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Journal

Proceedings of UCLA Health, 22(1)

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Publication Date

2018-02-27

CLINICAL VIGNETTE

Life-Threatening Venous Thrombosis and Bowel Ischemia Associated with Prothrombin G20210A and MTHFR Mutations – Report of Four Cases and Review of Literature

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Introduction

Prothrombin gene mutation G20210A was first shown to be associated with increased risk of venous thrombosis by Poort et al in 1996. Prothrombin G20210A mutation was present in 1% healthy controls compared to 18% in patients with venous thrombosis.¹ Heterozygotes for G20210A mutation have approximately 30% higher plasma prothrombin levels than normal controls.^{1,2} The prothrombin gene G20210A mutation is the second most common inherited thrombophilia after the factor V Leiden mutation.

Hessner et al studied six racial groups (African American, Asian Indian, Caucasian, Hispanic, Korean, Native American), and compared them to patients with thrombosis for the prothrombin G20210A, factor V Leiden and methylene tetrahydrofolate reductase (MTHFR) C677T mutations. The prothrombin G20210A and factor V Leiden allele frequencies in the thrombosis patients, 3.2% and 9.5%, were significantly higher than those in the random Caucasians, 1.3% and 1.8%, giving the relative risk of venous thrombosis being 2.4-fold for carriers of the prothrombin G20210A allele and 4.5-fold for carriers of the factor V Leiden. In addition to pulmonary embolism and deep vein thrombosis, prothrombin G20210A has been associated with other life-threatening thrombosis, such as cerebral vein thrombosis. Prothrombin G20210A was found in 103/868 of the patients with cerebral venous thrombosis and 105/3999 of the healthy control in a meta-analysis giving an overall odd ratio of 5.838; the OR 9.69 in Italian studies, 7.02 Brazilian studies, 3.77 German studies.^{3,4} Prothrombin G20210A has also been associated with abdominal vein thrombosis, hepatic vein, portal vein and mesenteric vein thrombosis,⁵ peripheral arterial disease of the lower limbs,^{6,7} myocardial infarction and ischemic stroke.⁷

When first described, some experts cast doubt to the significance of prothrombin G20210A mutation in venous thrombosis. Souto et al described 2 individuals homozygous for G20210A who did not exhibit symptoms while heterozygous individuals in the same family exhibited the disease, illustrating that G20210A may not be as strong as most of the previously described genetic risk factors.⁸ Girolami et al report that homozygous prothrombin G20210A mutation remain asymptomatic despite the presence of associated risk factors, casting doubt to the prothrombotic significance of this mutation.^{9,10}

Some speculate that prothrombin G20210A mutation by itself may not be enough to trigger thromboembolic disease.¹¹

We report four consecutive cases of life threatening thrombosis, 2 cases of PE/DVT and 2 cases of small bowel ischemia, associated with prothrombin G20210A mutation, each associated with additional thrombotic risk factors.

Case Histories

Case #1

A 41-year-old Hispanic male presented with acute onset of left chest pain, shortness of breath and left leg pain about 4 weeks after an arthroscopic surgery for a torn meniscus of the left knee. Venous doppler study of both lower extremity demonstrated acute deep vein thrombosis involving the left superficial femoral and popliteal veins. CT scan of the chest revealed possible filling defects in the lingula of left lung and right lower lobe suggestive of pulmonary embolism. He was started on enoxaparin and subsequently wardarin. His mother and maternal grandmother had history of deep vein thrombosis in the past. Lupus anticoagulant and antiphospholipid antibodies (cardiolipin and beta-2 glycoprotein I antibodies) were negative. Factor V Leiden was negative. Protein C, protein S, antithrombin III were normal. Blood homocystine level was 6.5 $\mu\text{mol/L}$ (normal: <10.4). MTHFR was homozygous for C677T mutation. Prothrombin gene was heterozygous for G20210A mutation.

