

Adult-onset methylenetetrahydrofolate reductase C677T mutation and its repercussion: A case report

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ABSTRACT

Methylenetetrahydrofolate reductase (MTHFR) is an enzyme that converts homocysteine into methionine by catalyzing the conversion of 5,10-methyltetrahydrofolate into 5-methyltetrahydrofolate. Deep vein thrombosis, coronary artery disease, peripheral vascular thrombosis, and cerebrovascular thrombosis are attributed to homozygous MTHFR mutations. We describe here a case of a 42-year-old male, who presented to us with subdural hemorrhage following systemic thrombolysis for pulmonary embolism. He was found to have hyperhomocysteinemia as a result of homozygous MTHFR C677T mutation. He underwent left fronto-temporo-parietal decompressive craniectomy and hematoma evacuation with the placement of a free bone flap in the right anterior abdominal wall and placement of an IVC filter to prevent recurrent venous thromboembolism. He was started on Vitamin B12, pyridoxine, and folic acid supplementation and was discharged in a stable condition with a plan for cranioplasty at a later date.

Key words: Homocysteinemia, Methylenetetrahydrofolate, Mutation


Methylenetetrahydrofolate reductase (MTHFR) is an enzyme that catalyzes the conversion of 5,10-methyl tetrahydrofolate into 5-methyl tetrahydrofolate and releases a methyl group that is utilized in the conversion of homocysteine into methionine. It thereby regulates folate and homocysteine metabolism. Nine polymorphisms and 34 mutations due to deletions have been identified and the most common mutation is 677C→T which is also the most common cause of hyperhomocysteinemia [1]. Patients typically present in the neonatal period with feeding problems, failure to thrive, muscular hypotonia, encephalopathy, or seizures. Vascular pathology is less frequent. Late-onset disease (>1 year old) occurs less frequently and with more variable manifestations including neurocognitive impairment, gait abnormalities, neurological disturbance compatible with myelopathy or ataxia, psychiatric disorders, or thromboembolic events [2]. Metabolic therapies were shown to be effective in children and adults to stop disease progression, and sometimes improve neurological disabilities [3].

CASE REPORT

A 42-year-old male, a known case of left popliteal vein thrombosis, presented to a hospital elsewhere with complaints of chest pain

followed by loss of consciousness for a few minutes. He was evaluated for the above-mentioned complaints and underwent coronary angiography which was suggestive of single vessel disease with right coronary artery thrombus. Two-dimensional echocardiography (2D ECHO) also revealed a thrombus in the right atrium. Further evaluation with computed tomography pulmonary angiography (CT angiography) showed pulmonary thromboembolism. He underwent systemic thrombolysis with streptokinase. Three days later, he complained of left-sided headache, nausea, and drowsiness for which a non-contrast computed tomography (NCCT) head was done which revealed left fronto-temporo-parietal subdural hemorrhage with mass effect (Fig. 1). He was referred to our center for further management.

On presentation to our center, he was drowsy but arousable and had slurred speech with right hemiparesis. He was afebrile, his pulse rate was 102/min, respiratory rate was 32/min, blood pressure was 152/68 mmHg, and oxygen saturation of 86% on room air. On systemic examination, central nervous system examination revealed features of left third cranial nerve palsy with left lid ptosis, anisocoria, and impaired extraocular muscle movement except for superior oblique and lateral rectus. His power was 3/5 in the right upper and lower limbs. Respiratory examination revealed bilateral coarse crepitations in the infrascapular region. Cardiovascular and per abdomen examinations were within normal limits.

