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Case Reports

Hyperhomocysteinemia due to Vitamin B12 Deficiency with MTHFR Gene Mutation, an Atypical Metabolic Cause of Young Ischemic Stroke: A Case Report

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Abstract

Background: *Vitamin B12 deficiency can impair the metabolism of homocysteine, leading to hyperhomocysteinemia that can cause thrombosis in the intracranial blood vessels resulting in a stroke.*

Case Presentation: *A 15-year-old Muslim young boy initially presented with pallor, slurred speech, right facial weakness, and right-sided hemiplegia. On examination, he was found moderately anemic, nonicteric, and with right-sided stroke evidenced by hypertonia, reduced muscle power jerk exaggerated with extensor plantar response. There was no lymphadenopathy, bony tenderness, intellectual impairment, or organomegaly, and normal vital parameters with the unremarkable cardiovascular examination. Laboratory investigations revealed pancytopenia, with reduced Vit B12, folic acid, and moderately increased homocysteine level. Bone marrow study suggestive of megaloblastic anemia. Immunological, infectious screens; and prothrombotic markers were found negative. CT scan of the head revealed a hypodense lesion in the left parieto-occipital region, DWI sequence on MRI Brain revealed diffusion restriction in the same area while an MR angiogram of the Brain revealed occlusion of the left middle cerebral artery due to thrombus sparing a small segment after its origin. In addition, he had MTHFR c677 C>T (Methyl tetrahydrofolate reductase) gene mutation and responded both clinically and biochemically after vitamin B12, folic supplementation along with aspirin in 5 months.*

Conclusion: *Vitamin B12 deficiency along with MTHFR c677 C>T gene mutation has increased the chance of thrombotic stroke. Vitamin B12 supplementation might be beneficial for patients with an MTHFR gene mutation positive.*

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Introduction

Till now, stroke is the second leading cause of death and the third leading cause of functional disability.[1] In low and middle-income countries, stroke is common among younger age groups associated with higher mortality.[2] Among the causes of young stroke hyperhomocysteinemia due to vitamin B12 deficiency is rare. In older adults, vitamin B12 deficiency is common and has a positive association with ischemic stroke. Another school of thought is that vitamin B12 deficiency can impair myelination which may impact neurological function and increase the risk of stroke.[3,4] Homocysteine concentrations range from 5-15 µmol/L in the fasting state is regarded as normal. Hyperhomocysteinemia has been classified into moderate (plasma concentrations of 15-30 µmol/L), intermediate, or high risk (plasma concentrations of 31-100 µmol/L), and severe (plasma Homocysteine concentrations of 100 µmol/L).[5] Male gender, increasing age, smoking, impaired kidney function, and medications like cyclosporine and corticosteroids are the

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acquired causes of hyperhomocysteinemia. Genetic causes include classic homocystinuria and methylenetetrahydrofolate reductase (MTHFR) gene mutations.[5] We report an unusual case of ischemic stroke in a young patient with pancytopenia due to vitamin B_{12} deficiency who had methylene tetrahydrofolate reductase (*MTHFR*) c677 C>T gene mutation and responded both clinically and biochemically after vitamin B12 supplementation.

Case Summary

A 15-year-old young boy initially presented with pallor, slurred speech, right facial weakness, and right-sided hemiplegia and was found to have a stroke (NIH Stroke Scale score of 9). There was no history of fever, jaundice, and blood transfusion. On examination, he was found moderately anemic, nonicteric and had facial deviation to left. His vital parameters were completely normal. There were no evidence of skin lesion or vitiligo, marfanoid body habitus, bony tenderness, lymphadenopathy, and intellectual impairment. Neurological examinations revealed right-sided stroke evidenced by hypertonia, reduced muscle power (3/5 in both right upper and lower limb), and jerk exaggerated with extensor plantar response. Cardiovascular examinations were completely normal. Oral Cavity and abdominal examinations were unremarkable. The rest of the systemic examinations were found completely normal. Laboratory investigations revealed reduced hemoglobin, neutropenia, thrombocytopenia, high MCV, normal reticulocyte count while peripheral blood film showed anisopoikilocytoses, many elongated cell with some macro-ovalocytes with thrombocytopenia. His liver, renal, and thyroid function test were completely normal. Coombs test, hemoglobin electrophoresis, and iron profile were found normal. However, vitamin B12 was moderately reduced but folic acid was mildly reduced. Immunological markers like ANA (Antinuclear antibody), Anti ds DNA, and anti-parietal cell antibodies were normal. Infection screens like Dengue NS1 Ag, Anti dengue IgM & IgG, ICT for malaria, and HBsAg, Anti HCV, Anti HIV antibody, and VDRL tests were negative (Table 1). However, the plasma homocysteine level was moderately increased. Chest X-ray, USG of the whole abdomen, and echocardiography were found unremarkable. At that time a CT scan of the head revealed a hypodense lesion in the left parieto-occipital region, DWI sequence on MRI Brain revealed diffusion restriction in the same area [figure 1], while MR angiogram of the head and neck revealed occlusion of the left middle cerebral artery due to thrombus sparing a small segment after its origin (figure 2).

