MEDWIN PUBLISHERS
Committed to Create Value for Researchers

Haematology International Journal
ISSN: 2578-501X

An Interesting Case of a Patient with Prothrombin Gene (G20210) Mutation Developing a Thromboembolic Stroke

Miller M[1,2]*, Klein J[1,2] and Raedy C[1,2]

[1]Michigan State University, College of Osteopathic Medicine, USA
[2]Henry Ford Health System, USA

***Corresponding author:** Mackenzie Miller, Michigan State University, College of Osteopathic Medicine, USA, Tel: 248-804-2724; Email: mill3507@msu.edu

Case Report
Volume 8 Issue 2
Received Date: September 23, 2024
Published Date: October 07, 2024
DOI: 10.23880/hij-16000263

Abstract

Introduction: Stroke is frequently diagnosed in the Emergency Department in older adults. Signs and symptoms are well-known within the patient population, leading to established stroke workups in the hospital setting. When a younger adult presents with a stroke, an extensive workup is warranted for non-modifiable risk factors including hypercoagulability states, malignancy, and medication.

Case Report: We present a case of a 51-year-old male with an extensive past medical history including ischemic strokes, left ventricular thrombus, and myocardial infarction, who presented with a stroke. After an extensive workup, he was diagnosed with Prothrombin gene (G20210A) mutation.

Discussion: Prothrombin gene (G20210A) mutation is the second most common inherited thrombocytopenia and is highly associated with venous clots. However, extremely rare cases have occurred involving arterial clots, specifically in the brain.

Conclusion: This case highlights the wide range of etiology for stroke and that extensive workup, particularly in patients under the age of 65, is critical to preventing future events.

Keywords: Thrombotic Stroke; Coagulopathy; Hematology; Neurology; Genetic Mutation

Abbreviations

CT: Computed Tomography; MRI: Magnetic Resonant Imaging; PTT: Partial Thromboplastin Time; PT: Prothrombin Time; PCR: Polymerase Chain Reaction; INR: International Normalized Ratio.

Introduction

Stroke is a broad term for neuronal injury due to vascular etiology. Stroke is the fifth leading cause of death in the United States, and the prevalence increases with age. 75% of all cases occur in patients over the age of 65, and 90% of all cases occur in patients over the age of 50 [1,2].

Stroke is categorized into two general types, ischemic and hemorrhagic. In the case of ischemic stroke, patients present with sudden onset neurological symptoms that correlate with the area of the brain where vascular supply is being occluded. Ischemic strokes are classified as being thrombotic or embolic in nature. Thrombotic strokes are a result of decreased vascularization of the brain due to vascular obstruction resulting from a clot. The typical workup includes a computed tomography (CT) scan with

CC BY

contrast, magnetic resonant imaging (MRI), complete blood count, cholesterol, EKG, echocardiogram, doppler/carotid ultrasound, and serum electrolytes [1].

Common etiologies of ischemic and hemorrhagic stroke in patients over 65 are atrial fibrillation, atherosclerosis, and hypertension, while there are additional young adult-specific causes of stroke including cervical dissections, vasculitis, connective tissue disorders, patent foramen ovale, and hypercoagulability states such as pregnancy, malignancy, medications, and genetic disorders [1].

Hypercoagulability is a pathologic state of over-coagulation or coagulation with no active bleeding. In the normal response to spontaneous bleeding, clot formation is dependent on both primary and secondary hemostasis. Primary hemostasis consists of platelets forming the initial plug-in response to exposure to the endothelial cell, while secondary hemostasis consists of the coagulation pathway. The coagulation pathway is divided into the intrinsic and extrinsic pathways that converge with fibrin activation. The intrinsic pathway consists of factors I, II, IX, X, XI, and XII. The pathway begins when factor XII is activated to XIIa, resulting in a cascading event of factor activation leading to coagulation [3]. In comparison, the extrinsic pathway is shorter and begins with tissue factor in response to vessel damage. Tissue factor activates VII, which in turn activates factor X and becomes the common pathway. The common pathway uses prothrombin, thrombin, the fibrin to add fibrin mesh and stabilize the final platelet plug. Antithrombin, protein C, and protein S all act to prevent over-coagulation. Antithrombin decreases coagulation by limiting factor X activation and protein C and protein S inactivating factors V and VIII. These proteins can be measured in the blood directly [3].

