Homocysteine: A Biomarker in Neurodegenerative Diseases.

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ABSTRACT

Homocysteine (Hcy) levels are high in Indians compared to westerners. Hyperhomocysteinemia (HHcy) is an independent, strong, graded and easily measurable earliest risk factor for stroke, MI and other vascular diseases. It can be due to either vitamin deficiency or genetic defect. Majority of Indians, being vegetarians, have low levels of Vitamin B12, Vitamin B6 and folic acid that are required for methionine metabolism. Epidemiological studies show positive dose dependent relationship between mild to moderate increase in plasma Hcy and the risk for neurodegenerative diseases. Hcy is a surrogate marker for vitamin deficiency and is a neurotoxic agent. Hyperhomocysteinemia is common in elderly people. The results of the present study showed elevated Hcy in patients with neurologic disorder. The elevation of Hcy is statistically significant in male and female patients. The Hcy levels are higher in male patients with neurological disorders. Availability of vitamins fortified food especially cereals will help to lower or delay the onset of age related neurological disorders in hyperhomocysteinemic high risk subjects.

Introduction

Over the past ten years there has been an explosion of interest in homocysteine. Hcy is an important risk factor for vascular diseases including psychosis, anoxia, Alzheimer’s (AD), Parkinsonism etc [1].

Very high Hcy concentration in patients leads to high incidence of atherosclerotic events [2]. Numerous observations have also reported an association between mild to moderately elevated Hcy levels and vascular risk in both the general population and in those with preexisting vascular diseases. The cardiovascular burden of Native Asian Indians is epidemic and the phenotype is rapidly evolving though natural history studies is few and rare [3].

Small vessel disease is associated with hyperhomocysteinemia. Rise of 1 mg of Hcy is associated with silent brain infarcts (SBI) and has a dramatic risk [4]. It is observed that Hcy is linked to SBI which is a risk factor for dementia. In a study in Japan it is pointed out that AD is associated with SBI. The level of Hcy is higher in these patients [5].

Besides stroke and dementia, HHcy causes abnormal movements and dystonia. A recent study has reported that high Hcy is associated with an increased risk of L-DOPA Dyskinesia in Parkinson’s disease [6]. In the current JAPI work done by two groups from western Indians reported an inverse correlation between vitamin B12 and Hcy.

A large number of women from MATTREY’S study have HHcy and are deficient in Vitamin B12. A significant negative correlation between Vitamin B12 and plasma Hcy levels is found in older women [7]. The CRESIS Cohort study of Yaynik’s group showed that low B12 concentration and high levels of Hcy are common in Indian men particularly vegetarians and urban middle class residents [7]. The above two studies attempt to reform the Hcy debate predominating in vegetarians.

Hcy has been shown to be associated with a number of neurological conditions like stroke, SBI, dementia, movement disorders, AD etc. The Ruby Hall study is the largest Indian study in stroke.

Several other neurologists in Pune, Madurai, Guwahati and Hyderabad have reported similar finding. In a study conducted at Guwahati, hyperhomocysteinemia is reported in 59.1 % of 110 ischemic stroke cases [8]. Likewise hyperhomocysteinemia is reported in 85% of the 58 patients of ischemic stroke studied in Lucknow [9].

MATERIALS

The study consists of 100 cases, 50 controls and 50 patients. The patient groups have equal numbers of male and female patients. All the patients are those attending OP/IP and diagnosed by expert neurologists at SK Hospital.

METHODS

Hcy is measured by the chemiluminescence microparticle immunoassay using ARCHITECT i1000SR of ABBOTT.
RESULTS.

Table 1 depicts the levels of Hcy in controls and patients. The mean Hcy levels in male controls is 6.32±1.588 µm/L. In neurodegenerative patients the levels of Hcy is elevated (mean 17.77 ± 4.304 µm/L) and the increase is statistically highly significant. An identical observation in made in females having neurodegenerative changes. The level of Hcy in female controls is 4.69±1.277 µm/L which is elevated to 15.81±1.364 µm/L in female patients. The Hcy levels is higher in males than in females, in agreement with other reports [10].

HOMOCYSTEINE LEVELS IN CONTROLS AND PATIENTS WITH NEURODEGENERATIVE DISEASES

<table>
<thead>
<tr>
<th>Numbers</th>
<th>HOMOCYSTEINE µm/L</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control (n=50)</td>
<td>6.32±1.588</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Patients (n=50)</td>
<td>17.77±4.304</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control (n=50)</td>
<td>4.69±1.277</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Patients (n=50)</td>
<td>15.81±1.364</td>
<td></td>
</tr>
</tbody>
</table>

DISCUSSION

Hcy is established as a risk factor and a risk marker for neurodegenerative causes. Hcy is a surrogate marker for vitamin B deficiency and it appears to be able to predict the occurrence and progression of dementia. Hcy can be used as a valuable prognostic and predictive biomarker for neurodegenerative processes. Hcy causes brain toxicity and may involve several complex pathways.

Hcy is toxic; several mechanism exist by which Hcy may damage the brain. Mild to moderate Hcy has been implicated in normal plasticity and neurodegenerative disorder in human studies [11].