The patient was then treated with supplemental vitamin B_{12} 1000 mcg daily, initially IM and then orally. He also received folinic acid supplementation along with aspirin 75 mg per day. Three months later, the patient's symptoms improved, with the resolution of his expressive aphasia and marked improvement of his right-sided hemiparesis. Laboratory data also showed improvement, as vitamin B_{12} level increased to 789 pg/ml and homocysteine level decreased to 21.7 μmol/L. Five months after his initial diagnosis, homocysteine levels further decreased to 11 ìmol/L while receiving supplemental vitamin B_{12} and folinic acid.

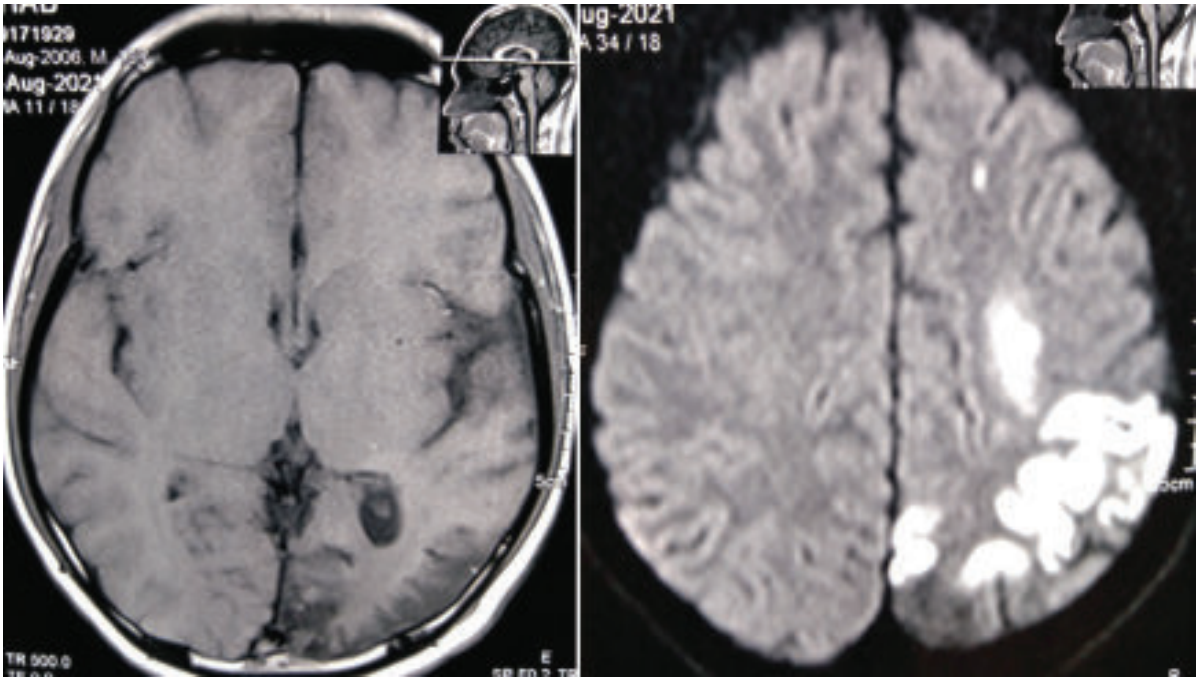

Figure-1. *MRI Brain T1 sequence revealed hypodense lesion in left parieto-occipital region, DWI sequence on MRI Brain revealed diffusion restriction in same area*