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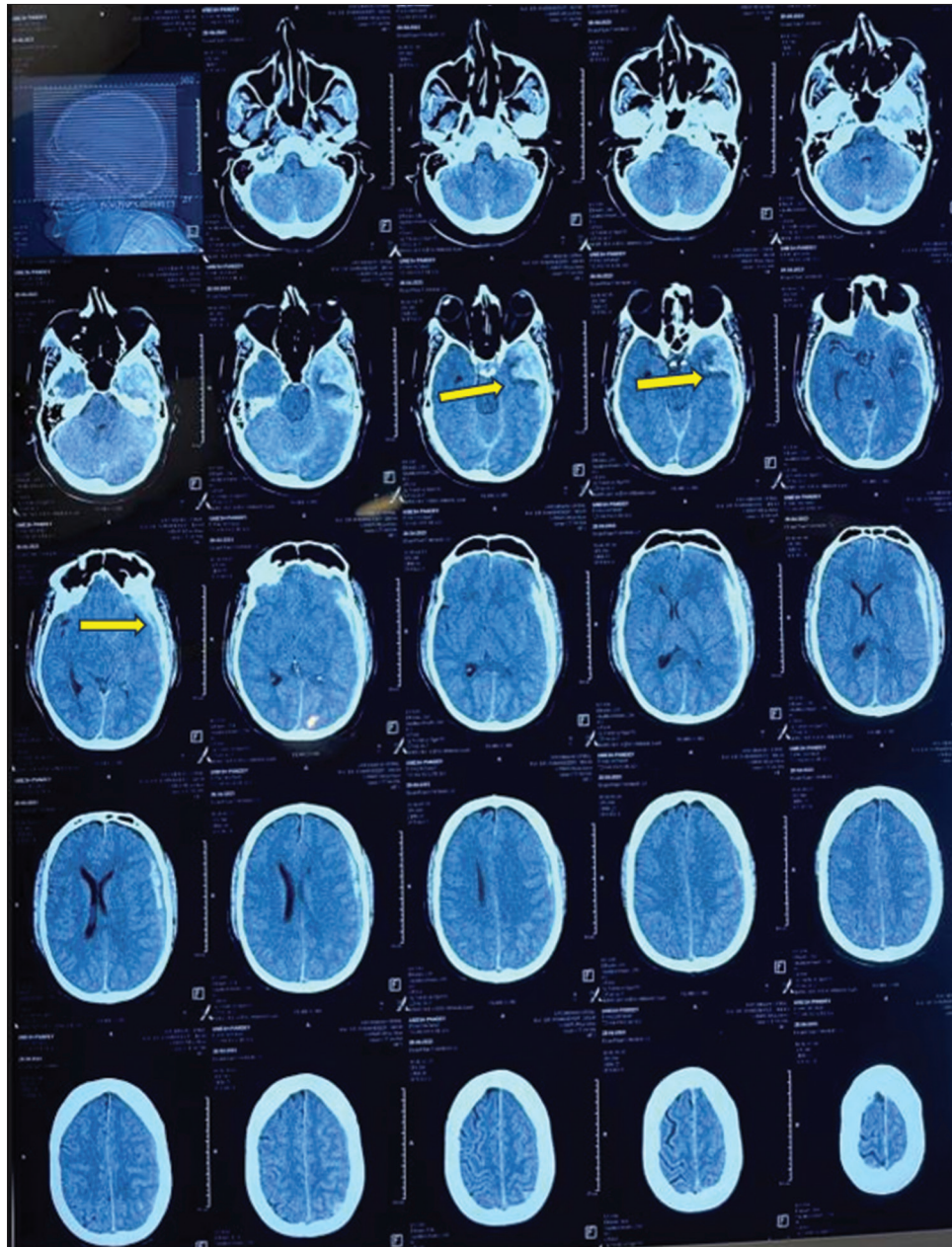


Figure 1: Non-contrast computed tomography brain showing subdural hematoma with mass effect

In view of decreased saturation on room air, poor respiratory efforts, and a Glasgow coma scale score of 8, he was intubated. He underwent left fronto-temporo-parietal decompressive craniectomy and hematoma evacuation with the placement of a free bone flap in the right anterior abdominal wall. The patient was further investigated to find out the cause of multiple thrombi.

His investigations revealed anemia with leucocytosis (Hemoglobin=8.2 g/dL, total leucocyte count=17.8 thous/mm³, Platelet 278 thous/mm³); slightly deranged liver enzymes (Serum glutamic oxaloacetic transaminase=28 IU/L, Serum glutamate pyruvate transaminase=86 IU/L) with hypoalbuminemia and normal renal functions (Blood urea nitrogen=17.24 mg/dL, creatinine 0.93 mg/dL, sodium 137 mmol/L, potassium 4.83 mmol/L). His ANA immunofluorescence test was negative. On extensive thrombophilia workup, he was tested negative for Drvvt screen, B2-microglobulin

Immunoglobulin (Ig) M and IgG, anticardiolipin antibody IgM and IgG, prothrombin mutation, Factor V Leiden mutation with normal anti-thrombin 3, Protein C and Protein S levels. However, his homocysteine levels were raised (33.03 umol/L) with normal vitamin B12 levels (677 pg/mL) and folic acid levels (4.18 ng/mL) and he was found to have homozygous C677T MTHFR polymorphism. Other investigations revealed hypertriglyceridemia (Total cholesterol-168 mg/dL, high-density lipoprotein-21 mg/dL, low-density lipoprotein (LDL)-95 mg/dL, Very LDL-42 mg/dL and triglycerides-252 mg/dL); Glycated hemoglobin=6.4%; Lactate dehydrogenase=401 IU/L; Direct Coomb's 2+ reaction with negative Indirect Coomb's test (Table 1). His G6PD level was within normal range. Since he developed a fever, endotracheal culture was sent which grew *Klebsiella pneumoniae* and was managed as per the sensitivity report.

