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Does COVID-19 Infection Increase the Risk of Hypercoagulability in Individuals with MTHFR Gene Mutation?

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Abstract

Background

COVID-19's clinical spectrum ranges from asymptomatic to severe illnesses. In addition, several complications such as venous thromboembolism have been reported. Methylenetetrahydrofolate Reductase (MTHFR) enzyme plays an essential role in converting homocysteine to methionine. However, genetic variation in the MTHFR gene impairs enzyme function, increasing hypercoagulability.

Objective

To report the associated risk of hypercoagulability in individuals with MTHFR gene mutation due to COVID-19 infection.

Method

A case series of 3 patients were admitted to our institution between 03/03/2021 and 08/20/2021 to manage venous thromboembolism. A retrospective chart analysis was done. History, basic work-up (complete blood count, comprehensive metabolic panel, D-dimer, PT/INR/PTT, and COVID-19 serology), and extended work-up for various congenital/ acquired causes of hypercoagulable states (MTHFR gene mutation, factor V Leiden mutation, prothrombin II mutation, antiphospholipid panel, protein C level, protein S level, and antithrombin 3 levels) were reviewed.

Results

Three previously healthy females, 15-17 years old, were referred to manage spontaneous thromboembolic diseases like deep venous thrombosis (DVT), infrarenal inferior vena cava thrombus, pulmonary emboli, and superior mesenteric vein clots. All three patients had either homozygous or heterozygous MTHFR mutation but with normal homocysteine levels. Incidentally, they all had COVID-19 infection as evidenced by positive COVID-19 IgG. There were additional risk factors in these patients: two patients were on oral contraceptive pills (OCPs) for more than six months before presentation, two had an extensive family history of clots, and one patient had a heterozygous G-20210-A prothrombin II mutation. All patients were treated with subcutaneous Enoxaparin @1mg/kg/dose BID with a target dose level of 0.6-1 IU/mL, significant improvements were noted in all three cases, and were discharged after six weeks of Enoxaparin.

Conclusion

Previously healthy young females with an underlying MTHFR gene mutation presented with unprovoked clots shortly after a COVID-19 infection. Despite having MTHFR gene mutations, no hyperhomocysteinemia was noted, thus raising concern for a possible association between COVID-19 infection and increased risk of hypercoagulability in individuals with MTHFR gene mutation. Therefore, more research is needed to study post-COVID-19 sequelae in patients with MTHFR gene mutations with normal homocysteine levels.

Introduction

After the COVID-19 pandemic, accumulated evidence showed that COVID-19 infections are associated with a prothrombotic state leading to various forms of venous thromboembolism **[1,2]**. Even after accounting for the effect of hospitalization and comorbidities, COVID-19 seems to have an additional impact. Dhawan et al. **[3]** described a unique COVID-19 effect or "signature" on vasculature leading to thrombotic events even in young and healthy individuals and those with mild COVID-19 infections. On a molecular level, Pretorius et al. **[4]** described that COVID-19 is shown to leave its mark on platelets, making them "hyperactivated" and "clumped together," even after weeks to months from recovery from COVID-19 infection.

The incidence of deep venous thrombosis (DVT) is increased in hospitalized COVID-19 patients than in the control group **[5]**. Even after hospitalization and resolution of symptoms, more than 30 % of the COVID-19 patients were found to have persistent elevated D-dimers **[4,6]**. A local pulmonary hypercoagulable state might be responsible for COVID-19-related pulmonary embolisms (PEs) rather than the classic deep venous thrombosis (DVT) embolisms **[7]**. Chevinsky et al. **[6]** reported 2.8 times increase in PEs in COVID-19 patients managed as outpatients in the 31 to 60 days post-infection, and a two-times increase in the 60 to 90 days post-infection **[6]**. A prior study has shown 4 previously healthy patients presenting with unusual clots for their age. They presented at a mean of 78 days after seroconversion **[8]**. Thus, literature supporting the prothrombotic nature of COVID-19 infection is robust and necessitates close monitoring of these patients.