Case #2

A 57-year-old Hispanic female with history of hypertension presented with progressive shortness of breath for two weeks. Emergent CT pulmonary angiogram showed extensive bilateral pulmonary embolism. Venous doppler study of the lower extremities showed deep vein thrombosis of the left popliteal vein. She was started on heparin infusion that was later switched to rivaroxaban. WBC 5,300/ μL , hemoglobin 9 g/dL, MCV 74.4 fL, platelet 364,000/ μL . Recent upper endoscopy and colonoscopy were unremarkable except for mild esophagitis and gastritis. Iron study with ferritin 103 ng/ml was consistent with anemia of chronic disease. Hemoglobin electrophoresis was

consistent with alpha-thalassemia carrier. Thrombophilia work-up showed presence of lupus anticoagulant with dilute Russell viper venom time (dRVVT) being prolonged but antiphospholipid antibody (cardiolipin and beta-2 glycoprotein I antibodies) was negative. Protein C, protein S and antithrombin III were normal. Blood homocysteine level was 4.1 $\mu\text{mol/L}$. Factor V Leiden was negative. Prothrombin gene was heterozygous for G20210A mutation. MTHFR was double heterozygous for MTHFR C677T and A1298C mutations. Tumor markers, CEA, CA19-9, CA125 and AFP, were normal. CT scan abdomen and pelvis with contrast showed no significant abnormality. She also complained of chronic knee pain with left knee effusion. Rheumatoid factor was elevated to 441 IU/mL and anti-nuclear antibody was positive with 1:1,280 titer and speckled pattern, suggestive of mixed connective tissue disease. Double-stranded DNA antibody was negative. C3 level decreased to 79 mg/dL, and C4 level 12 mg/dL.

Case #3

A 46-year-old Hispanic female woman presented with polyarthralgias and recurrent lower chest and abdominal pain, worse after eating, for eight months. She had menorrhagia and been taking birth control pills for several years. She was admitted to the hospital with CT scan abdomen and pelvis showing dilated small bowel loops suggestive of small-bowel obstruction, right pleural effusion and ascites. CT pulmonary angiogram showed no evidence of pulmonary embolism, but there was right pleural effusion and scattered small ground-glass opacities. She underwent emergent exploratory laparotomy that revealed ischemic small-bowel. An 88-cm segment of small-bowel was resected with primary anastomosis. The pathology revealed transmural acute ischemic enteritis with epithelial necrosis and marked hemorrhage, and subepithelial vessels with thrombosis. The mesentery showed vascular congestion, organizing thrombosis and acute inflammation. In view of polyarthralgias, pleural effusion, interstitial lung changes and markedly elevated C-reactive protein >400 mg/L, systemic vasculitis causing bowel ischemia was diagnosed by the rheumatologist. After surgery, the patient was started on high dose intravenous immunoglobulin, prednisone and mycophenolate. Subsequent testing for vasculitis showed: ANA <1:40, ENA antibody negative, ds-DNA antibody negative, C3 and C4 levels unremarkable, and Rheumatoid factor < 3 IU/ml. Cyclic citrullinated peptide antibody was negative. Mitochondrial, smooth muscle actin, myeloperoxidase and serine proteinase 3 antibodies were negative. Anti-phospholipid antibody panel was negative and Quantitative IgG, IgM and IgA were within normal limits. Serum protein electrophoresis showed no definite M-spike.

Postoperative abdominal CT angiogram showed chronic portal vein thrombosis with cavernous transformation and diffuse mesenteric stranding. With the new finding of portal venous thrombosis, the patient was started on heparin infusion. Thrombophilia workup revealed antithrombin III 83%, protein C activity 68%, protein S activity 80%. Factor V Leiden was negative. Prothrombin gene was heterozygous for G20210A

mutation. MTHFR showed double heterozygous C677T and A1298C mutations. Blood homocysteine level was 5 $\mu\text{mol/L}$. CEA, CA15-3 and CA 19-9 were normal. CA-125 was elevated to 455.6 IU/ml that decreased to 68 IU/ml three months later spontaneously. Ultrasound of the pelvis showed multiple leiomyomata. She was discharged on warfarin, mycophenolate and prednisone and instructed never to take hormonal contraceptives.

