

# Estimation of Serum Homocysteine Levels in Migraineurs With and Without Aura – A Cross-sectional Study

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## Abstract

**Introduction:** Migraine is a primary and chronic-intermittent headache disorder that affects approximately 15% of women and 6% of men. Homocysteine is a sulfur containing amino acid which is associated with vascular damage and increased risk of cardiovascular diseases and stroke. Migraineurs with aura are known to be at increased risk of cardiovascular diseases and stroke as stated by several studies. This study was undertaken to see whether the homocysteine levels were increased in Migraineurs.

**Aim:** The aim of the study was to compare and correlate the levels of serum homocysteine in migraineurs with and without aura with those of controls.

**Methodology:** This was a cross-sectional and observational study done at Kamineni institute of medical sciences, Sreepuram, Nalgonda district, Telangana, from October 2010 to September 2013. The subjects were categorized into three groups: GROUP-I (Migraineur with Aura), GROUP-II (Migraineurs without Aura), GROUP-III: Controls, with 30 subjects in each group. Patients in the age group between 20 and 60 years of both sexes were included and patients on treatment for migraine, hypertension, and chronic kidney diseases were excluded from the study. Serum homocysteine levels were estimated by ELISA method on fasting blood samples. Statistical analysis was performed using SPSS software.

**Results:** The male to female ratio in Group-I was 1: 3.34 and in Group-II was 1:4. It was observed that maximum cases of Group-I fall in the age group of 31–40 years of age, and of Group-II in the age group of 20–30 years. The serum homocysteine levels in migraine with and without aura were significantly increased when compared with controls. Migraineurs with aura had high levels of serum homocysteine ( $30.87 \pm 7.48 \mu\text{mol/L}$ ) when compared with Migraineurs without aura ( $12.82 \pm 2.56 \mu\text{mol/L}$ ) and controls ( $9.57 \pm 2.13 \mu\text{mol/L}$ ).

**Conclusion:** As hyperhomocysteinemia is an independent risk factor for cardiovascular diseases and stroke, serum homocysteine levels must be estimated in patients diagnosed with Migraine headache.

**Key words:** Cardiovascular disease, Homocysteine, Migraine

## INTRODUCTION

Migraine is a primary and chronic-intermittent headache disorder that affects a large proportion of the population, predominantly middle-aged women.<sup>[2]</sup> It affects approximately 15% of women and 6% of men.<sup>[1]</sup>

Clinical diagnosis of migraine is based on International Classification of Headache Disorders-II criteria specified by the International Headache Society, which classifies migraine into two major groups; without aura (MWOA) and with aura (MWA).<sup>[3]</sup>

Homocysteine (Hcy) is a sulfur-containing amino acid. Circulating levels of homocysteine are usually low due to its rapid metabolism through one of two pathways:

- (1) a cobalamine (vitamin B12) and folate dependent remethylation pathway that regenerates methionine, or
- (2) a pyridoxal 5' phosphate (PLP, vitamin B6) dependent

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trans sulfuration pathway that converts homocysteine into cysteine.

The occurrence of hyperhomocysteinemia indicates that homocysteine metabolism has in some way been disrupted and that the export mechanism is disposing into the blood excess homocysteine that has accumulated in the cell. This prevents toxicity to the cell but leaves vascular tissue exposed to the possibly deleterious effects of excess homocysteine.<sup>[4-6]</sup>

In 1995 Boushey *et al.* performed a meta-analysis of 27 studies correlating homocysteine to vascular disease. They concluded that a 1 µmol/L increase in Hcy concentrations was associated with a 10% increase in CHD risk.

Studies done in European countries have shown that homocysteine levels are altered in migraineurs. Prospective studies have linked migraine with increased incidence of stroke and cardiovascular diseases.<sup>[7,8]</sup> Hyperhomocysteinemia in Migraineurs with aura was associated with mutations in MTHFR gene.<sup>[9]</sup> The present study was undertaken to estimate the serum homocysteine levels in migraineurs and in controls.

**Aim**

The aim of the study was to compare and correlate the levels of serum homocysteine in migraineurs with and without aura with those of controls.

**Objectives**

The objectives of the study are as follows:

- To estimate serum homocysteine levels in cases and controls
- To compare and correlate the serum homocysteine levels in migraineurs with aura and without aura.

