Thrombosis Research 182 (2019) 75–78

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Full Length Article

High risk of thrombosis recurrence in patients with homozygous and compound heterozygous factor V R506Q (Factor V Leiden) and prothrombin G20210A

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ARTICLE INFO

Keywords:
Recurrence
Factor V Leiden
Hereditary thrombophilia
Prothrombin gene mutation
Thrombosis
Venous thromboembolism

ABSTRACT

Objective: Heterozygous Factor V R506Q [Factor V Leiden (FVL)] and prothrombin G20210A (PGM), the most common inherited thrombotic disorders in the Caucasian population, confer a low-moderate risk for first venous thromboembolic (VTE) event. We investigated the thrombotic complications of rare homozygous and compound heterozygous FVL and PGM.

Methods: A cohort of patients with homozygous and compound heterozygous FVL and PGM were evaluated at a major referral center in Central Pennsylvania, USA between June 2001 and March 2019. Data including incidence of first and recurrent thrombosis, associated risk factors, family history and demographics were collected.

Results: Seventy-five patients were eligible for analysis: 47 had homozygous FVL, three had homozygous PGM, 19 had compound heterozygous FVL and PGM, five had compound homozygous FVL and heterozygous PGM, and one had compound heterozygous FVL and homozygous PGM. Fifty-nine patients experienced 111 thromboembolic events. Forty-seven percent of first thrombotic events occurred in patients without clinical or surgical conditions predisposing to thrombosis. The rate of recurrent thromboembolism was 59%. The mean time to recurrence was 8.5 years. Ninety percent of recurrent events occurred during times when patients were not treated with anticoagulation.

Conclusion: Persons with homozygous and compound heterozygous FVL and PGM are at a significantly increased risk of first unprovoked and recurrent VTE. Patients with first thromboembolic events should be considered for long-term anticoagulation.

1. Introduction

Factor V R506Q [Factor V Leiden (FVL)] and prothrombin G20210A (PGM) are the most common inherited thrombophilias in the Caucasian population [1,2]. The heterozygous state of these two genetic variants confer a low-moderate risk of first venous thromboembolism (VTE), but are not thought to carry a significant risk for recurrent VTE unless associated with acquired or environmental prothrombotic conditions [3–5]. Homozygous and compound heterozygous FVL and PGM are rare and are generally thought to be associated with a high risk of VTE [6–8]. However, few observational studies, case series and retrospective analyses have addressed the occurrence of thrombosis in homozygous and compound heterozygous FVL and PGM and reported variable estimates of thrombotic risk associated with these conditions [5,9–12]. Some studies have reported significantly high risk of first and recurrent thrombotic events [5,9,10], while others noted similar or only modestly increased risk of thrombosis compared to heterozygous carriers of these variants [8,11]. Whether these patients require long-term anticoagulation after a first thrombotic event is an open question.

In this observational case series, we report the incidence of thrombosis, associated risk factors, family history and demographic data on 75 patients including 47 with homozygous FVL, 3 with homozygous PGM, 19 with compound heterozygous FVL and PGM, 5 with compound homozygous FVL and heterozygous PGM, and 1 with compound heterozygous FVL and homozygous PGM evaluated at a major academic referral center over an 18 year period.

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https://doi.org/10.1016/j.thromres.2019.07.030
Received 14 January 2019; Received in revised form 31 July 2019; Accepted 31 July 2019
Available online 01 August 2019
0049-3848/

Table 1
Characteristics of the cohort of 75 patients.

	Homozygous FVL, $n = 47$	Homozygous PGM, $n = 3$	Compound heterozygous FVL and PGM, $n = 19$	Homozygous FVL and heterozygous PGM, $n = 5$	Heterozygous FVL and homozygous PGM, $n = 1$
Female	57.4%	33.3%	68.4%	60%	100%
VTE	74.5%	100%	89.5%	60%	100%
Recurrent VTE	45.7%	33.3%	57.9%	20%	100%
Age at first VTE, years					
Mean					
Range	31.6 ± 15.5	42 ± 7.9	38.7 ± 14.4	47 ± 16.4	25
	0–62	31–49	16–69	24–61	25
Age at recurrent VTE, years					
Mean					
Range	41.7 ± 15.4	47	48.6 ± 12.1	67	25
	20–64	47	28–69	67	25
Family history of VTE	46.8%	0%	36.8%	100%	0%
Clinical and surgical conditions predisposing to thrombosis	46.8%	66.7%	52.6%	40%	100%

2. Methods

2.1. Patient cohort

Data from patients who tested positive for homozygous FVL, homozygous PGM and compound heterozygous FVL and PGM were collected and analyzed. Most of the patients were evaluated by the second author; a few were evaluated by other hematologists at our institution. Patients were referred because of personal history of VTE or history of VTE in first-degree relatives. Sixty-four percent of the patients continued follow-up at our institution. Of those who continued follow-up, mean length of follow-up was similar between those who had a personal history of VTE, 4.1 years, and those who did not, 3.7 years. Patient evaluation and testing occurred between June 2001 and March 2019 in Central Pennsylvania, USA.

