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# FREQUENCY OF RAISED PLASMA HOMOCYSTEINE LEVELS IN PATIENTS OF ISCHEMIC STROKE

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This descriptive study was conducted at Mayo Hospital, Lahore. A total number of 37 continuous patients with ischemic stroke were registered in one month. Imaging of the brain was done in each case. Both male and female patient of all age groups were included. Among these, 27 were males and 10 were females with the age range from 20 to 90 years. Nineteen patients (51.35%) had raised plasma homocysteine levels more than 15 $\mu$ mol/l. Among patients with raised homocysteine levels, 14(73.6%) were males and 5(26.3%) were females. Eighteen (48.64%) patient fell in to group between 41-60 years of age. Eleven patients were younger than 40 and 8 were more than 60 years of age at the time of presentation. Out of 19 patients with raised plasma homocysteine levels 5 (26.3%) were also smokers and others were either non smokers or had stopped smoking more than 5 years back from the time of presentation. Four out of 19 (21.04%) patients had no other known cause of their stroke except raised plasma homocysteine. These patients were all males and were 23, 42, 60 and 68 years old. From our study we conclude that in our population, plasma homocysteine levels are raised commonly in patients of ischemic strokes, and it has already been established, as risk factor for all vascular events. We recommend routine measurements of Homocysteine levels in all Ischemic stroke patients and administration of Folic acid and Vitamin B12 as secondary preventive therapy.

**Key Words:** Homocysteinemia, Stroke.

## INTRODUCTION

In 1969, McCully made the clinical observation linking elevated plasma homocysteine concentrations with vascular disease.<sup>1</sup> On the basis of this observation, he proposed that elevated plasma homocysteine (hyperhomocyst(e)inemia) can cause atherosclerotic vascular disease. Abundant epidemiologic evidence has demonstrated that the presence of mild hyperhomocysteinemia is an independent risk factor for atherosclerosis in the coronary, cerebral, and peripheral vasculature.<sup>2,3</sup>

Homocysteine is a sulfur-containing amino acid formed during the metabolism of methionine. Homocysteine is metabolized by one of two pathways: remethylation and transsulfuration. In the remethylation cycle, homocysteine is salvaged by the acquisition of a methyl group in a reaction catalyzed by methionine synthase. Vitamin B<sup>12</sup> (cobalamin) is an essential cofactor for methionine synthase, N<sup>5</sup>-methyl-tetrahydrofolate is the methyl donor in this reaction, and N<sup>5</sup>,N<sup>10</sup>-methylene tetrahydrofolate reductase functions as a catalyst in the remethylation process. Under conditions in which an excess of methionine is present or cysteine synthesis is required, homocysteine enters the

transsulfuration pathway. In this pathway, homocysteine condenses with serine to form cystathionine in a reaction catalyzed by the vitamin B<sup>6</sup>-dependent enzyme cystathionine  $\beta$ synthase. Cystathionine is subsequently hydrolyzed to form cysteine, which may in turn be incorporated into glutathione or further metabolized to sulfate and excreted in the urine.<sup>4,5</sup>

The majority of the clinical studies involving homocysteine have relied on the measurement of total plasma homocysteine, which includes homocysteine, mixed disulfides involving homocysteine, homocysteine thiolactone, free homocysteine, and protein-bound homocysteine. Normal total plasma homocysteine concentrations range from 5 to 15  $\mu$ mol per liter in the fasting state<sup>(6)</sup>. Kang and coworkers have classified hyperhomocysteinemia as moderate homocysteine concentration, 15 to 30  $\mu$ mol per liter), intermediate (>30 to 100  $\mu$ mol per liter), and severe (>100  $\mu$ mol per liter) on the basis of concentrations measured during fasting.<sup>2</sup>

Nutritional deficiencies in the vitamin cofactors (folate, vitamin B12, and vitamin B6) required for homocysteine metabolism may promote hyperhomocysteinemia. Selhub and colleagues have suggested that inadequate

plasma concentrations of one or more B vitamins are contributing factors in approximately two thirds of all cases of hyperhomocysteinemia.<sup>7</sup>

