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A Case Report Exploring the Controversial Link: Hyperhomocysteinemia as a Risk Factor for Neurodegenerative Diseases

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ABSTRACT

Hyperhomocysteinemia (HHcy) is an abnormal increase in blood homocysteine levels, usually above 15 µmol/L. This syndrome disturbs the homocysteine-methionine cycle, which allows homocysteine, a byproduct of methionine metabolism, to be remethylated into methionine or transformed into cysteine. Deficits in vitamins B6, B12, and folate disrupt these processes, leading in HHcy. While the link between HHcy and ischemic stroke is well-documented, its relationship with neurodegenerative disorders is still controversial.

Case studies show a close correlation among high homocysteine levels and vitamin B12 deficiency, oxidative stress, and vascular dysfunction. Successful therapies, such as antiplatelet therapy, anticoagulation, and vitamin supplementation, have been found to reduce the vascular and neurological effects of HHcy. Chronic HHcy promotes neuronal injury, oxidative stress, and tau hyperphosphorylation, pathways associated with Alzheimer's and other neurodegenerative diseases. These observations underscore the necessity of ensuring sufficient vitamin intake and controlling HHcy to avoid ischemic events and neurodegeneration.

Keywords: Hyperhomocysteinemia (HHcy), Vitamin B12 deficiency, Neurodegenerative diseases, Alzheimer's disease, Parkinson's disease, Ischemic stroke, Antiplatelet therapy, Low-molecular-weight heparin (LMWH), Vitamin B6.

INTRODUCTION

Hyperhomocysteinemia (HHcy) is an increased level of homocysteine in the blood. Normal homocysteine levels are between 5 µmol/L and 15 µmol/L, and a level above 15 µmol/L is diagnostic of HHcy. The cycle of homocysteine-methionine is an important metabolic pathway that cleaves methionine to homocysteine. The process starts with the synthesis of S-adenosylmethionine (SAM), which transfers a methyl group for biological methylation reactions. SAM is cleaved to S-adenosylhomocysteine, which is split to give homocysteine. Homocysteine may either be remethylated to methionine (with the help of vitamin B12 and 5-methyltetrahydrofolate) or proceed along the transsulfuration pathway to give cysteine (with the help of vitamin B6 as a cofactor).Levels of SAM control the balance between these pathways by favoring transsulfuration at higher concentrations and remethylation at lower concentrations. HHcy is linked with cardiovascular andneurological diseases, commonly resulting from deficiencies in vitamins B6, B12, and folate. There is evidence from studies that the levels of these vitamins in the blood are inversely correlated with the concentration of serum homocysteine. Although HHcy's link with ischemic stroke is well established, its role in neurodegenerative diseases is controversial. New evidence indicates that high homocysteine levels can lead to oxidative stress, neuronal injury, and beta-amyloid fibril formation. The high homocysteine levels could be one of the causes owing to smoking and tobacco consumption.

CASE REPORT – 01

A 28-year-old male presented with transient left upper limb weakness lasting 20 minutes, accompanied by headache and nausea. He had experienced four similar episodes since November 30, 2024. The patient had no significant medical, personal, familial, or social history.

General Examination: The patient was conscious, oriented, and afebrile, with fair hydration. No pallor, edema, or lymphadenopathy was observed.