**METHODOLOGY**

This study was done at Kamineni Institute of Medical Sciences, Sreepuram, Nalgonda district, Telangana with approval of Institutional Ethics Committee.

A total of 60 cases, clinically diagnosed of migraine headache, reporting the general medicine department in Kamineni Hospital, Sreepuram, during the period from October 2010 to September 2013, were selected.

**Type of Study**

This was a cross-sectional study.

**Inclusion Criteria**

- Age group between 20 and 60 years of both sexes was included in the study.

**Exclusion Criteria**

The following criteria were excluded from the study:

- Patients who are already on treatment for migraine.
- Patients with disorders which can increase Homocysteine levels such as CAD, chronic kidney diseases, pre-eclampsia, and hypertension.
- In the present study, serum homocysteine levels were estimated in 60 migraine patients and 30 controls.

**The Subjects were Categorized into 3 Groups**

GROUP-I: Migraineurs with Aura: This group included 30 patients.

GROUP-II: Migraineurs without Aura: This group included 30 patients. People in case group were selected according to migraine diagnosis on the basis of ICDH-H standards and being not affected with heart and renal or any other serum homocysteine level effecting diseases.

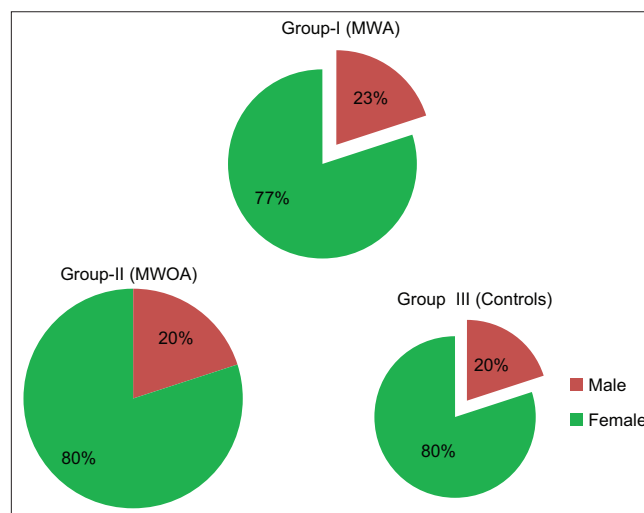
GROUP-III: Controls: Thirty age- and sex-matched apparently healthy individuals reporting for health checkup.

**Sample Collection**

Patients were advised to avoid Protein rich meals late in the day before sampling. After about 8–10 h fasting, 5 ml of venous blood was drawn from the migraine patients and matched controls. The sample was centrifuged at 3000 rpm

**Table 1: Division of total study population into different study groups**

Category	No. of patients
Group-I: Migraine with aura	30
Group-II: Migraine without aura	30
Group-III: Controls	30
Total	90



**Chart 1: Sex-wise distribution of patients in study groups**

for 10 min and serum was separated and stored in deep freezer at  $-20^{\circ}\text{C}$  until processed.

Serum homocysteine was estimated by ELISA Kit method using standard curve.

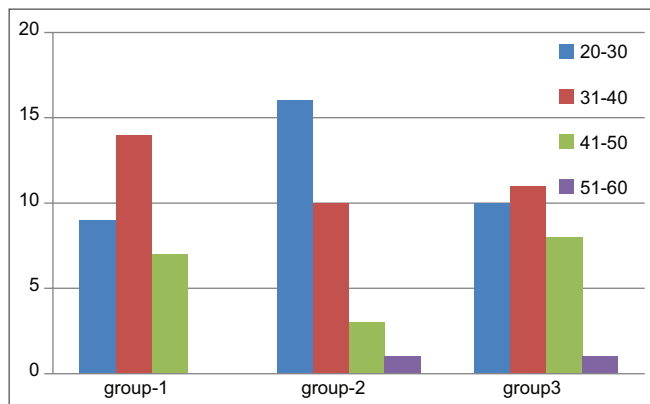


Chart 2: Age distribution among study groups

Table 2: Age distribution among study group

AGE (years)	Group-I (n=30)	Group-II (n=30)	Group-III (n=30)
20–30	9 (30%)	16 (53.3%)	10 (33.33%)
31–40	14 (46.66%)	10 (33.33%)	11 (36.66%)
41–50	7 (23.33%)	3 (10%)	8 (3.33%)
51–60	-	1 (3.33%)	1 (3.33%)
TOTAL (N)	30	30	30
MEAN±SD	35.53±6.78	32.23±7.83	35.4±8.71