Genetic factors play a substantial role in thrombogenesis and have been attributed to causing 60 % of DVT. Many reported genes have been discovered over time, one of which is relevant to our cases: The MHTFR gene **[9]**. The MTHFR mutation may result in hyperhomocysteinemia which increases the risk for hypercoagulability.

We present three interesting cases of thromboembolism in young and previously healthy teenage girls all of whom were found to have an MTHFR mutation along with a recent COVID-19 infection.

Case descriptions

Case I

A 17-year-old female with vertebral disc herniation and scoliosis presented with left lower extremity pain and swelling. This was associated with intermittent chest pain, 8/10 in intensity, radiating to the back, and shortness of breath. Physical examination revealed tenderness on deep palpation of the left thigh and a positive Homans' sign on left. There was no cyanosis or clubbing or gross deformities. Ultrasound (US) venous duplex of left lower extremity confirmed deep venous thrombosis (occlusive thrombi of greater saphenous, common femoral, and profound femoris; and partial occlusion of a superficial femoral vein). Computerized Tomography Angiography (CTA) chest showed large bilateral pulmonary emboli. The patient was started on Enoxaparin at 1 mg/kg/dose subcutaneously every 12 hours with an anti-factor Xa goal of 0.6-1.0 IU/mL. Further investigations demonstrated positive COVID-19 serology for IgG. History was also significant for OCPs consumption that was started for menstrual cycle regulation. She was advised not to take estrogen-containing pills. Thrombophilia workup revealed homozygous C677T MTHFR mutation and normal homocysteine level at 8.9 mcmol/L (0-11 mcmol/L). The patient improved clinically and was discharged on Enoxaparin 60 mg BID for six weeks with advice to discontinue high-intensity and high-contact sports until cleared.

Case II

A 17-year-old female presented with a 5-day history of sharp, continuous, left shoulder pain, 7/10 in intensity, aggravated by inspiration. There was an associated abdominal pain and shortness of breath. Due to post-exertional worsening pain, a workup including labs and imaging was initiated. The abdominal ultrasound reported an infrarenal inferior vena cava thrombus. Computed Tomography Angiography (CTA) chest showed small segmental and subsegmental pulmonary emboli in the left lower lobe pulmonary artery and non-enhancing thrombus within the right aspect of the infrarenal inferior vena cava, measuring 3.7 x 1.2 x 0.9 cm. The patient was referred to our institution for further management. On further exploring the history, the patient was on OCPs that were started 9 months ago due to heavy periods. She had a significant family history of the hypercoagulable condition (her maternal grandfather had a myocardial infarction at the age of 34 years). Physical examination was remarkable for diminished breath sounds at both bases and crackles on the left lower base. Further investigation revealed a positive COVID-19 IgG status. D-dimer was increased. Treatment with Enoxaparin was started with anti-factor Xa activity measured to reach the goal of 0.6-1 IU/mL. The patient clinically improved and was discharged on a therapeutic dose of Enoxaparin. Thrombophilia workup was remarkable for heterozygous C677T MTHFR and a heterozygous G-20210-A prothrombin II mutation. Homocysteine level was also normal at 6.5 mcmol/L (0-11mcmol/ L).

Case III

A 15-year-old female presented with fever and right lower quadrant (RLQ) pain a week following an appendectomy. On physical examination, her abdomen was soft, mildly distended, and tender in right lower quadrant. Rovsing's sign, rebound sign, and McBurney's sign were all positive. A CT scan of the abdomen was done, which showed 5 x 3 x 2 cm abdominal fluid collection and found a superior mesenteric vein clot. The patient was found to have a family history of blood clots in the mother and maternal grandfather. Investigation revealed COVID-19 IgG positive. Thrombophilia work-up showed compound heterozygous C677T and A1289C MTHFR mutation. The homocysteine level was normal at 8.9 mcmol/L (0-11 mcmol/L). Enoxaparin was started at a treatment dose of 1 mg/kg/dose every 12 hours with the goal of an anti-factor Xa level between 0.6-1 IU/mL. The patient improved significantly and was discharged on Enoxaparin.