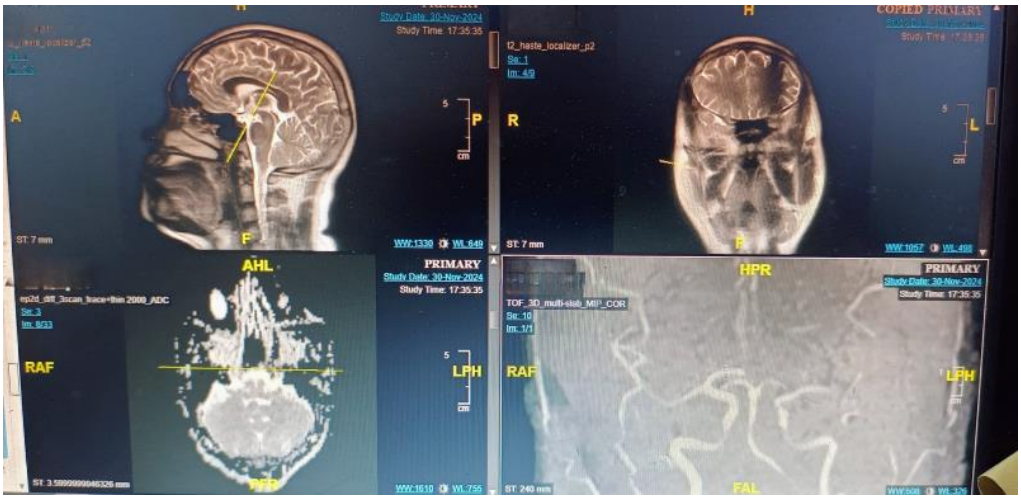
Systemic Examination:

- CVS: S1 and S2 present.
- RS: Normal vesicular breath sounds.
- P/A: Soft, no organomegaly, bowel sounds present.
- CNS: Conscious, oriented, obeying commands, moving all four limbs.

Laboratory investigations revealed normal levels of creatinine (0.9 mg/dL), sodium (138 mmol/L), potassium (3.6 mmol/L), and bicarbonate (19 mmol/L). Elevated homocysteine levels (77.17 µmol/L) and low vitamin B12 (< 159 pg/mL) were noted.

Imaging: MRI revealed thrombosis in the anterior and middle portions of the superior sagittal sinus and cortical veins at both bilateral cerebral convexities, without venous infarcts.

Management: The patient was treated with antiplatelet agents, proton pump inhibitors (PPIs), low-molecular-weight heparin (LMWH), and other medications, including levetiracetam injections, tablet Homin, and Inj. Rexite Plus. The patient showed symptomatic improvement and was discharged with appropriate advice.



MRI BRAIN (STROKE PROTOCOL)

Technique: DW sequences of the brain were correlated with the corresponding ADC maps.

Findings: No acute infarction or hemorrhage. The cortical sulci and Sylvian fissures were normal. The patient's ventricular system was normal. No midline shift. The brainstem was normal.

MR Venogram: Thrombosis was noted in the anterior and middle parts of the superior sagittal sinus and cortical veins along the bilateral cerebral convexities.

MR Angiogram: No significant stenosis.

Impression: Thrombosis in the anterior and middle parts of the superior sagittal sinus and cortical veins along the bilateral cerebral convexities. No venous infarction.

CASE REPORT – 02

A 53-year-old male, presented to the Neurology department with acute onset of loss of consciousness (2-3 episodes), blurring of vision for three days, giddiness, and headache of the same duration. He was admitted , with a known history of diabetes mellitus, systemic hypertension, hyperhomocysteinemia, and B12 deficiency. He also had a history of a left ankle fracture four months ago. On general examination, the patient was conscious, oriented, and afebrile with stable vitals (BP: 130/90 mmHg, PR: 80/min, RR: 20/min). CNS examination revealed no focal neurological deficits, and the patient moved all four limbs. Systemic examination findings were unremarkable. Laboratory investigations showed elevated homocysteine levels (19.66 µmol/L), low serum vitamin

B12 (153 pg/mL), normal creatinine (0.7 mg/dL), eGFR >60 mL/min/1.73m², sodium 136 mmol/L, potassium 3.7 mmol/L, chloride 102 mmol/L, bicarbonate 23 mmol/L, and random blood glucose of 134 mg/dL. Hematological parameters revealed hemoglobin 15.7 g/dL, total leukocyte count 7.45x10³/µL, platelet count 299x10³/µL, and other indices within normal limits. ECHO findings showed concentric left ventricular hypertrophy, adequate systolic function, and LV diastolic dysfunction. MRI confirmed acute bilateral embolic occipital infarcts. The patient was managed with intravenous fluids, antiepileptics, statins, vitamin B12 supplementation, and other supportive measures. He showed symptomatic improvement and was discharged in a stable condition with advice for regular follow-up and continued medications.

