

Secondary Thromboprophylaxis in Hereditary Thrombophilia

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Authors' contributions

This work was carried out in collaboration between all authors. Authors TMB and MB designed the study, provided the laboratory findings and wrote the first draft of the study. Authors LP and MV provided the clinical findings and images for the study. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Aims: The aim of this study is to show how the coagulation laboratory and clinical findings worked together in the management of a patient with hereditary thrombophilia and pulmonary embolism (PE) in terms of diagnosis, the choice of anticoagulation treatment and the duration of secondary thromboprophylaxis.

Study Design: A case report with the presentation of clinical and laboratory findings, treatment and long-term follow up of the patient.

Place and Duration of Study: Institute of Transfusion Medicine and University Clinics of Cardiology, St Cyril and Methodius University, Skopje, Macedonia in the period from February 2015 and December 2017.

Case Presentation: Computer tomography confirmed the diagnosis of PE in a 32-year-old man who was admitted to the cardiology emergency department with D-dimer level of 5980 ng/mL after an episode of syncope. After the initial anticoagulation with unfractionated heparin 30.000i.e./24 h,

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enoxaparin 80 mg/12 h and acenocoumarol were introduced. The therapeutic INR rang could not be achieved so the acenocoumarol was switched to rivaroxaban 2x15 mg/day. One year later the anticoagulation with rivaroxaban 20 mg/day was discontinued. Thrombophilia testing included: prothrombin (PTB), Factor V Leiden and methylene tetrahydrofolate reductase (MTHFR) C677T gene mutation, as well as antiphospholipid antibodies, antithrombin, protein C and S.

Results: The patient was homozygous for the PTB. His parents were heterozygous for the same mutation; his mother also being heterozygous for MTHFR C677T. His brother was compound heterozygote for PTB and MTHFR C677T and his sister was heterozygous for the PTB. Coagulation status monitoring showed hypercoagulability (APTT was 24-26 seconds) and increment of D-dimer (2100-2400 ng/ml) when rivaroxaban was discontinued and normal APTT (28-38 seconds) and D-dimer (< 500 ng/mL) when it was reintroduced.

Conclusion: According to the laboratory findings and also having in mind that this was a second episode of a thrombotic event, we decided for an extended secondary thromboprophylaxis. Although it sometimes implies that it will be continued life-long we consider worthwhile to apply the patient-oriented approach to the decision when and whether to terminate anticoagulation.

Keywords: Hereditary thrombophilia; pulmonary embolism; prothrombin mutation; rivaroxaban.

ABBREVIATIONS

DVT: Deep venous thrombosis; PE: pulmonary thromboembolism; VTE: Venous thromboembolism; PTB: Prothrombin; FVL: Factor V Leiden; MTHFR: Methylene tetrahydrofolate reductase; APA: Antiphospholipid antibodies; LA: Lupus anticoagulant; UFH: Unfractionated heparin; VKA: Vitamin K antagonist; DOACs: Direct acting oral anticoagulants.

1. INTRODUCTION

The coagulation and fibrinolytic system are two separate but linked enzyme cascades that regulate the formation and breakdown of fibrin as long as there is a haemostatic balance. The understanding of both the coagulation and fibrinolysis pathway has helped to determine specific factors that can cause an imbalance in hemostasis. Early discoveries of genetic prothrombotic risk factors involved gene mutations that resulted in altered concentration or function of certain coagulation proteins.

A hereditary thrombophilia results when an inherited factor, such as factor V Leiden (FVL), methylene tetrahydrofolate reductase (MTHFR) C677T gene mutation or prothrombin G20210A gene mutation leads to over activity of coagulation or to a deficiency of natural anticoagulants, such as antithrombin, protein C or S deficiency. This condition increases the risk for unprovoked thrombosis in younger people which usually presents with deep vein thrombosis (DVT) and pulmonary embolism (PE) and with great likelihood of recurrence. A homozygous abnormality or combination of two or more heterozygous abnormal factors can lead to clinically apparent thrombotic disorder at an early age. However, milder heterozygous traits, when existing alone, are more often discovered by laboratory investigation.