If hypercoagulability syndromes are suspected workup includes a more detailed family history and evaluation of risk factors, as well as confirmation blood and genetic testing [4]. Primary hemostasis is measured using the bleeding time, and the intrinsic pathway and extrinsic pathways are measured by partial thromboplastin time (PTT) and prothrombin time (PT), respectively. The international normalized ratio (INR) is PT divided by PTT [3,5]. Antithrombin, protein C, and protein S are screened using functional assays [4]. Genetic testing uses polymerase chain reaction (PCR), with the most common mutations involving Factor V Leiden, prothrombin, Factor VIII, antithrombin, protein C, and protein S [4].

Here we present a case of a 51-year-old male who developed a thromboembolic stroke and was later found to have a prothrombin gene (G20210A) mutation.

Case Report

A 51-year-old male with a past medical history of both ischemic and hemorrhagic strokes, ventricular thrombus, coronary artery disease status post-CABG, and ulcerative colitis, presented to the emergency department for altered mental status and fever. The patient was discharged two days prior from a different hospital after an ulcerative colitis flare, *Clostridium difficile* infection, and recurrent gastrointestinal bleeding. In that prior hospital visit, the patient's long-term Warfarin therapy was discontinued due to active gastrointestinal bleeding and no visualization of the ventricular thrombus on imaging. During this emergency department visit, the patient was altered with an NIH stroke scale of 25, had a Pre-Modified Rankin scale of 3, and had urinary incontinence. The last known normal was at 10:30 pm the night before. On exam, the patient was ill-appearing and diaphoretic; his vitals were significant for a blood pressure of 94/53 and a pulse of 143. Upon neurological exam, the patient had a right gaze deviation, tremor of the right upper extremity, no spontaneous movements of the left upper extremity nor the bilateral lower extremities, and global aphasia.

The patient was intubated and CT scan without contrast which was negative for hemorrhagic or ischemic changes. CT with contrast and subsequent angiography revealed acute infarct within the mid to distal right anterior cerebral artery (ACA) distribution. Complete blood cell count showed a white blood cell count (WBC) of 22.5, haemoglobin of 8.2, and a platelet count of 628. Additional abnormal laboratory values included a Troponin of 251, a BNP of 709, and an elevated lactic acid and alkaline phosphatase. The electrocardiogram showed chronic first-degree AV block.

The patient was initially diagnosed with stroke and septic shock, stabilized, and moved to the intensive care unit for post-stroke treatment. The decision was to not perform a thrombectomy was made because interventional neurosurgery determined the ACA and vertebral artery infarcts were chronic. In the ICU, the patient was hypotensive and bradycardic, requiring cardiopulmonary resuscitation and the initiation of vasopressor.

Throughout the next days, the patient was optimized, and neurologic function was improving but continued to have 0/5 strength in the left face, upper extremity, and lower extremity. MRI revealed multiple acute and subacute ischemic strokes scattered in the bilateral cerebral hemispheres and bilateral cerebellar hemispheres. The largest infarcts were in the right cerebral hemisphere. The right frontal and parietal lobes also showed blood products and hemorrhagic transformation. Upon further history taking, family history obtained from

Copyright© Miller M, et al.

the patient's wife was significant for the patient's niece dying of a massive pulmonary embolism in her early thirties, and the patient's aunt dying of a "thrombus" at an early age. The patient was also noted to have an extensive history of thromboembolic events, including previous ischemic strokes, left ventricular thrombus, and a myocardial infarction, all within the last 10 years. Hematology was consulted for a workup of a hypercoagulable etiology workup. Laboratory values showed increased antithrombin III, but normal cardiolipin, lupus panel, protein S, and phospholipids. This prompted further genetic testing which found a prothrombin G20210 mutation.

The patient was started on warfarin 3 mg and apixaban 5 mg and was later moved to a general medicine floor, then transferred to inpatient rehabilitation, and eventually discharged to a nursing facility.