Obecid and Herrmann in 2006 have reviewed the mechanisms by which Hcy causes brain damage [12]. Role of Hcy in causing hypermethylation [13], NO, system [14], oxidant stress [15] and the role of thiolotones in brain damage [16] have been established. In contrast to the western reports, Indian studies examining the prevalence of hyperhomocysteinemia in the community has reported an incidence of 52 to 84% [16]. Majority of the Indians being vegetarians, it is likely that these could be due to deficiency of B12 and folic acid. In a study involving 441 young men, 149 from rural areas, 142 from slums and 150 from urban middle class, overall 67% of the men had low B12 and 58% had hyperhomocysteinemia [17].

In the urban middle class 81% had low B12 and 79% high levels of Hcy [17]. Another important factor that predisposes Indians to homocysteinemia is a genetic defect in the enzymes cystathionine synthase and/or methylene tetrahydrofolate reductase [9,18].

Thus the dietary deficiency of Vitamin B12 and folic acid superimposed as a back ground of MTHFR deficiency seems to be responsible for the alarmingly high levels of homocysteinemia noticed in Indian population. In India the conditions are quite different from US and other countries where HOPE 2 study was conducted and reported that vitamin B12 supplementation lowered the Hcy levels.

Perhaps the most striking results of vitamin supplementation came from the studies of stroke epidemiology in US and Canada from 1990 to 2002. In the US, from 1990 to 1998, stroke mortality was falling steadily at 0.3% per year. After 1998, introduction of folic acid supplementation in cereals registered a fall in mortality to 2.9% per year [19]. Similarly, in Canada mortality rate from stroke fell to 5.4% per year after the vitamin supplementation [19].

In the present study the Hcy levels are found to be higher in males than in females even in healthy controls. The levels of Hcy in increased substantially in males with neurodegenerative diseases and the elevation is statistically significant (<0.0001) Females with neurodegenerative diseases are having high Hcy compared to corresponding controls. The difference is also statistically significant (Table 1).

Several studies point out that Indians are having higher levels of Hcy compared to westerners. This is alarming since this could mean high risk for dementia, psychosis, atoxia, neuropathy and even ischemic stroke. Hyperhomocysteinemia is independent of other risk factors like smoking, hypertension, diabetes mellitus and hyperlipidemia.

India is facing an epidemic of cardiovascular diseases. Indians have been reported to have the highest incidence of CAD [19]. The prevalence is about 80-120 per 1000 population. It also occurs more often affecting people below the age of 40 years [19].

Asian Indians have significantly higher levels of Hcy which is believed to cause twice as many CAD deaths as compared to Europeans and Americans. In vitro and in vivo studies demonstrate a plethora of biologically possible mechanisms that implicate Hcy in promoting atherosclerotic and thrombotic vascular diseases.

A high level of Hcy has been shown to be associated with a number of neurological conditions like stroke, SBI, dementia, AD, movement disorder and dystonia.

Majority of Indians are vegetarians and may have low levels of B12 and folic acid which can aggravate the disorder due to HHcy. As Indians are proved to have high levels of Hcy compared to Westerners a large scale, long term, multicentric longitudinal studies in Indian patients to examine the implications of HHcy lowering is warranted. Such a study might take a long time to be completed. Meanwhile as Indians have high risk for neurodegenerative and cardiovascular diseases due to HHcy it may be evaluated and lowered by vitamin supplementation, as needed.

The incidence of neurodegenerative diseases and cardiovascular disorders are high in India. Several studies point out the presence of high Hcy levels in India which is age related. Hyperhomocysteinemia and can be lowered by polyvitamin supplementation –B12, B6 and folic acid. This is all the more important since majority of Indians are vegetarians. Public strategies like awareness of high prevalence of HHcy and age related dementia, AD, SBI, arterial and vascular occlusion, movement disorder dystonia and several others as well as the benefits of reducing Hcy by B12, B6 and folic acid vitamins will have far reaching benefits in lowering the incidences of neurodegenerative and cardiovascular disorders. Vitamin
therapy is comparatively less expensive and well tolerated and may be effective in decreasing the incidence of vascular diseases. Cereals fortified with the vitamins may be made available to the public so that they can adapt to vitamin supplementation. Along with the screening for homocysteinemia as well as measurement of Hcy in plasma at least in patients presenting with cerebral infarction or with other cardiac vascular risk factor which are not prominent will be promising. Large randomized clinical studies alone can establish the association of HHcy and vascular diseases and benefit, if any by vitamin supplementation. Until such times doctors and neurologists should remember that raised Hcy is a very common and important vascular disease risk factor in Indian commoner than diabetes mellitus, smoking and even hypertension, carrying the same risk roughly as each of the above three. Hyperhomocysteinemia is a strong graded independent risk factor for stroke, MI and other vascular diseases. But it is the earliest of the risk factor, easily detectable by screening as well as measurement of Hcy and could be readily modified by multi vitamin therapy.

CONCLUSIONS

There is strong epidemiologic evidence that elevated plasma Homocysteine levels constitute an important independent risk factor for vascular diseases including ischemic stroke. Homocysteine levels in Indians is higher than in westerners. Majority of Indians being vegetarians there could be deficiency of vitamins, especially B6, B12 and folic acid which are involved in methionine metabolism. Hyperhomocysteinemia along with Vitamin B deficiency could be the major risk factor for age dependent neurological disorder seen in elderly people. Homocysteinemia is a genetic disorder modifiable by supplementation with vitamins. Measurement of plasma Hcy and supplementation of vitamins in cases with low levels of vitamins could lower/prolong the precipitation of neurological disorders at old age in India.

REFERENCES


