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A Rare Case of Deep Vein Thrombosis Secondary to Protein S Deficiency and Antithrombin III Deficiency with MTHFR (C677T) Heterozygous Mutation, and Crohn's Disease

ANUSHA GARG
JSS ACADEMY OF HIGHER EDUCATION AND RESEARCH, anusha.garg838@gmail.com

VANAMA LAKSHMAN SAI
JSS ACADEMY OF HIGHER EDUCATION AND RESEARCH

ANKIT SINGH
JSS ACADEMY OF HIGHER EDUCATION AND RESEARCH

ADITI RAO
JSS ACADEMY OF HIGHER EDUCATION AND RESEARCH

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A Rare Case of Deep Vein Thrombosis Secondary to Protein S Deficiency and Antithrombin III Deficiency with MTHFR (C677T) Heterozygous Mutation, and Crohn's Disease

Abstract

Deep vein thrombosis is a condition wherein a thrombus develops in the deep veins of the body, most commonly in the legs, due to increasing tendency of the blood to coagulate. One such reason is the MTHFR gene mutation, wherein an increase in homocysteine levels causes irritation of the blood vessel endothelium, causing a disturbance in Virchow's triad, hence triggering clot formation. [1]

The MTHFR gene is responsible for instructing the body to produce an enzyme called methylene tetrahydrofolate reductase(MTHFR) [2]. MTHFR gene mutations can lead to a wide range of disorders, either as a result of the elevated levels of homocysteine in the blood, or due to folate deficiency. In about 25% of individuals globally, there is a mutation of MTHFR. The MTHFR 677C>T mutation is predominantly seen in the Hispanic ethnicity, whereas the MTHFR 128A>C is predominantly seen in the ethnicity groups belonging to south east Asia. In the Indian population, the MTHFR mutation prevails a low frequency of 2.9%.

Diagnosis and treatment are required only in cases where secondary diseases occur as a result of MTHFR polymorphism, or if there is significant family history [4]. The treatment is along the same lines as that of another diagnosed individual without the mutation.

In this case, the correlation between a genetic mutation of the MTHFR gene and Protein S and Antithrombin III deficiency, along with Crohn's disease, which resulted in the development of DVT in a middle aged, male individual and its management is discussed.

Keywords

Hyper coagulability, Anaemia, DVT, MTHFR gene mutation, IBD

TITLE: A Rare Case of Deep Vein Thrombosis Secondary to Protein S Deficiency and Antithrombin III Deficiency with MTHFR(C677T) Heterozygous Mutation and Crohn's disease.

CLINICAL HISTORY:

A 51 year old male patient, farmer by occupation, from Chamarajanagar, came with the complaints of left lower limb swelling since 1 week, initially confined to foot and has gradually progressed to entire left lower limb up to mid thigh, associated with pain dragging in nature, increased on movements, non radiating. Patient complains of abdominal pain more over the suprapubic region, intermittent in nature, squeezing in type, associated with multiple episodes of loose stools, blood tinged, about 4-5 episodes/day for last 4 days. The patient is a k/c/o Crohn's disease, diagnosed 5 yrs back, was on medication (Mescal) for 2 yrs, but currently not on medication, and a k/c/o CVT 1.5 years ago. Patient continues to take Acitrom 1 mg daily.

EXAMINATION: On general examination, the patient had normal vital signs, with pallor and left lower limb swelling present up to mid thigh, with non pitting oedema, associated with tenderness. Right lower limb normal. . Systemic examination revealed tenderness present in the suprapubic region, no organomegaly, bowel sounds present, with a normal CVS, RS AND CNS.