Discussion

Prothrombin gene (G20210) mutation is the second most common inherited thrombophilia behind Factor V Leiden. It is a mutation of prothrombin, or Factor II, at the G20210A position [6]. This is an autosomal dominant inheritance pattern, found more commonly in the heterozygous state. The overall prevalence is 2% of the general population. It is more common in southern European heritage and less common in African or Asian descent [7]. The mutation causes a single nucleotide polymorphism of guanine to adenosine on the 3' untranslated region of chromosome 11. The increase in hypercoagulability is believed to be due to an increase in prothrombin mRNA and protein expression from the increase in efficacy of the polyadenylation site on chromosome 11 [6]. Diagnosis is through genetic testing using PCR. There is no treatment to correct the mutation, so management targets anticoagulation. Duration is based on risk factors and symptoms. A gene mutation alone is not an indication for long-term anticoagulation [8].

The state of hypercoagulability from prothrombin G20210 mutation will cause a 3-4-fold increase in risk for deep venous thrombosis and pulmonary embolism [6]. However, much less is known about the effects of the G20210A on the arterial system. In the Genetics of Early Onset Stroke study from 2014, prothrombin G20210A mutation was associated with ischemic stroke in young adults [9]. The younger the onset of the patient's first stroke, the stronger the association between the prothrombin G20210A mutation and ischemic stroke. Previous meta-analyses have shown a 3.8-fold increase in ischemic stroke in patients under the age of 57 in homozygous or heterozygous prothrombin mutations without other vascular risk factors [9].

In our patient's case, he had multiple cardiovascular risk factors, was pulled recently discontinued anticoagulation at his last hospitalization, and was discovered to have the heterozygous mutation on further genetic testing. While homozygous state is a stronger risk factor for arterial thrombosis, heterozygosity is more commonly associated with ischemic stroke [10]. According to multiple studies, the homozygous prothrombin mutation follows Hardy-Weinberg equilibrium and therefore is increasingly rare, which may have led to the greater association between heterozygous mutations and ischemic stroke. The heterozygous mutation also typically remains asymptomatic until early adulthood, while the homozygous mutation presents in childhood and is subsequently treated earlier [11].

Conclusion

Stroke is a common cause of disability and death in the United States. Basic coagulopathies are often investigated in the initial stroke workup. In this case, a more extensive hypercoagulable state work-up was warranted and led to the diagnosis of a prothrombin G20210A mutation. The patient's increased tendency to clot is a possible explanation for his diffuse ischemic stroke during this hospital presentation, as well as his previous left ventricular thrombus, STEMI, and past ischemic strokes. If a more extensive workup had been done on prior hospitalizations, subsequent thromboembolic events may have been prevented. Although currently there is no cure, patients with this mutation are started on long-term anticoagulation to prevent future overproduction of factors of the coagulation cascade.

References

1. Bukhari S, Yaghi S, Bashir Z (2023) Stroke in Young Adults. J Clin Med 12(15): 4999.

2. DeSai C, Hays SA (2021) Cerebral Ischemia. National Library of Medicine.

3. Chaudhry R, Babiker HM (2019) Physiology, Coagulation Pathways. National Library of Medicine.

4. Benjamin S, Prasanna T, Hajira B, Arif J (2020) Hypercoagulability. National Library of Medicine.

5. Shikdar S, Bhattacharya PT (2019) International Normalized Ratio (INR). NIH.

6. Elkattawy S, Alyacoub R, Singh K, Fichadiya H, Kessler W (2022) Prothrombin G20210A Gene Mutation-Induced Recurrent Deep Vein Thrombosis and Pulmonary Embolism: Case Report and Literature Review. J Invest Med High Impact Case Rep 10: 232470962110584.

7. Rosendaal FR, Doggen M, Zivelin A, Arruda R, Aiach M, et al. (1998) Geographic Distribution of the 20210 G to

Copyright© Miller M, et al.

A Prothrombin Variant. Thrombosis and Haemostasis 79(4): 706-708.

8. Kujovich J (2016) Prothrombin thrombophilia. Europe PMC.

9. Baijia J, Kathleen A, Ali H, Yuching C, Mary J, et al. (2014) Prothrombin G20210A Mutation Is Associated with Young-Onset Stroke. Stroke 45(4): 961-967.

10. Poudel S, Zeb M, Kondapaneni V, Gutlapalli SD, Choudhari J, et al. (2020) Association of G20210A Prothrombin Gene Mutation and Cerebral Ischemic Stroke in Young Patients. Cureus 12(12): e11984.

11. Kujovich JL (1993) Prothrombin Thrombophilia. NIH.

Copyright© Miller M, et al.