Hyperhomocysteinemia Presenting As Acute Ischemic Stroke And Central Retinal Artery Occlusion In A Young Male.

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Abstract: Hyperhomocysteinemia considered “the cholesterol of nineties”, is an independent risk factor of cardiovascular disease and premature atherosclerosis. It is defined as a medical condition characterized by abnormally high levels of homocysteine in the blood. Rapidly accumulating evidence links elevated homocysteine levels to thrombosis via several mechanisms such as increased tissue factor expression, attenuated anticoagulant processes, increased generation of thrombin, augmented factor V activity, fibrinolytic potential impairment and vascular injury. Atherogenic nature of homocysteine has a vital role in the development of cardiac or cerebral ischemic strokes. Several observational studies also show the association between hyperhomocysteinemia and recurrent venous thrombosis. We present a 45 year old male ,who presented to us with acute ischemic stroke and central retinal artery occlusion due to hyperhomocysteinemia.

Keywords: Hyperhomocysteinemia; Acute ischemic stroke; Central retinal artery occlusion

I. Introduction

Homocysteine (Hcy) is a sulphhydryl-containing amino acid metabolite of methionine, a compound essential for intracellular metabolism [1]. It is generally not obtained from diet[2] and is synthesized from methionine via S-Adenosyl methionine cycle or used to create cysteine and alpha-ketobutyrate[3]. It can be recycled into methionine, this process uses N5-methyl tetrahydrofolate as the methyl donor and cobalamin (vitamin B12) related enzymes[4]. Thus deficiencies of vitamin B-12, folic acid and vitamin B-6 can lead to high levels of homocysteine [5]. There are various other causes that can lead to hyperhomocysteinemia in the blood: TABLE- 1 [8].

High level of homocysteine in the blood(hyperhomocysteinemia) makes the person more prone to endothelial cell injury, which leads to inflammation in the blood vessels, which in turn may lead to atherogenesis, thus resulting in ischemic injury[6].

Hyperhomocysteinemia recently has been recognized as a early modifiable risk factor of hypercoagulability states and atherosclerotic cerebro or cardiovascular diseases[7].

<table>
<thead>
<tr>
<th>SOME OF THE CAUSES OF HYPERHOMOCYSTEINEMIA</th>
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<tr>
<td>GENETIC DEFECTS</td>
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<td>• Cystathionine-B-Synthase Deficiency</td>
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<td>• 5,10 Methylenetetrahydrofolate Reductase Deficiency</td>
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<td>• Methioninesynthase Deficiency</td>
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<td>• Genetic Defects In The Vitamin B-12 Metabolism</td>
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<td>VITAMIN DEFICIENCIES</td>
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<td>• Lack of folic acid</td>
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<td>• Lack of vitamin B-6</td>
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<tr>
<td>OTHER FACTORS</td>
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<tr>
<td>• Sex</td>
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<tr>
<td>• Lifestyle (smoking, coffee, alcohol)</td>
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<tr>
<td>• Chronic renal insufficiency</td>
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<td>• Diabetes mellitus</td>
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<td>• Hepatic dysfunction</td>
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II. Case Report

A 45 year old male patient presented to us with sudden onset weakness of right upper limb and lower limb of 4 days duration along with sudden loss of vision in the right eye. Patient did not complain of loss of consciousness, headache, vomiting, seizures and bowel and bladder incontinence. Patient was not a known case of hypertension, diabetes mellitus and ischemic heart disease. There was no significant past history.

On examination patient was moderately built. Pulse was 88 beats per min regular normal volume. Blood pressure was 138/78 mm Hg. Respiratory rate was 16 breathes per min. His oxygen saturation was 99% while breathing ambient air. There was no pallor, icterus, cyanosis. Patient did not have oedema. JVP was not raised. Cardiovascular and respiratory system examination was normal.

Central nervous system examination: Higher mental functions were intact. Ophthalmologic examination: vision was PR PL in the right eye. Left eye vision was 6/6. Fundus examination: In the right eye revealed pale disc with ghost vessels in supra and infra temporal segments suggesting Central retinal artery occlusion (figure 1). Ophthalmologic examination was completely normal in the left eye. Other cranial nerve examinations normal. Motor examination power was 3/5 in right upper and lower limb. Plantar reflex extensor on the right side. Sensory system examination was normal.