Case #4

A 65-year-old Hispanic male with history of hypertension, hyperlipidemia and end-stage renal disease on hemodialysis presented with acute onset of severe and diffuse abdominal pain. CT scan abdomen and pelvis without contrast showed extensive pneumatosis intestinalis involving the mid to distal small bowel loops, as well as inside the liver. There was severe aortoiliac atherosclerosis (Figures 1 & 2). He underwent emergent exploratory laparotomy that revealed gangrenous small bowel. A 120cm-long small bowel segment was resected with primary anastomosis. Pathology revealed small bowel with ischemic and necrotic changes. Postoperatively, the patient was started on heparin infusion and later was switched to oral warfarin upon discharge. Thrombophilia workup revealed protein S, protein C and antithrombin III levels being normal. Lupus anticoagulant by dRVVT was negative and antiphospholipid antibody was negative. Factor V Leiden was negative. CEA, CA 19-9, PSA and alpha-fetoprotein were within normal limits. WBC was 2,300/ μL , hemoglobin 7.6 g/dL, and platelet 103,000/ μL . Flow cytometry of the blood was negative for PNH phenotype. MTHFR was heterozygous for C677T mutation. Blood homocysteine level was 8.3 $\mu\text{mol/L}$. Prothrombin gene was heterozygous for G20210A mutation. The ischemic small bowel was most likely due to heterozygous MTHFR and prothrombin gene mutation and extensive atherosclerosis. For the pancytopenia, antinuclear antibody, Hepatitis B and C serology were negative. Iron panel, vitamin B12 and folate levels were normal. Because of persistent pancytopenia, bone marrow examination two months later was unremarkable with normocellular trilineage hematopoiesis. Cytogenetic study of the bone marrow showed 46,XY[20], and fluorescence in situ hybridization study using the MDS probes (chromosome 5, 7, 8 and 20 probes) was negative.

Discussion

All our cases of prothrombin G20210A are heterozygous mutations that presented at relatively older age, i.e. over 40. (see Table) They are all associated with MTHFR mutations, one homozygous C677T, one heterozygous C677T and two double heterozygous C677T/A1298C mutations. All our patients are Hispanics. The allelic frequency of MTHFR mutation has been reported to be very high among American Hispanics, 0.41 for C677T and 0.20 for A1298C.¹² Given the prevalence of MTHFR homozygous C677T is 19.4% in Mexican-Americans, compared to 1.2% in non-Hispanic blacks and 11.6% non-Hispanic whites,^{13,14} it is not uncommon that prothrombin

G20210A and MTHFR C677T mutations may co-exist in the same individual of Hispanic descent.

MTHFR catalyzes the reduction of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate that serves as a co-factor in methylation of homocysteine to methionine. Homozygous C677T mutation MTHFR is associated with 70% reduction in MTHFR enzyme activity and heterozygous mutation with 35% reduction¹⁵ resulting in accumulation of homocysteine; A1298C mutation has a similar reduction in enzyme activity.^{16,17} MTHFR mutations have been associated with increased venous thrombosis, presumably due to elevated blood homocysteine levels.^{18,19} It is intuitive that being positive for both prothrombin G20210A and MTHFR mutations would explain the life-threatening thrombosis of all four patients. However, recent studies revealed that homozygous MTHFR C677T mutation was not a significant risk factor for venous thrombosis, either alone or in combination with the prothrombin G20210A and/or the factor V Leiden.^{20,21} Of note, all our patients have normal blood homocysteine levels.