A number of other factors influence homocysteine metabolism, including several disease states and medications. Plasma homocysteine concentrations increase with elevations in creatinine and are typically elevated in chronic renal failure.<sup>8</sup> A number of reports have linked hyperhomocysteinemia to hypothyroidism<sup>9</sup>, pernicious anemia<sup>10</sup>, and several types of carcinoma, including breast, ovarian, and pancreatic cancer<sup>11</sup>. In addition, acute lymphoblastic leukemia is associated with marked elevations in plasma homocysteine; after chemotherapy for this disorder, homocysteine concentrations decrease dramatically<sup>12</sup>.

Several drugs including Methotrexate, Phenytoin<sup>13</sup>, Theophylline<sup>14</sup> increase homocysteine levels. Cigarette smoking also interferes with the synthesis of pyridoxal phosphate, and it has recently been reported that smokers have significantly lower pyridoxal phosphate concentrations than nonsmokers. These results suggest another important mechanism whereby smoking may promote atherogenesis<sup>15, 16</sup>.

Abundant evidence has demonstrated relationship between atherosclerosis and raised homocysteine levels in different case control studies<sup>9, 17, 18, 19, 23</sup>. Nygård and colleagues reported that relation between homocysteine and mortality was strongest for total homocysteine concentrations above 15  $\mu\text{mol}$  per liter<sup>21</sup>. We conducted a study to demonstrate frequency of raised homocysteine level in local patients of ischemic stroke and compare it with international data.

## STUDY DESIGN AND METHODS

This prospective observational study was conducted in Neurology Department Mayo Hospital, Lahore. Thirty seven consecutive patients of ischemic cerebral stroke were included in the study over one month.

### Inclusion Criteria:

Patients of all ages and both sexes were included in study with CT scan evidence of ischemic stroke.

### Exclusion Criterion:

Patients of hemorrhagic stroke were excluded from the study.

## RESULTS

A total of thirty seven consecutive patients of CT

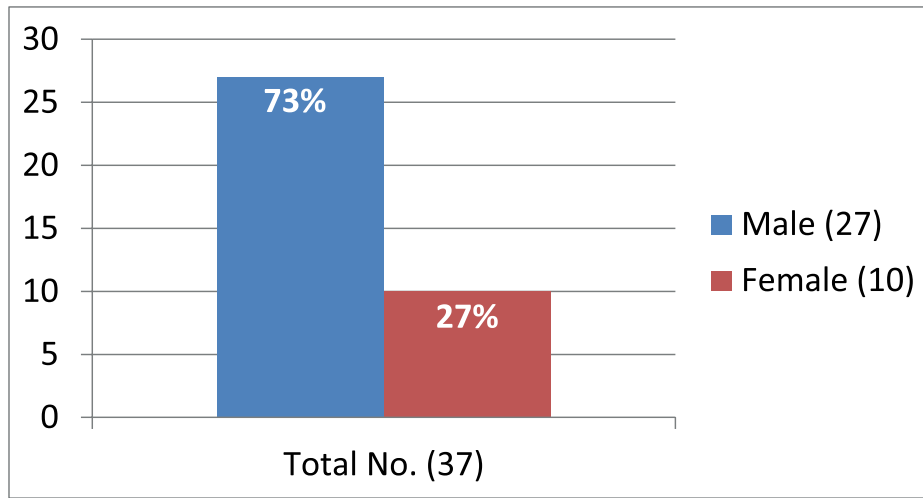
documented ischemic stroke were included in the study. Twenty seven (73%) patients were male and ten (27%) were female. The age ranged from twenty to ninety years. Nineteen among total of thirty seven patients (51.35%) had raised homocysteine levels (more than 15  $\mu\text{mol/lit.}$ ). Among these nineteen patients fourteen (73.6%) were male and five (26.3%) were female. Among total twenty seven males fourteen (51.35%) and among total ten females five (50 %) had raised homocysteine levels. Four patients (21%) out of 19 had Homocysteine between 30-100 others between 15-29  $\mu\text{mol/Lit.}$  In all 37 patients five males (13.51%) had history of smoking which came out to be 26.3% among total male patients. No female had history of smoking. Four patients among all nineteen patients with raised homocysteine levels had Homocysteine as lone factor while other fifteen had additional risk factors also (including Hypertension, Diabetese Mellitus, Hyperlipidemia and previous stroke). Maximum patients with raised Homocysteine and stroke belonged to age group of more than forty (14/19). However, patients with Homocysteine as single risk factor (4/19, 21%) were distributed in all age groups and they were 23, 42, 60 and 68 years old at the time of presentation. Other risk factors for stroke were also noted.