On investigation:

Haemoglobin was 12.4gm/dl, MCV was 105 fl. Total leucocyte count and platelets were normal. Kidney function and liver function tests were normal. C-ANCA, ANA, RA factor, ESR, Protein C, protein S, antithrombin III levels, factor V leiden mutation were normal. Serum vitamin B-12 levels estimated which was 98 ng/ml (normal:200–900 ng/ml). Serum homocysteine levels estimated which was 60.1micromol/l(normal:4.9-15micromol/l). ECG suggested normal sinus rhythm. 2D echo revealed normal study, carotid Doppler study showed complete thrombotic occlusion of right internal carotid artery from its origin. There was sub acute to chronic occlusion of right internal carotid artery just from its origin with no reformation. MRI with MR-angiography revealed multiple bilateral parietal sub acute infarcts with hemorrhagic infarct in right parietal occipital region and thrombosis of right ICA in cervical, cavernous and supra clenoid segments with involvement of right ophthalmic artery (figure 2,3), non visualization of cavernous part of internal carotid artery with narrowing proximally. Digital subtraction angiogram confirmed the same. (figure 4).

Patient was started on inj.vitamin B-12 1000μg i.m daily for seven days and advised to continue injections once weekly for four weeks and then monthly for life long. Folic acid 5mg was started orally, Tab. Ecosprin 150mg was added tab pyridoxine 40mg per day was added, he was also given physiotherapy. Patients Vision did not improve. Patients power improved to 4/5 in right upper and lower limb. Patients was discharged on day 7 and awaiting follow up.

Fig-1: FUNDUS RIGHT EYE; Showing pale disc with ghost vessels in supra and infra temporal segments suggesting CRAO in the right eye.
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Fig-2: MRI scanBrain

Fig-3: MR Angiography

Suggesting of multiple bilateral parietal sub acute infarcts with hemorrhagic infarct in right parietal occipital region and thrombosis of right ICA in cervical, cavernous and supra clenoid segments with involvement of right ophthalmic artery

Fig-4: Digital subtraction angiogram showing internal carotid artery obstruction
III. Discussion

It is well established that Hcy increases the risk of developing large and small vessel strokes. Hyperhomocysteinemia has a multifactorial origin. The factors attributed for the development of hyperhomocysteinemia may be genetic, nutritional, pharmacological, and pathological. Epigenetic contributions in form of ethnicity and diet are also known. An increased homocysteine level is associated with a higher risk of strokes. Carotid plaque thickness is affected in a graded fashion with increased levels of homocysteine[10]. Increased carotid plaque thickness is linearly associated with high homocysteine and low B-12 levels[11,12].

The deleterious effect of hyperhomocysteinemia is mediated primarily via a proatherogenic effect and less likely due to prothrombotic effect, which might be contributory in the large vessel disease[13]. A study revealed that elevated homocysteine levels were associated with cerebral microangiopathy and not with cardioembolic or macroangiopathy-associated ischemic stroke, again emphasizing the proatherogenic effect[14].

All the evidences suggest that hyperhomocysteinemia is both atherogenic and prothrombotic. The various mechanisms through which these proatherogenic state is achieved are; direct endothelial injury, mitogenic effect on smooth muscle cells leading to smooth muscle cell proliferation, impaired endogenous fibrinolysis, endothelial nitrous oxide response, and alteration in arachnoid acid metabolites like thromboxane induced vasoconstriction and platelet aggregations[15].

Central retinal artery occlusion (CRAO) is uncommon in the young population[16,17]. Various isolated case reports have reported a diverse and multifactorial etiology which includes cardiac valvular disorders and various vascular inflammatory disorders[18].

In an Indian study which was conducted to determine the etiological factors for central retinal artery occlusion concluded that the commonest factor was hyperhomocysteinemia (21.9%) cases[19]. Elevated homocysteine and low methionine are known factors for retinal vascular occlusions and our patient was having low vitamin B-12 levels and hyperhomocysteinemia[20].

Treatment of hyperhomocysteinemia is replacement of pyridoxine, vitamin B 12 and folic acid. These three in combination reduces the homocysteine levels and also provide some clinical benefits. Aniplatelet agents like aspirin, clopidogrel and dipiridamol have been suggested for secondary stroke prophylaxis, secondary stroke prevention basically rest on risk factor reduction[21].

IV. Conclusion:

Our patient was simultaneously having CRAO with stroke. He had diffuse disease involving the internal carotid artery and its branches. Other investigations ruled out etiological factors of stroke in young. Increased homocysteine level, MCV and reduced vitamin B-12 levels makes this case unique suggesting hyperhomocysteinemia and B-12 deficiency causing diffused intracranial vascular disease. Physicians, neurologist dealing with young stroke should keep a possibility of hyperhomocysteinemia in such cases which is the commonest preventable cause in Indian population.

References


[10]. Yoo et al studied both intracranial and extracranial vessels by MR angiography and reported that homocysteine levels were higher in patients with 2- or 3-vessel stenoses than in those with 1-vessel stenosis.


[19]. Ratra D, Dhupper M. Retinal arterial occlusions in the young: Systemic associations in Indian population. Indian J Ophthalmol 2012;60:95-100

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