Discussion

Since the beginning of the COVID-19 pandemic, we have seen increasing numbers of thrombosis in young, healthy individuals. Different studies have shown the association between COVID-19 infection and an increase in the incidence of a hypercoagulable state. Our patients developed significant thrombi in the form of DVT, infrarenal inferior vena cava thrombus, pulmonary emboli, and superior mesenteric vein clots. An extensive workup was done to elicit the congenital/ acquired etiology of the thrombus (See Table 1) All the 3 cases we present are females ranging from 15-17 years old. Two patients had an extensive family history of a clot. While OCPs may have contributed to the thrombus in two of the three patients, the fact that they had been on OCPs for a considerable length of time before the thrombus raises the possibility of a more recent trigger to thrombus development. One patient had heterozygous G-20210-A prothrombin II mutation. All three patients had a mutation on the MTHFR gene (one with homozygous C677T mutation, one with heterozygous C677T mutation, and one compound heterozygous for C677T and A1289C mutation). Found on chromosome 1, this gene encodes the rate-limiting enzyme in the series of reactions forming methionine from homocysteine. A deletion in this enzyme would lead to hyperhomocysteinemia, which has been the proposed link between MHTFR mutations and hypercoagulability **[10]**, despite some studies showing controversial results **[11]**. C677T MHTFR mutation is a common mutation that is linked to hyperhomocysteinemia and thus hypercoagulability **[10,12]**. The C677T mutation alone, even in its heterozygous form, is shown to increase the risk of ischemic stroke by 30 % if present **[14]**. This mutation substitutes an alanine with a valine, decreasing the activity of the resulting protein. If homozygous, it leads to hyperhomocysteinemia, which is thought to increase hypercoagulation risk **[14]**. Homocysteine level was normal in all three patients making this mutation unlikely to be a triggering event. All the patients were managed on a therapeutic dose of Enoxaparin for 6 weeks which resulted in successful clot resolution.

In summary, it is interesting to note that despite having inherited or acquired risk factors for thrombophilia, the thrombotic event was preceded by COVID-19 infection in each of the three patients. The hypercoagulable state is likely a culmination of all these risk factors, and it is impossible to determine the extent of contribution of each of these risk factors to thrombus formation.

Table 1: Summary of the patient profile and the work-up labs

Case	Age/ Sex	Presenting complaints	Diagnosis	Hypercoagulable family history	Acquired risk factors	Inherited risk factors	D-Dimer	Homocysteine
I	17yo/ F	Chest pain & left leg pain	DVT (occlusion of greatersaphenous, common femoral, and profunda femoris) & B/l pulmonary emboli	Unremarkable	OCPs & COVID-19 IgG +ve	Homozygous C677T MTHFR mutation	23.16 mg/L (0.19-0.5)	8.9 mcmol/L (0-11)
II	17yo/ F	Abdominal pain & left shoulder pain	Infrarenal IVC &Pulmonary emboli	Maternal grandfather had myocardial infarction at 34 years old	OCPs & COVID-19 IgG +ve	HeterozygousC677T MTHFR Mutation & Heterozygous G-20210-A prothrombin II mutation	> 35.20 mg/L (0.19-0.5)	6.5 mcmol/L (0-11)
III	15yo/ F	Fever & RLQ pain	Superior mesenteric veinclot	Extensive family history of blood clots	COVID-19 IgG +ve	Compound heterozygous C677T & A1289C MTHFR mutation	n/a	8.9 mcmol/L (0-11)

Conclusion

In conclusion, this case series highlights the association between MTHFR gene mutation and COVID-19 infection that led to the development of a thrombus. Patients with COVI-19 infection should thereby undergo a thorough evaluation of all risk factors for thrombophilia and whenever necessary, laboratory investigation should be performed to determine their risk status. Timely identification of risk status and implementation of prophylactics measures can prevent significant thrombus in high-risk patients. Further research needs to be done to verify the association between the MTHFR gene and COVID-19 infection.

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