INVESTIGATIONS:

- Routine blood examination showed microcytic hypo-chromic anaemia with neutrophilic leucocytosis with thrombocytosis
- RFT within normal limits
- LFT showed mild hypoalbuminemia
- PT/INR was elevated
- ECG and Chest X ray – Normal
- USG ABDOMEN – Diffuse circumferential of bowel loops with wall thickening 5 mm, Adjacent echogenic mesenteric fat and surrounding inflammatory changes, Splenomegaly and minimal ascites noted.
- LEFT LOWER LIMB VENOUS DOPPLER showed DVT.
- Thrombophilia workup was done and showed the following :
    - DECREASED ANTITHROMBIN ACTIVITY
    - DECREASED PROTEIN S LEVELS
    - MTHFR GENE HETEROZYGOUS MUTATION

FINAL DIAGNOSIS:

- Left lower limb DVT secondary to protein S and Anti thrombin III deficiency, and MHFTR gene mutation
- Severe anemia secondary to active IBD- Crohn's disease
- Old CVT

TREATMENT GIVEN:

- Patient was admitted in ICCU in view of lower GI Bleed and severe anaemia .
- 2 PRBC was given and started on LMWX 40 MG S/C 1-0-1 with IV antibiotics and analgesics.
- Gastroenterologist opinion was taken and started on Mesocol (Mesalamine).
- Patient improved, bleeding stools decreased and was shifted to wards.

DISCUSSION:

The MTHFR gene is responsible for instructing the body to produce an enzyme called methylene tetrahydrofolate reductase. [1,2] Individuals have two copies of the MTHFR gene, found on chromosome 1. One is derived from the maternal genome and the other from the paternal genome. In about 25% of individuals globally, there is a mutation of the MTHFR, resulting in the MTHFR 677C>T and MTHFR 1298A>C variants. MTHFR gene mutations can present either as minor differences in eye colour, hair colour, or blood type or as more serious conditions like homocystinuria, alopecia areata, anencephaly, spina bifida, autism, colon cancer, IBS, stroke, blood clots, peripheral neuropathy, *etc*. These diseases occur as a result of the elevated levels of homocysteine in the blood, or due to folate deficiency. [2,3] Diagnosis of this condition can be done with the help of genetic testing, via a simple blood test. [4]

MTHFR mutations don't necessarily require medical treatment, if asymptomatic. However, supplementing the diet with folic acid is always advised. During pregnancy, it is imperative for mothers with the MTHFR gene mutation to consume 400mcg of folic acid each day. [5]. In the case of onset of other disorders as a result of MTHFR mutation, the treatment is along the same lines as that of another diagnosed individual without the mutation.

While studying the above case, investigations revealed that the patient had elevated platelet counts and prolonged PT/INR, suggestive of thrombophilia. On further evaluation, it was found that he had MHFTR gene mutation, along with Protein S and Anti thrombin III deficiency. The patient is also a known case of Crohn's disease (IBD), which could have developed as a result of MTHFR gene mutation. [6] In individuals with Crohn's disease, as a result of the chronic vasculitis, there is development of multiple vascular infarcts in the intestinal circulation and fibrin deposition, which itself becomes a risk factor for the development of DVT. [7]

To conclude, in the case, the presence of MTHFR gene mutation, active Crohn's disease, Protein S and Anti thrombin III deficiency, all played a significant interconnected role in the development of DVT.

Treatment of DVT includes usage of pharmacological anticoagulants like LMWH, vitamin K antagonists (warfarin) or new direct oral anticoagulants (rivaroxaban, apixaban, edoxaban and dabigatran). Mechanical thrombolysis can also be done. In this case the patient was started on LMWX 40 MG S/C 1-0-1. All patients with IBD and MTHFR gene mutation should also receive low dose folic acid and vitamin B12 therapy to protect against the thromboembolic complications of raised homocysteine levels. [6]

CONCLUSION:

DVT is a thrombotic disease wherein a blood clot develops in the deep veins of the body, most commonly the legs. In MTHFR gene mutation, increased homocysteine levels irritate the blood endothelium, leading to disturbance in Virchow's triad and inciting the increasing clotting tendency. In IBD, chronic inflammation, dehydration, and steroid use leads to the same. Treatment of DVT in individuals with MTHFR is along the same guidelines as an individual without the gene mutation. It includes pharmacological anticoagulants and mechanical thrombolysis. All patients with IBD and MTHFR gene mutation should also receive low dose folic acid and vitamin B12 therapy to protect against the thromboembolic complications of raised homocysteine levels, and is important for life-long anticoagulation treatments.

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