SERUM HOMOCYSTEINE AS A RISK FACTOR FOR STROKE: A PROSPECTIVE STUDY FROM A RURAL TERTIARY CARE CENTRE

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ABSTRACT

Objective: Stroke is one of the leading causes of mortality and long-term disability in both developed and developing countries. Serum homocysteine level is one of the emerging modifiable risk factors for atherosclerosis which may result into a cerebrovascular accident. This study was designed to study the association of Serum Homocysteine level with the development of acute stroke at a rural tertiary care centre in North India.

Methods: The present study was a prospective cross-sectional study conducted in the Department of Medicine, Maharishi Markandeshwar Institute of Medical Sciences and Research, Mullana, Ambala. The study population included 100 patients presenting with Stroke (either ischemic or hemorrhagic) in the indoor and outdoor facilities in the Department of Medicine. 50 age and sex-matched healthy individuals were taken as controls. Serum total Homocysteine level was measured in all the cases and controls.

Results: Majority of the patients suffered from ischemic stroke (78%), while only 22% patients had hemorrhagic stroke. The mean Serum Homocysteine level in stroke patients (19.68±8.78 µmol/l) was significantly higher than in controls (10.48±4.39 µmol/l) (p<0.01). In a subgroup analysis, stroke patients with a positive history of smoking had significantly higher homocysteine level as compared to non-smokers (p<0.05).

Conclusion: Increased level of Serum Homocysteine is significantly associated with risk of cerebrovascular accident, which is independent of the risk attributed to traditional risk factors.

Keywords: Homocysteine, Stroke, Ischemic, Hemorrhagic, Risk factors.

INTRODUCTION

Vascular disease of the brain remains a very important cause of neurologic morbidity and mortality. Stroke is a cerebrovascular disorder resulting in the rapidly developing loss of brain functions. This can be due to ischemia or hemorrhage. Stroke is one of the leading causes of mortality and long-term disability in both developed and developing countries. There are various non-modifiable and modifiable risk factors for stroke [1]. Plasma homocysteine concentration is one of the emerging modifiable risk factors for atherosclerosis which may manifest as a cerebrovascular accident [2,3].

Homocysteine is a sulfhydryl amino acid that is readily oxidized to homocysteine and homocysteine-cysteine mixed disulfide in the plasma. Mechanisms by which hyperhomocysteinemia increases risk of cerebrovascular accidents are not clear, but several possible mechanisms have been proposed [4]. Hyperhomocysteinemia is associated with premature atherosclerosis. Experimental studies both in vivo and in vitro show that homocysteine causes endothelial injury and cell detachment. Endothelial cell injury, platelet activation, deleterious effect on thrombomodulin expression, protein C activation, and an increased oxidizability of low-density lipoprotein have been described as a few possible mechanisms by which homocysteine provokes arteriosclerosis and thrombosis [5,6]. Animal studies have also shown that raised Homocysteine levels may induce marked remodeling of the extracellular matrix in the arterial wall [7]. An ideal homocysteine level is <9 µmol/L. Hyperhomocysteinaemia is the term used for elevated levels of homocysteine in plasma, i.e., >15 µmol/L.

India, with more than 1 billion inhabitants, is undergoing remarkable economic and demographic changes in recent years. This has resulted in a rapid increase in lifestyle related noncommunicable disorders including cardiovascular and cerebrovascular diseases. Given the anticipated increase in the burden of stroke in coming years and limited availability of organized stroke care services to the majority of people in India, it is important to place greater emphasis on population-based stroke prevention strategies. The present study is, therefore, undertaken to look for the association between Serum Homocysteine and cerebrovascular accidents.

METHODS

The present study was a prospective cross-sectional study conducted in the Department of Medicine, Maharishi Markandeshwar Institute of Medical Sciences and Research, Mullana, Ambala. The study population included 100 patients presenting with Stroke (either ischemic or hemorrhagic) in the indoor and outdoor facilities in the Department of Medicine. 50 age and sex-matched healthy individuals were taken as controls. The study was done in 2012–2013 after approval from the Ethical Committee of the institute. The total duration of the study was 1 year.

Inclusion criteria

The following criteria were included in this study:
1. Patient diagnosed with stroke
2. Age >18 years.

Stroke was defined as rapidly developing signs of a focal or global neurological deficit with no apparent cause other than vascular, documented by computed tomography (CT) or magnetic resonance imaging done within 24 h of admission.
The statistical analysis was carried out using SPSS version 13-computer software. The data for continuous variables were expressed as Mean±SD, and categorical data were expressed as frequencies and percentages. p<0.05 was considered significant.

RESULTS AND OBSERVATIONS
A total of 100 cases of Stroke and 50 controls were evaluated in this study. The baseline demographic and clinical characteristics of cases and controls are shown in Table 1. There was no statistically significant difference in the two groups with regard to age and sex. The mean age in stroke patients and controls was 59.02 years and 56.44 years, respectively (p>0.05). Maximum number of cases of stroke were in the age group of 61–70 years (36%) followed by 51–60 years age group (23%). Majority of stroke patients were males (68%). Body mass index (BMI), systolic blood pressure, and diastolic blood pressure were significantly higher in stroke patients as compared to controls (p<0.05). Majority of the patients suffered from ischemic stroke (78%), while only 22% patients had a hemorrhagic stroke.