Various other factors for congenital thrombophilia have been described including elevated factor VII, VIII, IX and XI, factor XII deficiency, plasminogen deficiency, elevated lipoprotein a and dysfibrinogenemia. Studies have also shown that these factors may co-exist with other inherited defects leading to thrombophilia which may in fact be the result of the combination of two or more gene defects in a family [1].

Challenging clinical issues include the decisions regarding when to test for a mutation and how to manage individuals with the mutation, either in the setting of venous thromboembolism (VTE) or as an incidental finding.

The aim of this study is to show how the coagulation laboratory and clinical findings worked together in the management of a patient with hereditary thrombophilia and PE in terms of diagnosis, the choice of anticoagulation treatment and the duration of the secondary thromboprophylaxis.

2. PRESENTATION OF CASE

A 32-year-old man, non-smoker, no known comorbidity, presented to the emergency department (ED) of University Clinic of Cardiology, because of an episode of syncope without any seizure activity. He was complaining of mild shortness of breath and dizziness few hours before the attendance. From the past

medical history he referred episode of deep vein thromboses 4 years ago, treated for 3 months with anticoagulation therapy. There was no family history of sudden death or heart disease. On initial examination, he was dizzy and diaphoretic, with cold peripheries. His pulse was 115 beats per minute, blood pressure was 97/64 mmHg, respiratory rate 28 breaths per minute, with 98% oxygen saturation on room air, a normal lung exam, a normal cardiac exam, no oedema or cyanosis, and intact radial and pedal pulses.

Under suspicion of pulmonary embolism, urgent echocardiography was performed and it revealed normal left ventricular size and function with an ejection fraction of 56%. The interventricular septum was mildly attended and there was hypokinesis of the anterior free wall of the right ventricle, suggestive of right ventricular (RV) pressure overload. There was moderate tricuspid regurgitation, moderate pulmonary artery hypertension (PAH), dilated RV with McConnell's sign (decreased movement of RV free wall as compared to apex).

During echocardiography examination the patient experienced another episode of syncope with bradypnea, after short assisted ventilation he regained his consciousness. He was transferred to the intensive care unit (ICU). Levels of serum electrolytes, glucose, blood urea and creatinine, and complete blood counts were normal, D-dimer level was 5980 ng/ml. The fibrinolytic therapy with tissue plasminogen activator (100 mg intravenously over 2 hours) was introduced immediately. Anticoagulation therapy was continued with unfractionated heparin 30.000i.e./24h.

CT angiography of the thorax performed the next day revealed centrally located intra-luminal thrombi at the bifurcation level of both main pulmonary arteries. There were also thrombi in lobar and segmental branches for inferior lobes bilateral (Fig. 1). The RV/LV ratio was <1 (Fig. 2).

A Doppler scan of the legs revealed a non-occlusive thrombus in right femoral vein.