2.2. Laboratory testing

Genetic testing was performed in a single clinical laboratory within the authors' institution between 2003 and 2018. Four patients had testing performed prior to 2003 which was completed by a clinical laboratory outside of the institution by flap endonuclease and fluorescence resonance energy transfer signal detection according to a method previously described by Ledford et al. [13]. Tests performed between January 2003 and March 2012 utilized the same method. Testing between April 2012 and April 2016 utilized a PCR reaction, fluorescent labeling, hybridization, and imaging for genotyping as described by Weyant et al. [14]. Testing performed from May 2016 to August 2018 utilized a GenMark Diagnostics eSensory Thrombophilia Risk Test which includes a PCR reaction, ferrocene labeling, hybridization, and voltammetry for genotyping.

2.3. Data collection

Clinical data on each patient including sex, age at evaluation, type and location of thromboembolism, age at first thromboembolism, recurrence of thromboembolism, family history of thromboembolism, conditions predisposing to thrombosis, and anticoagulant treatment and duration were collected at the time of initial clinical evaluation and at last follow-up evaluation. Type and location of thromboembolism included lower and upper extremity deep vein thrombosis, pulmonary embolism, cerebral vein thrombosis, internal jugular vein thrombosis, vena cava thrombosis, visceral thrombosis, catheter-associated thrombosis, superficial venous thrombosis, and arterial thrombotic events. Conditions predisposing to thrombosis included: recent major surgery, central venous catheter, trauma, immobilization, malignancy, pregnancy and postpartum, oral contraceptives or hormonal therapy, heart failure, antiphospholipid syndrome, myeloproliferative neoplasms, inflammatory bowel disease, nephrotic syndrome, and paroxysmal nocturnal hemoglobinuria.

3. Results

Seventy-five patients were identified who were eligible for analysis: 47 had homozygous FVL, three had homozygous PGM, 19 had compound heterozygous FVL and PGM, five had compound homozygous FVL and heterozygous PGM, and one had heterozygous FVL and homozygous PGM. Age at initial evaluation ranged from birth to 70 years. The mean age at initial evaluation was 39.8 years. Sixty-one percent of patients were female ($n = 46$). Patient characteristics are shown in Table 1.

Of the total cohort, 55 (73%) patients experienced only venous thromboembolic events, two (3%) patients, one with homozygous FVL and one with compound heterozygous FVL and PGM, experienced both arterial and venous thromboembolic events, and two (3%) patients with homozygous FVL experienced only an arterial thrombotic event. One patient with compound heterozygous FVL and PGM died of pulmonary embolism and cerebral vein thrombosis. Sixteen (21%) patients experienced no thrombotic events. Forty-seven percent of first thrombotic events occurred in patients without clinical or surgical conditions predisposing to thrombosis. The mean age at first thrombotic event was 34.9 years and the median age was 30 years. Thirty-six (61%) patients who experienced any arterial or venous thromboembolic event were female. Data regarding duration of anticoagulation were available for 78% of patients who experienced a first thromboembolic event. Forty-three percent received long-term anticoagulation. Three patients, whose first thrombotic events were superficial vein thromboses, did not initially receive anticoagulation. The mean duration of anticoagulation for the remaining patients was 10.4 months (range 7 days to 5 years).

The rate of recurrent VTE was 59%, 65% amongst patients with compound heterozygous FVL and PGM, 60% amongst patients with homozygous FVL, 33% amongst patients with homozygous PGM, 33% amongst patients with homozygous FVL and heterozygous PGM. The single patient with heterozygous FVL and homozygous PGM experienced recurrent VTE. The mean interval between first VTE and recurrent VTE was 8.5 years. Sixty-six percent of recurrent thromboembolic events occurred at the same anatomical location as the first event. Ninety percent of recurrent events occurred during times when patients were not treated with anticoagulation. Four recurrent events occurred during treatment with warfarin; one patient had a therapeutic INR, one patient had a sub-therapeutic INR, and INR was unavailable for two patients. One recurrent event occurred during treatment with prophylactic apixaban.

Forty-nine patients experienced deep vein thrombosis (DVT) and/or

Table 2
Type and location of 111 thromboembolic events in 59 patients.

	Homozygous FVL, $n = 35$, events = 66	Homozygous PGM, $n = 3$, events = 4	Compound heterozygous FVL and PGM, $n = 17$, events = 34	Homozygous FVL and heterozygous PGM, $n = 3$, events = 5	Heterozygous FVL and homozygous PGM, $n = 1$, events = 2
Lower extremity DVT	57.6%	50%	52.9%	100%	100%
Pulmonary embolism	21.2%	25%	23.5%		
Unusual site venous thrombosis	13.6%	25%	5.9%		
Arterial thrombosis	4.5%		5.9%		
Catheter-associated thrombosis	1.5%		2.9%		
Superficial vein thrombosis	1.5%		8.8%		

Unusual site venous thromboses include upper extremity DVT, thromboses in cerebral veins, internal jugular, vena cava, and visceral thromboses.

pulmonary embolism (PE). Rates of DVT were higher in males, 59%, than females, 47%, whereas rates of PE were lower in males, 5%, than females, 17%. Of 29 patients with homozygous FVL who experienced DVT or PE, 18 (62%) were diagnosed with DVT, four (14%) with PE and seven (24%) with both DVT and PE. There were 111 thromboembolic events affecting 59 patients in the cohort. Type and location of thromboembolism are shown in Table 2. Twelve unusual site thromboses included five upper extremity DVT, two cerebral sinus thromboses, one internal jugular thrombosis, two vena cava thromboses, and two visceral thromboses.