DISCUSSION

Stroke is a common health problem because it has a high prevalence, is associated with high mortality, and causes long-term disabilities, thereby becoming one of the biggest challenges for health care systems globally. One of the significant risk factors associated with ischemic stroke as well as other vascular and neurological conditions is hyperhomocysteinemia (HHcy), which is defined by increased levels of homocysteine in the blood. Cigarette smoking and environmental factor increases homocysteine levels through several mechanisms, primarily by causing nutritional deficiencies in essential B-vitamins like folate and vitamin B12, which are crucial for homocysteine metabolism. Additionally, smoking induces oxidative stress and endothelial damage, leading to impaired vascular function and promoting inflammation. The HHcy condition is also related to the pathogenesis of diseases such as Alzheimer's and Parkinson's disease, as it leads to the formation of beta-amyloid plaques, tau protein deposition, mitochondrial dysfunction, and excitotoxicity, aggravating brain injuries. Deficiencies in diet, especially vitamin B12 and folate, are frequent causes of HHcy, necessitating targeted nutritional therapies. Genetic susceptibility, i.e., MTHFR polymorphisms, also increases vulnerability to Hyperhomocysteinemia. These two cases demonstrate that hyperhomocysteinemia and vitamin B12 deficiency can manifest in various forms of cerebrovascular events, including both venous thrombosis and arterial infarcts. This broadens our understanding of the implications of these deficiencies beyond traditional vascular risk factors. Future research should focus on clarifying the mechanisms behind these associations, and on refining therapeutic approaches that can reduce the burden of thromboembolic events in these patients. Clinically, the management of hyperhomocysteinemia and vitamin B12 deficiency must be more closely integrated into treatment protocols for patients with neurological symptoms, particularly in those with other comorbidities.

Evidence from Studies

Research has provided mixed results about the relationship between HHcy and brain diseases. Some studies show that high homocysteine levels speed up cognitive decline in Alzheimer's patients, while experiments on animals reveal that HHcy can harm neuron repair and reduce the brain's ability to adapt. However, not all studies agree, because there is no standard definition of what qualifies as high homocysteine .

Future Research Goals

To better understand Hyperhomocysteinemia and its effects, future studies should:

1. Determine whether reducing homocysteine levels can prevent or slow neurodegenerative disorders.
2. Investigate how lifestyle and genetics affect homocysteine levels.
3. Standardize Hyperhomocysteinemia measurement to facilitate cross-study comparisons.
4. Investigate therapies such as vitamin supplements to determine whether they can help lessen the dangers linked with Hyperhomocysteinemia.

CONCLUSION

This case underlines a significant relationship between hyperhomocysteinemia (HHcy) and an elevated risk of ischemic stroke as well as possible neurodegenerative diseases. The increasing homocysteine leads to endothelial dysfunction, vascular damage, and neuronal injury. Such hyperhomocysteinemia aggravates the outcomes of stroke and accelerates cognitive impairment. The patient's condition underscores the importance of finding and treating underlying causes of HHcy, such as vitamin B12 and folate deficiencies, which are often reversible with supplementation. Lifestyle modifications, including dietary adjustments and physical activity, may also help reduce homocysteine levels and associated risks. Although further studies are required to understand the mechanisms better by which HHcy links stroke and neurodegenerative diseases, this case points out the necessity for early intervention before complications set in to prevent it from occurring and for recovery with improvement in overall outcomes for patients. Routine monitoring of homocysteine levels could help in managing such patients and prevent them from neurological long-term damage.

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