Table 3A: Mean±S.D of serum homocysteine (5–15  $\mu\text{mol/L}$ ) in different groups

Group	Mean±S. D
Group-I (MWA) n=30	30.87±7.48
Group-II (MWOA) n=30	12.82±2.56
Group-III (Controls) n=30	9.57±2.13

Table 3B: Analysis of variance (Anova) for serum homocysteine levels levels ( $\mu\text{mol/L}$ ) in all the three groups

Source	df	Sum of squares	Mean square	F	significance
Between Groups	2	7887.25	3943.62	171.86	0.000
Within Groups	87	1996.36	22.95		
Total	89	9883.61			

Table 3C: Multiple comparisons of serum homocysteine levels by *post hoc* test in all the three groups

Dependent variable	(I) group	(J) group	Mean difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
						Upper bound	Lower bound
Serum Hcy	Group-I	Group-II	18.11*	1.24	0.000	20.56	15.64
		Group-III	21.24*	1.24	0.000	23.70	18.78
	Group-II	Group-I	-18.11*	1.24	0.000	-15.64	-20.56
		Group-III	3.14*	1.24	0.013	5.60	0.68
	Group-III	Group-I	-21.24*	1.24	0.000	-18.78	-23.70
		Group-II	-3.14*	1.24	0.013	-0.68	-5.60

### Statistical Analysis

The statistical analysis was performed using SPSS software version 11.0. The descriptive results were expressed as mean and standard deviation. Significance of difference between and within groups was assessed by applying *post hoc* test and ANOVA study. The *P*-values were expressed along with mean values and standard deviation.  $P < 0.05$  was considered statistically significant and values  $<0.001$  were considered highly significant.

### RESULTS

Group I, II, and III included 30 cases of Migraineurs with Aura, Migraineurs without Aura, and apparently healthy individuals, respectively [Table 1].

In the present study, the male to female ratio in Group-I is 1:3.34 and in Group-II is 1:4 [Chart 1].

It is observed that maximum cases of group-I fall in the age group of 31–40 years of age, and maximum cases of group-II fall in the age group of 20–30 years [Chart 2].

The average age of patients in Group-I was  $35.53 \pm 6.78$  years and in Group-II was  $32.23 \pm 7.83$  years and that of Group- III was  $35.4 \pm 8.71$  years. According to this, there was no statistical significant difference between two groups [Table 2].

The serum homocysteine levels in migraine with and without aura are increased when compared with controls. Migraineurs with aura had high levels of serum homocysteine when compared with other two groups [Table 3A].

Serum homocysteine levels are significantly increased ( $P = 0.000$ ) when compared within the groups and between the groups [Table 3B].

The mean level of homocysteine in case groups was significantly more than control group ( $P < 0.001$ ) [Table 3C].

## DISCUSSION

Migraine is a primary chronic intermittent headache disorder characterized by pulsating unilateral severe pain attacks with associated autonomic and gastrointestinal symptoms. In some patients, transient neurologic symptoms mostly visual disturbances can occur that are known as “migraine aura.”

According to the present study, the incidence of migraine headache is more in females than in men. The ratio of female: male is 4:1. We found serum homocysteine levels to be significantly increased in MWA and MWOA. In addition, serum homocysteine levels were lower in MWOA than in MWA. Homocysteine might have a direct role to play in migraine causation, especially keeping in view the role of homocysteine in terms of vascular damage and migraine being regarded as a neurovascular disorder.

Several studies have shown association between plasma tHcy concentrations and CHD and Stroke.<sup>[10,11]</sup> They have reported elevated plasma tHcy as an independent risk factor for CHD and stroke.<sup>[12,13]</sup> These findings were supported by the results of a meta-analysis which indicated that total Hcy is a modest predictor of IHD and stroke risk in a healthy population independent of traditional cardiovascular risk factors.<sup>[15-17]</sup>

## CONCLUSION

As hyperhomocystenemia is an independent risk factor for cardiovascular diseases and stroke, serum homocysteine levels must be estimated in patients diagnosed with migraine headache. Migraineurs with aura must be kept under follow-up with supplementation of tetrahydrofolate and genetic analysis must be done to rule out MTHFR gene mutations<sup>[14]</sup> as they are at increased risk for stroke and cardiovascular episodes.

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