• CASE REPORT •

Autosomal-dominant Inheritance of the Prothrombin Gene Mutation in a Puerto Rican Family: A Case Study

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Splenic infarction is rare and the prothrombin gene mutation (PGM) is not commonly observed in Puerto Rico. PGM is present in 1% of the general population, and in 7% of the people with deep venous thrombosis (DVT); it is found in up to 40% of patients with splenic-portal-mesenteric thrombosis. Our study has identified a Puerto Rican family of four generations whose members all have inherited PGM in an autosomal dominant manner. The eldest member of the family, an 82-year-old male, presented with DVT of the lower extremity. The man's 62-year-old daughter had suffered a splenic infarction; his 37-year-old grandson presented with superficial and deep vein thrombosis (SDVT), and his great-grandson of 8 years was asymptomatic at the time of the report. This is the second report of PGM as the cause of a hypercoagulable state and the first reported PGM-related splenic infarction in Puerto Rico. We need to test for genetic hypercoagulable states in the members of Puerto Rican families with thromboembolism. Once testing has revealed the existence of such states in a given family, it is important that the family members receive genetic counseling. [*P R Health Sci J 2012;4:232-234*]

Key words: Prothrombin Gene Mutation, Spleen Infarct, Puerto Rico

Venous thromboembolism (VTE) is a multifactorial disease that promotes venous thrombus formation; VTE generally occurs in the presence of three factors known collectively as Virchow's triad: alterations in blood flow (i.e., stasis), vascular endothelial injury, and alterations in the constituents of the blood (i.e., inherited or acquired hypercoagulable state). It is generally accepted that the eventual clot formation is caused by the interaction of genetic and other factors (1). Among the inherited risk factors are single nucleotide polymorphisms (SNP's) and (the most common) PGM (2). PGM is the most recent cause of hereditary thrombophilia to have had the genetic mutation elucidated. It is prevalent in white populations and has an overall carrier rate of 1.0% (3). In 1996, Poort et al. (4) described a guanine to adenine substitution in the 3'untranslated region of the prothrombin gene with the only apparent phenotypic manifestation being an elevated plasma concentration of prothrombin (115% to 130%). The mechanism for the hypercoagulable state is still under study, but it is reasonable to conclude that the elevated plasma prothrombin concentration provides an increased substrate for thrombin formation (4). Elevated levels of PGM may also inhibit the activated protein C (APC)- mediated inactivation of factor V Leiden leading to a procoagulant state (5).

In carriers, the relative risk for VTE is increased between two-and-six-fold over that risk found in non-carriers (2). It is associated with cerebral vein thrombosis (6) and ischemic stroke (7, 8, 9), the recurrence of DVT's following discontinuation of anticoagulant therapy and arterial thrombosis (10, 11), multiple hepatic infarctions (12), thrombophilia in pregnancy (10), and portal-splenic-mesenteric venous thrombosis (13, 14).

We describe a Puerto Rican family of four generations, the members of which have thrombophilia and were identified as having PGM. One of them presented with splenic infarction, which is a rare manifestation of this hypercoagulable state: only one case, has so far been reported in the medical literature.

Case Report

Case no. 1

A 62-year-old female presented with non-specific gastrointestinal symptoms and marked left upper-quadrant abdominal pain in March of 2006. She had diabetes type II, high blood pressure, and peripheral venous insufficiency. An examination revealed that she had a normal pressure and pulse. There was generalized upper abdominal tenderness, but no guarding or rebound. There was no hepatosplenomegaly. Her cardiorespiratory examination was unremarkable. Nuclear

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imaging of the liver and spleen showed a photopenic defect in the spleen area suggestive of ischemic spleen infarct. A thrombophilia screen for anticardiolipin antibodies, lupus anticoagulant, protein C and S deficiency, factor V Leiden mutation and paroxysmal nocturnal haemoglobinuria was negative. She was found to have one copy of the prothrombin G20210A mutation. Her father, two brothers, one daughter, and two sons were subsequently tested and her father (case no. 2) and one son (case no. 3) were found to be positive for PGM, with one copy of the G20210A mutation.

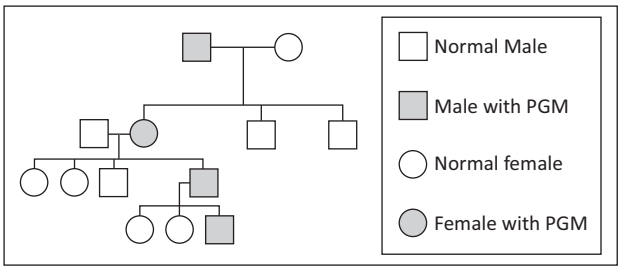

Figure 1. Autosomal Dominant Inheritance of PGM. Family pedigree showing PGM inheritance.