Table 1. *Laboratory Findings of Patients*

Trait	Value	Reference
Hemoglobin	7.6 g/dl	11.5-15.5 g/dl
White Blood Cell	3700 mm3	4-11000 mm3
Platelet	75000 mm3	1,50000- 4,500000 mm3
CRP	3.12 mg/L	<6 mg/L
MCV	112 fL	76-96 fL
MCH	29 pg	27-32 pg
MCHC	33 g/dl	30-35 g/dl
PBF	anisopoikilocytoses, with some macro-ovalocytes with pancytopenia; no immature or blast cell.	
Reticulocyte Count	1.45%	0.20-02%
Urine R/E	Unremarkable	
S. Creatinine	0.76 mg/ dl	0.5-1.2 mg/dl
SGPT	18 IU	10-40 IU
S. Bilirubin	0.6 mg/dl	0.3-1.2 mg/dl
Coombs Test (direct & indirect)	Negative	
Vitamin B12	86 pg/ml	187-883 pg/ml
Folic Acid	2.6 ng/ml	3.1-20.5 ng/ml
S. Iron	19 ìmol/L	8-24 µmol/L
Homocystine	>70 ìmol/L	< 18 µmol/L
LDL Cholesterol	145 mg/dl	< 100 mg/dl
HDL Cholesterol	32 mg/dl	> 50 mg/dl
Total Cholesterol	198 mg/ dl	< 150 mg/dl
APTT	32 second	28- 36 second
D-dimer	0.34 ìg/ml	< 0.5 µg/ml
ANA	Negative	< 1
Anit-ds-DNA	Negative	< 30 Iu/ml
Anti parietal Cell antibody	Negative	
Anti Cardiolipin AbIg MIgG	1.32.4	< 15 U/ml
Anti Beta 2 Glycoprotein 1 AntibodyIg MIg G	4.9 6.5	< 40 U/ml
Protein C & S	150%	70-130%
Anti-thrombin III	92%	80-120%
p- ANCA	1.91 U/ml (negative)	< 5 U/ml
c- ANCA	2.32 U/ml (negative)	< 5 U/ml
S. TSH	1.98 ìIu/ ml	0.85-4.54 µIu/ ml
FT4	1.12 ng/dl	0.7-1.48 ng/dl
Infection ScreenDengue NS1 AgAnti Dengue Ig M & Ig GHBsAg, Anti HCVAnti HIV (1,2) AntibodyVDRL	**Negative**	
Bone Marrow Study	Marked erythrocytosis, erythroid precursors show megaloblastic changes, nuclear budding and nuclear irregularity. Myeloid lineage cells are reduced in number. Neutrophils show hypersegmentation. Megakaryocytes are reduced in number.	
MTHFR c677 C>T Gene Mutation	**Positive**	

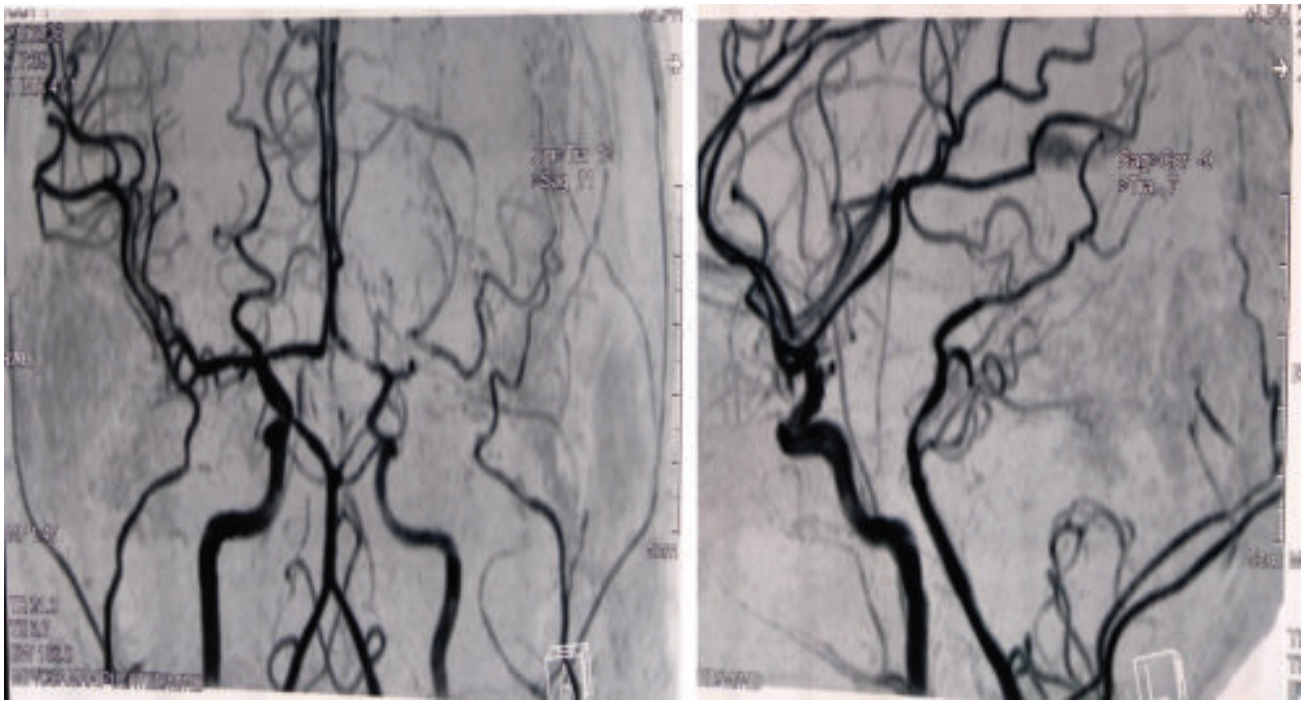

Figure 2. *MR angiogram of the head and neck revealed occlusion of the left middle cerebral artery due to thrombus sparing a small segment after its origin*