## DISCUSSION

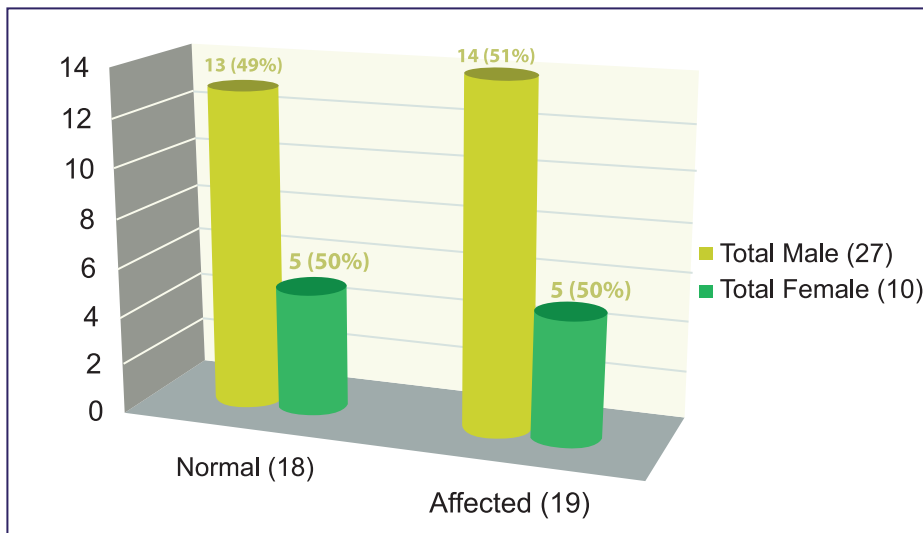
We studied thirty seven patients of acute ischemic stroke in one month. Demographic data was entered. Ischemic origin of the stroke was confirmed on imaging of the brain (CT scan or MRI) and each patient was evaluated for Homocysteine levels and other common risk factors at presentation.

Out of total thirty seven patients twenty seven were males and ten were female. Nineteen patients (51.35%) in our study had raised plasma Homocysteine levels, which is higher than reported by Clarke and Colleagues who showed raised Homocysteine levels in 28% patients of peripheral vascular disease, 30% of coronary artery disease and 42% patients of cerebrovascular disease<sup>22</sup>. Ling Hao and colleagues reported a higher Levels of Homocysteine in men than women (16.1vs 10.6  $\mu\text{mol/lit}$  in the north and 10.7 vs 7.9  $\mu\text{mol/lit}$  in the south<sup>23</sup>. However in our study the mean plasma Homocysteine level in Male vs female was 17.38 vs 17.22  $\mu\text{mol/lit}$  respectively with no significant difference. Taking the individual population of male and females patients, 51.35% (14/27) males and 50 % (5/10) had raised Homocysteine levels showing that association of raised Homocysteine levels and stroke is not gender based. The same is shown in a study by Chery D et, al<sup>24</sup>.

**Fig.1** Gender Distribution of the Sample



**Fig.2** Frequency of male and female stroke patients with normal and raised Homocysteine



**Fig.3** Frequency of raised and normal Homocysteine in smokers and non-smokers