Table 1: Investigations of the patient

Investigation	Values
Hemoglobin	8.2 g/dL
Total Leukocyte Count	17800/mm ³
Platelet	2,78,000/mm ³
Total Bilirubin/Direct Bilirubin	1.8/1.1 mg/dL
Serum glutamic oxaloacetic transaminase/Serum glutamate pyruvate transaminase	28/86 IU/L
ALP/GGT	379/216 IU/L
Blood urea nitrogen/Creatinine	17.24/0.93 mg/dL
Na ⁺ /K ⁺	137/4.83 mEq/L
DRVVT Screen	Negative
B2-microglobulin IgM	Negative
B2-microglobulin IgG	Negative
Anti-cardiolipin IgM	Negative
Anti-cardiolipin IgG	Negative
Prothrombin mutation	Negative
Factor V leiden mutation	Negative
Anti-thrombin III levels	Within normal limits
Protein C levels	Within normal limits
Protein S levels	Within normal limits
Serum Homocysteine	33.03 umol/L
Vitamin B12	677 pg/mL
Folic acid	4.18 ng/mL
MTHFR polymorphism	Homozygous C677T polymorphism
Triglycerides	252 mg/dL
Lactate dehydrogenase	401 IU/L
Glycated hemoglobin	6.4%
Direct Coomb's	2
Indirect Coomb's	Negative

In view of homozygous MTHFR polymorphism, Vitamin B12, folic acid, and pyridoxine were added to the treatment regimen. In view of the risk of recurrent venous thromboembolism and left popliteal deep vein thrombosis, the patient underwent insertion of an IVC filter on post-operative day-1. The patient's sensorium improved gradually. Repeat NCCT brain revealed post-operative changes in the left frontoparietotemporal region with an area of collection noted in the middle cranial fossa region with the focus of air within it with left temporal lobe herniation. He was discharged in a hemodynamically stable condition with improved sensorium (conscious, oriented, and following simple commands) with a plan for cranioplasty at a later date.

DISCUSSION

The most common inborn error of folate metabolism is MTHFR polymorphism [1]. This gene encodes instructions for the conversion of folic acid into its active form that further catalyzes various other biochemical reactions like the conversion of homocysteine to methionine. In 1988, a variant for this enzyme was identified that caused mild-to-moderate elevation of serum homocysteine levels [4]. With the help of cDNA isolation

techniques perfected in 1994, the defect was isolated at base pair (bp) 677 where cytosine was found to be substituted (C677T) [5]. This variation is now recognized as the most common genetic cause of hyperhomocysteinemia [1]. It is associated with neural tube defects, arterial and venous thrombosis, cardiovascular disease, increased risk of schizophrenia but decreased risk of ALL, and carcinoma colon.

Another variant was identified later involving the substitution of adenosine with cytosine at bp 1298 (A1298C); however, its effect on enzyme activity and outcomes is poorly understood [1]. *In vitro* and *in vivo* data suggest that the C677T variant in conjunction with severe MTHFR deficiency may modulate the enzymatic activity [1]. The NLHBI Family Heart Study found that MTHFR polymorphism was associated with higher serum homocysteine levels; however, further analysis revealed that this association was true only in the presence of low serum folate levels [6].

In another study by Goyette *et al.*, it was found that the C677T variant was evenly distributed in both populations – those with increased serum homocysteine levels and the control group. However, the former had multiple mutations, of which at least two were severe [7]. Uncertainty exists regarding the relationship between elevated homocysteine levels and thrombosis, including if it just serves as a risk factor. Evidence suggests that elevated serum homocysteine levels may only be a marker for an increased risk of cardiovascular diseases and not their actual cause, with Vitamin B6 (pyridoxine), Vitamin B12, and folic acid supplements not reducing the risk of cardiovascular diseases or venous diseases such as pulmonary embolism or deep vein thrombosis in such patients [8].

Folic acid, Vitamin B6, and Vitamin B12 supplementation are not advised for the primary prevention of cardiovascular or venous illnesses or for the treatment of such individuals because it does not reduce the chance of developing these conditions. It is also because vitamin supplements do not reduce the incidence of repeated clots and MTHFR mutations [8].

Subdural hemorrhage is an infrequent complication of IV thrombolysis. The UPET II trial showed that the rate of major hemorrhage in patients treated with streptokinase was 22%. However, the risk was lower as compared to other agents [9]. However, in a deteriorating patient with acute subdural hematoma, an emergency craniotomy should be performed. As per experimental studies, hyperhomocysteinemia can cause endothelial dysfunction, an increase in the production of matrix metalloproteinase-9, and disruption of the blood-brain barrier and can be a contributory factor in hemorrhagic transformation post-IV thrombolysis [3,10-12]. Li *et al.* found that hyperhomocysteinemia was associated with both hemorrhagic and ischemic stroke and suggested starting therapy to lower the levels of plasma homocysteine [13].

CONCLUSION

The MTHFR homozygous mutation is a significant contributor to hyperhomocysteinemia, which is linked to several venous and

cardiovascular disorders. Patients presenting with thrombotic complications should be assessed for MTHFR gene mutation as these patients may have hemorrhagic transformation post-thrombolysis. Numerous clinical investigations on MTHFR variations have produced inconsistent results, and it is still unclear which genetic and environmental factors interact with this gene to affect illness risks.

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