Case No. 2

This is an 82-years-old male with benign prostatic hyperplasia with a history of having had a transurethral resection of the prostate (in 1996); in June of 2001, he presented with a swollen and tender left leg, which - according to the patient - had evolved over the previous few days. A venous Doppler/duplex of his lower extremities revealed an acute DVT of the left common deep and superficial femoral veins and one of the peroneal veins. He was admitted and anticoagulated successfully for 3 moths. Since his daughter was a carrier of PGM, a work-up of the patient was done; it revealed that he had one copy of the G20210A mutation.

Case no. 3

A 37-year-old male presented with superficial vein thrombosis of the right laser saphenous vein in February of 2005. He had a history of having had peripheral vein insufficiency since childhood and in March of 2004 had had outpatient surgery for varicose veins (right leg); he has been using aspirin since then. Since both his mother and his maternal grandfather with PGM and TVE, thrombophilia screen was performed, and he was also found to have one copy of the prothrombin G20210A mutation. In view of the strong family history of PGM-related thrombophilia, his three children were screened in 2005; one son, 8 years old, was found to have one copy of PGM (case no. 4).

Case no. 4

An 8-year-old old child, asymptomatic, healthy, and with normal development, was found upon examination to be positive for PGM, as stated above. He was not taking any medication.

Discussion

A 21-kb pair gene localized on chromosome 11 encodes prothrombin. Poort et al. identified PGM in 1996, and since then several cases have been reported; these individuals also report suffering from DVT of the upper and lower extremities, celiac axis, spleen, liver, portal system, mesentery, central nervous system (CNS), among other sites (15).

The cases discussed herein go together with those already report in the current literature and add PGM as a cause of hypercoagulable states in Puerto Rican patients (7, 8). Prior reports on Puerto Rican patients include that of Y. Reyes-Iglesias et al., which describes the coexistence of the primary antiphospholipid syndrome and protein S deficiency (two recognized prothrombotic states) in two adults from the same family who both suffered from ischemic strokes (8), and that M. Cruz-Amy and R. Hunter-Mellado, which describes three patients with Factor V Leiden mutation, two of which patients were found to have the prothrombin G20210A mutation (7). We present the second case of splenic infarction associated with PGM (case 1). The first case describes a fifteen-year-old female who was taking a third-generation combined oral contraceptive pill to treat dysmenorrhea and presented with abdominal pain and vomiting. A computed tomography scan was performed and revealed coeliac axis thrombosis and splenic infarction. PGM was discovered to be heterozygous in the patient as well as her mother and younger brother (14).

With respect to the members of these families, it is important that health care providers be aware that patients with thrombophilia should undergo genetic testing and receive genetic counseling (as recommended by Elizabeth A. Varga) (16). Genetic counselors, help both physicians and patients to identify individuals and families at risk for inherited thrombophilia; they offer and explain genetic testing to patients and families, facilitate patient-focused decision-making, obtain informed consent prior to testing, interpret test results, explain inheritance patterns, discuss the implications of thrombophilia to family members, and provide education and support resources. So, genetic counseling was provided to each member of the family.

Conclusion

We need to search for PGM in our Puerto Rican families with thrombophilia. Once identified, individuals with this inherited mutation need to be educated in order to prevent and reduce the morbidity and mortality associated with these conditions. Our description of splenic infarction related to the PGM illustrates that an unusual or atypical localization of venous thrombosis may be a manifestation of thrombophilia. This emphasizes the importance of genetic screening in these cases, even when there are no other specific signs or symptoms.

Resumen

El infarto del bazo es raro y la Mutación del Gene de Protrombina (MGP) no es común en Puerto Rico. La MGP se encuentra en 1% de la población general, 7% de la gente con trombosis venosa profunda (TVP) y hasta un 40% de los pacientes con trombosis esplénica-portal-mesentéricas. Se ha identificado una familia puertorriqueña con cuatro generaciones con herencia autosómica dominante de la MGP. El paciente de mayor edad se presentó con un TVP de las extremidades inferiores. La hija tuvo un infarto del bazo, el nieto tuvo trombosis venosa superficial y profunda (TVSP) de las extremidades inferiores y el biznieto es un niño asintomático hasta el momento de este reporte. Este es el segundo reporte de MGP como una causa de estado hypercoagulable y el primero relacionado a infarto del bazo en Puerto Rico. Nosotros tenemos que investigar los estados hypercoagulable genéticos en familias puertorriqueñas con trombo-embolismo. El aspecto relevante de estas familias es que tenemos que realizar consejería genética una vez se obtengan estas pruebas.