In addition to the co-existing MTHFR mutations, all our patients with heterozygous prothrombin G20210A mutations

also have other thrombotic risk factors, namely, post-arthroscopic knee surgery, over-weight, connective tissue disease, vasculitis, hormonal contraceptives and extensive atherosclerosis. These findings are in keeping with the suggestion that prothrombin G20210A mutation by itself may not be enough to trigger thromboembolic disease.²²

Prophylactic use of systemic anticoagulation is not indicated in incidental finding of prothrombin G20210A mutation without thrombosis. For patients with thrombosis and prothrombin G20210A mutation, what should be the optimal duration of systemic anticoagulant? For the case 1, DVT/PE was probably provoked by the recent arthroscopic knee surgery, and we recommend systemic anticoagulant for 6 months. For case 2, since the DVT/PE was spontaneous and unprovoked, we recommend at least one full year of systemic anticoagulant. According to CHEST guidelines in 2016, life-long anticoagulant is recommended for patients with unprovoked thromboembolism with otherwise low or moderate risk of bleeding.²³ For cases 3 and 4, because of the severe life-threatening nature of the thrombosis and the underlying prothrombotic diseases, we recommend life-long anticoagulation.

Table - Summary of the Four Cases

	Presentation	Prothrombin G20210	MTHFR	Others
Case 1 M/41	PE/DVT	Heterozygous G20210	Homozygous MTHFR C677T	Arthroscopic knee surgery; BMI 29.53
Case 2 F/57	PE/DVT	Heterozygous G20210	Double heterozygous MTHFR C677T/A1298C	Connective tissue disease; BMI 15.52
Case 3 F/46	Ischemic small bowel	Heterozygous G20210	Double heterozygous MTHFR C677T/A1298C	Systemic vasculitis, hormonal contraceptive; BMI 27.1
Case 4 M/65	Ischemic small bowel	Heterozygous G20210	Heterozygous MTHFR C677T	Extensive aortic atherosclerosis; BMI 19.64

Figures



Figure 1: Extensive pneumatosis intestinalis of the small bowel and portal veins on admission and complete resolution after surgery.

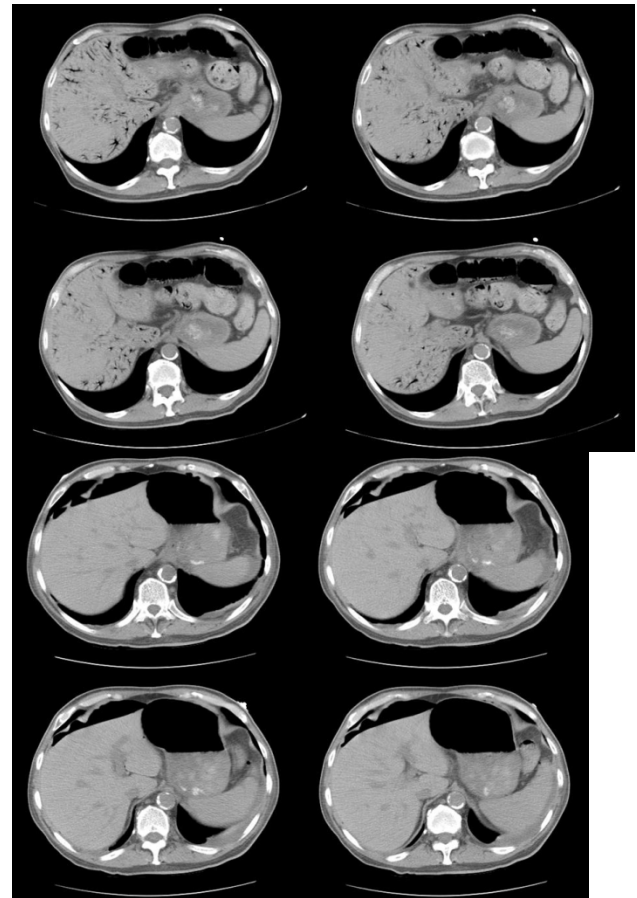


Figure 2: Extensive pneumatosis intestinalis of the small bowel and portal veins on admission and complete resolution one week after surgery.

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Submitted February 27, 2018