Discussion

Homocysteine can cause vascular disease by a variety of mechanisms. Raised plasma homocysteine concentrations leads to increased blood coagulation, increased cholesterol synthesis, reduced synthesis of apolipoprotein A1 leading to reduced concentrations of high-density lipoprotein, increased oxidative stress, upregulated adhesion molecules, and several other mechanisms that can injure endothelium.[6] Therefore, patients with hyperhomocysteinemia due to vitamin B12 deficiency are at high risk for coronary artery disease, stroke, and peripheral vascular disease.[3] A Deficiency of vitamin B12 causes both hematological and neurological manifestations. Common hematological manifestations are megaloblastic anemia, pancytopenia, hypersegmented neutrophils, and sometime macrocytosis.[7] Neurological manifestations include dementia, depression, acute psychosis, stroke, myelopathy, subacute combined degeneration, and peripheral neuropathy.[8] Our patients presented with pancytopenia with acute ischemic stroke comprising both hematological and neurological manifestations. The cause of ischemic stroke in our patient due to occluding thrombus in the left middle cerebral artery. Considering other causes of thrombosis we worked out all of those possibilities and found everything normal except hyperhomocysteinemia. We went further to find out any genetic predisposition. Interestingly, we found MTHFR mutation positivity in our patient. That explains the increased thrombosis and thrombotic stroke in our patient. Zacharia G et al.[9] reported a case where a patient had an MTHFR mutation presented with recurrent ischemic stroke due to thrombus with bicytopenia. The gray zone is vitamin B12 supplementation in patients with young stroke due to respective vitamin deficiency. Does Vitamin b12 supplementation prevent recurrent stroke? It is still a debate. The Vitamin Intervention for Stroke Prevention trial was conducted in the US and included 3680 participants that were administered 25 mg of folic acid, 25 mg of pyridoxine (B6), and 400 μg cyanocobalamin (B12). The trial showed no benefit in recurrent stroke or in secondary outcomes, including coronary heart disease and cardiovascular disease prevention.[10] The Heart Outcomes Prevention Evaluation trial showed a reduction in homocysteine levels in the supplemented group in comparison to the placebo group; however, vitamin B supplementation did not reduce cardiovascular disease risk.[11] The China Stroke Primary Prevention Trial demonstrated supplementation with folic acid in combination with enalapril, an angiotensin-converting enzyme inhibitor used to treat hypertension, reduced the risk of stroke by 24% in hypertensive patients.[12] Interestingly, Zhao et al. showed the dietary levels of vitamin B12 that were above the median when combined with the benefits of supplementation were transferred to patients with a

polymorphism in the gene for methylenetetrahydrofolate reductase (MTHFR).[13] Further, subgroup analysis showed by Zhang et al.[14] that younger male patients with low folate & Vitamin B12 levels and higher systolic blood pressure, hypercholesterolemia, hyperglycemia, and the MTHFR C677 CT or TT genotype had the most lifelong benefit. A follow-up study investigated by Qin et al [15] described the interaction between folate, vitamin B12, and enalapril on the risk of ischemic stroke where serum B12 levels above the median (from diet) were associated with a 72% reduction of stroke with folic acid and enalapril on MTHFR TT heterozygotes. In our patient we have given Vit B12, folic acid daily as an additive along with aspirin 75 mg and Atorvastatin 20 mg daily. Our patient responded gradually over 5 months evidenced by correction of anemia, homocysteine level return to normal along with improvement of muscle power and expressive aphasia.

Conclusion

It is worthwhile to mention that recent guideline does not recommend vitamin B12 supplementations but those who have MTHFR CT or TT gene mutations might be benefited from lifelong supplementations. So, a large prospective study is mandatory to evaluate the role of vitamin B12 supplementations in patients who have MTHFR CT or TT gene mutation.

Declaration Section

Ethics Approval and Consent to Participate

Written informed consent was obtained from the patient and ethical approval was also taken from the IRB of the National Institute of Neurosciences and Hospital.

Consent for Publications

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. An ethical copy of the consent is available for review by the Editor-in-Chief of this journal. IRB of the National Institute of Neurosciences and Hospital has permitted this case report for publication.

Availability of data and material

Not applicable.

Competing interests

The authors declare no competing interests.

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