Table 2 shows the comparison of serum homocysteine level between cases and controls. The mean serum homocysteine level in stroke patients (19.88±8.78 µmol/l) was significantly higher than in controls (10.48±4.39 µmol/l) (p<0.01). Serum Homocysteine level was significantly higher in stroke patients with a history of smoking as compared to non-smokers (p<0.05). No significant difference was seen in Serum Homocysteine levels with a history of smoking as compared to non-smokers. Serum Homocysteine level was significantly higher in stroke patients as compared to controls (p<0.05). Majority of the patients had a hemorrhagic stroke.

Table 3 shows the Serum Homocysteine level in stroke patients subgrouped according to the presence of established risk factors of stroke. Serum Homocysteine level was significantly higher in stroke patients with a history of smoking as compared to non-smokers (p<0.05). No significant difference was seen in Serum Homocysteine levels with relation to other risk factors (HT, DM, BMI, and family history).

The comparison of Serum Homocysteine level in patients with ischemic and Hemorrhagic Stroke is shown in Table 4. Mean homocysteine levels in ischemic and hemorrhagic stroke were 20.27 and 19.76 µmol/l, respectively, which was statistically non-significant (p>0.05).

DISCUSSION
Stroke is a major health problem worldwide and is one of the leading causes of mortality and long-term disability. Ischemic stroke accounts for more than 80% patients of stroke worldwide [8]. In the present study, 78 patients had ischemic stroke while only 22 patients presented with Hemorrhagic Stroke. Primary and secondary prevention by managing the various modifiable risk factors for stroke is the key to reducing the incidence of stroke and its impact on health-care resources [9]. Hyperhomo-cysteinemia is one of the recently recognized modifiable factors that increase the risk of cardiovascular and cerebrovascular disease [4].
In the present study, we evaluated the association of Serum total homocysteine level with Stroke. Hyperhomocysteinemia is defined as serum homocysteine level >15 µmol/l. In our study, the proportion of stroke patients with hyperhomocysteinemia (44%) was significantly higher than that seen in controls (8%). The mean fasting Serum homocysteine level in stroke patients (19.98±8.78 µmol/l) was significantly higher than the controls (12.30 µmol/l) (p<0.01). Furthermore, on subgroup analysis based on gender, significantly higher homocysteine levels were seen in male stroke patients as compared to controls (10.48±4.39 µmol/l) (p<0.05). On comparing the two subtypes of stroke, it was found that mean serum homocysteine level in ischemic stroke patients (20.47±9.74) was higher than that of hemorrhagic stroke patients (17.36±7.44), although this difference was not found to be statistically significant (p>0.05). Although the role of homocysteine in ischemic stroke has been established by many studies in the past, its role in Hemorrhagic Stroke is still uncertain. In a meta-analysis done to evaluate the association between elevated plasma homocysteine levels and the risk of different types of strokes, He et al. showed that although elevated homocysteine levels are associated with an increased risk for ischemic strokes and recurrent strokes they showed no distinct association with hemorrhagic strokes [15]. On the contrary, in a recent systematic review and meta-analysis, Zhou et al. showed that high homocysteine level may act by aggravating the process of atherosclerosis, which is positively associated with a high risk of intracranial hemorrhage [16].

**CONCLUSION**

Increased level of serum homocysteine is significantly associated with risk of cerebrovascular accident, which is independent of the risk attributed to traditional risk factors.

**AUTHORS' CONTRIBUTIONS**

All the authors have contributed equally in design, data collection, manuscript preparation, and editing for this article.

**CONFLICTS OF INTEREST**

The authors declare that they have no conflicts of interest.

**REFERENCES**


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**Table 3: Comparison in serum homocysteine levels in the patient group (n=100) with or without different stroke risk factors**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Number of patients &quot;n&quot;</th>
<th>Serum homocysteine level (in µmol/l)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (&lt;60 years)</td>
<td>41</td>
<td>19.23±8.25</td>
<td>0.383</td>
</tr>
<tr>
<td></td>
<td>59</td>
<td>20.80±9.53</td>
<td></td>
</tr>
<tr>
<td>HT Present</td>
<td>48</td>
<td>20.17±9.24</td>
<td>0.730</td>
</tr>
<tr>
<td>Absent</td>
<td>52</td>
<td>19.56±8.36</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>29</td>
<td>19.27±8.58</td>
<td>0.476</td>
</tr>
<tr>
<td>Absent</td>
<td>71</td>
<td>20.64±8.76</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>26</td>
<td>23.23±9.91</td>
<td>0.023*</td>
</tr>
<tr>
<td>Absent</td>
<td>74</td>
<td>18.71±8.11</td>
<td></td>
</tr>
<tr>
<td>BMI &lt;25 kg/m²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family history of stroke</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>8</td>
<td>19.75±8.68</td>
<td>0.968</td>
</tr>
<tr>
<td>Absent</td>
<td>92</td>
<td>19.62±8.94</td>
<td></td>
</tr>
</tbody>
</table>

(*p=0.05-significant, *p=0.01 highly significant). HT: Hypertension, BMI: Body mass index

**Table 4: Comparison of serum homocysteine level between patients of ischemic and hemorrhagic stroke**

<table>
<thead>
<tr>
<th>Type of stroke</th>
<th>Number of patients &quot;n&quot;</th>
<th>Serum homocysteine level (in µmol/l) (Mean±SD)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic stroke</td>
<td>78</td>
<td>20.47±9.74</td>
<td>0.235</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>22</td>
<td>17.36±7.44</td>
<td></td>
</tr>
</tbody>
</table>

(*p=0.05-significant, *p=0.01 highly significant)


