respectively.

Out of 30 migraine patients included in our study the ratio of male:female was nearly 1:3. The results of a cross-sectional study performed in Isfahan City, Iran, in 2013 had similar ratio, while case control study performed had 38.5% male and 61.5% female. This suggests that the ratio of male:female is comparable in all the studies, which we have encountered.

Significant history of migraine was present in one or more family members in 11 (36.7%) patients in migraine group as compared to 19 (63.3%) who did not have any such history. This is much less than seen in study conducted in Iran, which had family history of migraine in as much as 61%. The reason for this discrepancy maybe due to small number of patients included in our study.

In our study, the patients with migraine were divided in four groups on the basis of severity of migraine using MIDAS questionnaire. They were evaluated for number of episodes occurring in preceding 3 months, mean duration of each episode (in hours) and average number of days with headache. Our study revealed that group 1 with minimal disability had 0 participants, group 2 had 2 participants, group 3 had 9 participants and group 4 had 19 participants.

Each group was assessed separately for above-mentioned parameters, which revealed that median duration of an episode of headache was 12-24 hours and the average number of days with headache was 11 (5-25) days. In comparison to alike research work done at Iran,²¹ which revealed average duration of migraine attack was 17.0 ± 1.1 hours and the frequency per month were 9.8 ± 0.5 days. These figures are quite similar to the result of our endeavour.

Our study revealed the prevalence of hyperhomocysteinemia in patients of migraine to be 13.3%,

i.e. 4 out of 30 had raised serum homocysteine level. Study performed in 2013²⁴ noted the prevalence of hyperhomocysteinemia to be 29.16%. Another study had suggested the presence of significantly high serum homocysteine level in patients suffering from migraine as compared to normal people.

The present study has revealed mean serum homocysteine level in 30 migraine patients to be 10.8 ± 3.4 $\mu\text{mol/L}$. In 22 female and 8 male migraine patients, the mean serum homocysteine level was calculated as 11.17 and 9.8 $\mu\text{mol/L}$, respectively. A study performed in 2014 found that mean serum homocysteine levels in migraine patients were 8.6 ± 0.25 $\mu\text{mol/L}$ and 27 patients (2 males and 25 females) had hyperhomocysteinemia.

Another similar study calculated the mean level of serum homocysteine in migraine group was 14.49 ± 5.03 $\mu\text{mol/L}$. According to this, the mean level of homocysteine level is significantly higher in male migraine patient, than female counterparts ($p=0.01$). In our endeavour, mean serum homocysteine level was calculated in all 4 groups divided on the basis of severity of migraine and there was no significant association between the severity of migraine and serum homocysteine level. Similar results were observed in studies done at Iran. Significant relationship between serum levels of homocysteine and characteristics of migraine attacks such as severity, frequency and duration were not found.

Another determinant, which we tried to quantify in our study was loss of performance either at workplace or at home due to migraine. Our study revealed that almost 8 days of daily activities in a month are severely hampered due to attacks of migraine. We are yet to come across any studies, which have quantified the performance loss due to migraine to the horizon of our knowledge.

SUMMARY

The present study was undertaken to find out the prevalence and correlates of hyperhomocysteinemia in patients with migraine and also to find the demographical characteristics in migraine patients. To start, it was hypothesised that hyperhomocysteinemia is commoner in migraine patients as compared to normal population. Ours was a descriptive, observational, cross-sectional study in the natural history of disease of migraine with additional diagnostic tool as surrogate marker.

A total of 30 migraine patients participated in the present study including 22 females and 8 males. The study was directed towards the aim of finding out the prevalence of hyperhomocysteinemia in migraine patients, which came out to be 13.3% and other aim is to show association if any between homocysteine level and severity of migraine in which we found no direct relationship between serum homocysteine level and severity of migraine. Other objective includes comparison of homocysteine level between normal population and cases of migraine, which in case group was found to be 10.8 ± 3.4 $\mu\text{mol/L}$ as compared to 9.3 ± 2.65 $\mu\text{mol/L}$ in control group, which was not statistically significant.

Majority of the study subjects (migraine patients) were in the age group of 25-36. Among them, 73.3% were female and remaining 26.7% were male. 63.3% patient presented with family history of migraine and remaining 36.7% were having no family history of migraine. 40% patients were found to have normal weight and remaining 33.3%, 26.7% fell into the category of underweight and overweight respectively and none of the patient was obese.

Medial loss of performance secondary to migraine reported by patients either at workplace or at home was 24 days in 3 months duration (range=6-40 days). Other secondary objective was to find median duration, which revealed out to be 12-24 hours and days of headache per months varied from 5-25 days.

Certain aspects of causation of migraine related to homocysteine were not clear, which may require further studies in future.

CONCLUSION

Prevalence of hyperhomocysteinemia in migraine was found to be 13.3% and there was no significant relation found between serum homocysteine levels and severity of migraine. Mean serum homocysteine level was found to be higher in migraine patient as compared to control, but the association did not come out to be statistically significant.

Patient reported considerable amount of loss of performance secondary to migraine, which emphasise on the need for undertaking studies, which could further investigate the causal association between homocysteine and migraine.

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