References

1. Hirsh J, Colman RW, Marder VJ, George JN, Clowes AW. Overview of thrombosis and its treatment. In Colman RW, Hirsh J, Marder VJ, Clowes AW, George JN (editors). Hemostasis and Thrombosis: Basic Principles & Clinical Practice, 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2001;1071-1084.
2. Zivelin A, Rosenberg N, Faier S, Kornbrot N, Peretz H, Mannhalter C, et al. A single genetic origin for the common prothrombotic G20210A polymorphism in the Prothrombin Gene. Blood 1998;92:1119-1124.
3. Naeem MA, Anwar M, Ali W, Ayyub M, Nasiruddin N. Prevalence of prothrombin gene mutation (G-A20210 A) in general population: A pilot study. Clinical and Applied Thrombosis/Hemostasis 2006;12:223-226.
4. Poort SR, Rosendaal FR, Reitsma PH, Bertina RM. A common genetic variation in the 3'-untranslated region of the prothrombin gene is associated with elevated prothrombin levels and an increase in venous thrombosis. Blood 1996;88:3698-3703.
5. Smirnov MD, Safa O, Esmon NL, Esmon CT. Inhibition of activated protein C anticoagulant activity by prothrombin. Blood 1999;94:3839-3846.
6. Huberfeld G, Kubis N, Lot G, Ripoll L, Chaine P, Drouet L, Woimant F. G20210A prothrombin gene mutation in two siblings with cerebral venous thrombosis. Neurology 1998;51:316-317.
7. Cruz-Amy M, Hunter-Mellado R: Factor V Leiden thrombophilia: presentation of three patients and a literature review. Bol Asoc Med PR 2006; 98:213-221.
8. Reyes-Iglesias Y, Ortíz AA, Goitía DM, Meléndez R. Coexistence of primary antiphospholipid syndrome and protein S deficiency in a hispanic man with ischemic stroke. South Med J 1998;91:296-298.
9. De Lucia D, Papa ML, Ammendola F, Pezzella S, Del Giudice V, Marrotta R, Renis V et al. Association of elevated levels of prothrombin fragment 1+2 and Arg506 to Gln mutation in patients with a history of ischemic stroke. Journal of Neurosurg Sci 1999;43:45-50.
10. Frenkel EP, Bick RL: Prothrombin G20210A gene mutation, heparin cofactor II defects, primary (essential) thrombocythemia, and thrombohemorrhagic manifestations. Semin Thromb Hemost 1999;25:375-386.
11. Almawi WY, Tamim H, Kreidy R, Timson G, Rahal E, Nabulsi M, et al. A case control study on the contribution of Factor V-Leiden, Prothrombin G20210A, and MTHFR C677T mutations to the genetic susceptibility of deep venous thrombosis. J Thromb Thrombolysis 2005;19:189-196.
12. Emmanuelle T, Husein B, Iqbal J , Macheta M, Isaacs P: Concomitant homozygosity for the prothrombin gene variant with mild deficiency of antithrombin III in a patient with multiple hepatic infarctions: a case report. J Med Case Rep 2010;4:122.
13. Frutos Bernal MD, Fernández Hernández JA, Carrasco Prats M, Soria Cogollos T, Luján Mompeán JA, Hernández Agüera Q, Parrilla Paricio P. Portal-splenic- mesenteric venous thrombosis secondary to a mutation of the prothrombin gene [in Spanish]. Gastroenterol Hepatol 2005;28: 329-332.
14. Gould J, Deam S, Dolan G. Prothrombin 20210A polymorphism and third generation oral contraceptives – a case report of coeliac axis thrombosis and splenic infarction. Thromb Haemost 1998;79:1214-1215.
15. Marder VJ, Matei DE. Hereditary and acquired thrombophilic syndromes. In Colman RW, Hirsh J, Marder VJ, Clowes AW, George JN (editors). Hemostasis and Thrombosis: Basic Principles & Clinical Practice, 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2001: 1243-1275.
16. Varga EA. Genetic counseling for inherited thrombophilias. J Thromb Thrombolysis 2008;25:6-9.