Of the 16 patients without any thromboembolic events, 3 (19%) received long-term prophylactic anticoagulation. Two patients received prophylactic anticoagulation only during pregnancy and postpartum and two patients received prophylactic anticoagulation only postoperatively. The mean age at evaluation of patients without any thromboembolic events was 30.9 years and the median age was 27.5 years. The percentage of patients who did not experience any thrombotic event was similar amongst males, 21%, and females, 22%.

4. Discussion

Homozygous and compound heterozygous factor V R506Q (Factor V Leiden) and prothrombin G20210A occur infrequently in comparison with the relatively high prevalence of the heterozygous FVL or heterozygous PGM. The homozygous and compound heterozygous variants are thought to carry a high risk of VTE. The findings from this case series support this hypothesis. We observed a high incidence of first and recurrent thrombosis in patients with homozygous and compound heterozygous FVL and PGM. Slightly more than half of first thromboembolic events were provoked by clinical or surgical conditions predisposing to thrombosis. The rate of recurrent thrombosis was lower amongst patients with homozygous PGM than those with homozygous FVL or compound heterozygous FVL and PGM. However, this case series included only four patients with homozygous PGM and the true rate of recurrent thrombosis may not differ amongst patients with homozygous PGM versus homozygous FVL. Nearly all recurrent events occurred during times when patients were not treated with anticoagulation, suggesting that anticoagulation is an effective method for prevention of recurrent thromboembolism.

We found a significantly increased prevalence of homozygous FVL compared to homozygous PGM in this cohort, which does not reflect the incidence in large population based studies. This may be due to the prevalence of these variants in the population served by our hospital or due to selection bias. Also, in this patient cohort there are significantly more females than males. We suspect that this is due to increased incidence of other prothrombotic conditions in female patients such as use of hormonal contraception, pregnancy, and related conditions. Alternatively, it could be related to a referral bias in favor of females.

There has been an entity referred to in the literature as the Factor V Leiden paradox which suggests that the incidence of DVT is increased disproportionally compared to PE in persons with FVL, not PGM [15]. Data from our cohort supports this assumption: amongst patients with compound FVL and PGM, distribution of DVT and PE was similar to those with homozygous FVL. Of a total of 18 patients with compound FVL and PGM who experienced DVT or PE, eleven (61%) were diagnosed with DVT, two (11%) were diagnosed with PE and five (28%) were diagnosed with both DVT and PE. The number of patients with homozygous PGM was insufficient to assess for the presence or absence of the FVL paradoxical distribution.

A previous study described the risk of recurrent VTE in homozygous carriers and double heterozygous carriers of FVL and PGM in a cohort of families with thrombophilia. Twenty-seven individuals had homozygous FVL or homozygous PGM of which 44% experienced recurrent VTE. Forty-nine individuals had compound heterozygous FVL and PGM of which 41% experienced recurrent VTE [9]. Another study identified 68 patients with homozygous FVL and heterozygous PGM, 31 with

heterozygous FVL and homozygous PGM, and 1 patient with homozygous FVL and homozygous PGM. Seventy-one percent experienced venous thromboembolism, 4% experienced only arterial thromboembolism, and 6% experienced both venous and arterial thromboembolism. Nineteen percent had not experienced any thrombotic event. The rate of recurrence was 37% [12]. Data from our study is consistent with these findings, demonstrating a high rate of recurrent VTE.

A limitation of this study is the inherent selection bias in the design of the study. Patients were referred due to personal or family history of thrombosis. These patients are likely to represent only a subset of all persons in the population who carry homozygous and compound heterozygous FVL and PGM. It would be challenging to overcome this limitation, however, due to the low prevalence of these conditions.

In conclusion, we found that the rates of first unprovoked thromboembolic event and recurrent thromboembolic event were high in patients with homozygous and compound heterozygous FVL and PGM. Anticoagulation decisions should be determined based on patient specific factors. Patients with a first thromboembolism should receive long-term anticoagulation given the high risk of recurrent thromboembolism. In patients who have not experienced VTE, we suggest prophylactic anticoagulation in the setting of anticipated increased thrombotic risk such as postpartum and surgery or during times of prolonged immobilization. These recommendations are similar to consensus guidelines for management of anticoagulation in patients with homozygous FVL.

Declaration of competing interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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