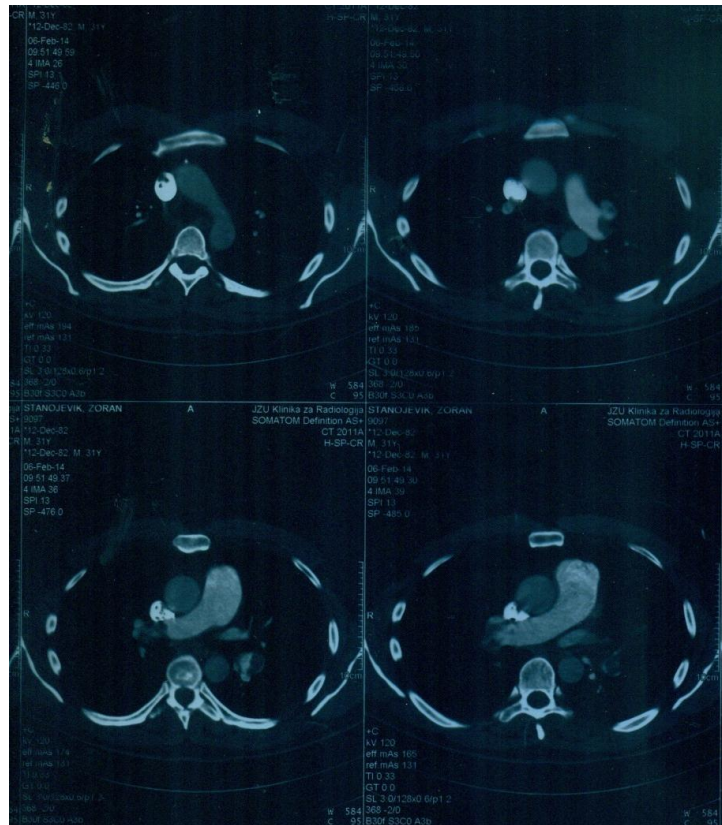


Fig. 1. Computed tomography scan of the chest demonstrating an occlusive pulmonary embolus in the right pulmonary artery and subocclusive thrombus in one of the left branches

Patient has improved gradually over a period of 1 week, with normal pulse and respiratory rate and maintaining oxygen saturation on room air. Screening coagulation tests results were in concordance with the anticoagulant (expected prolongation of TT and APTT). Afterwards, enoxaparin 80 mg/12 h and acenocoumarol were introduced. INR was monitored every day and the acenocoumarol dose was adjusted to achieve a therapeutic value of 2-3. After 7 days of acenocoumarol therapy, INR was still below the therapeutic range (2-3). The D-dimer level remained high in the first 7 days (> 4000 ng/ml) and there was an only mild regression of the thrombotic substrate according to the control CT. The decision was made to switch the anticoagulation from acenocoumarol to rivaroxaban 2x15 mg/day. We discontinued acenocoumarol and started with rivaroxaban immediately because the INR was below 2.0. After 7 days of rivaroxaban therapy the CT showed significant regression of the thrombi (Fig. 3) and normalization of the RV/LV ratio (Fig. 4).

After 20 days of hospitalization, the patient was dismissed from hospital with rivaroxaban 2x15 mg/day for another 2 weeks and 20 mg/day for

next six months. The patient had complete resolution of the thrombi in the lungs as well as in the right femoral vein.

2.1 Thrombophilia and Coagulation Status Assessment Results

Thrombophilia genetic testing for the factor V Leiden (G1691A mutation), the G20210A mutation in prothrombin (PTB) gene and the C677T mutation in the methylene tetrahydrofolate reductase (MTHFR) gene was performed six months after the diagnosis of PE. The activity of antitrombin, protein C, protein S and screening for lupus anticoagulant (LA) and antiphospholipid antibodies (APA) was also performed after the first discontinuation of the anticoagulant therapy. The patient was homozygous for the prothrombin gene mutation. Both of his parents were heterozygous for the same mutation. His mother was also heterozygous for MTHFR C677T gene mutation. His brother was compound heterozygote for PTB and for MTHFR C677T and his sister was heterozygous only for the PTB mutation. The laboratory results from thrombophilia testing of the patient are shown in Table 1.



Fig. 2. The ratio of right versus left ventricle - bigger than one

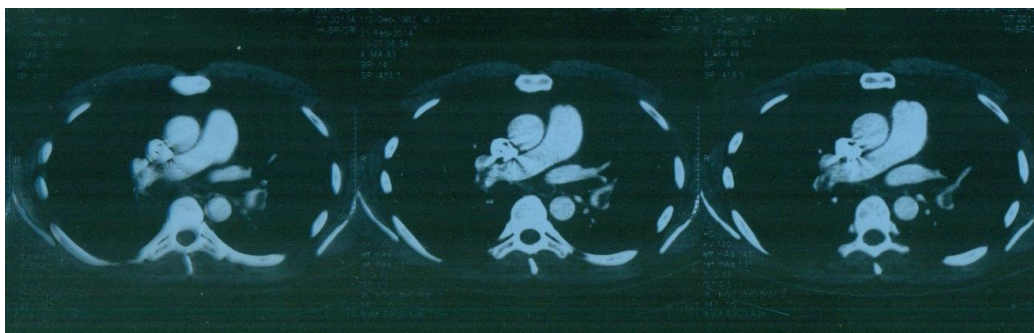


Fig. 3. Control CT scan showing subsegmental thrombi in both sides



Fig. 4. Normalized ratio of right versus left ventricle

Table 1. Laboratory assessment of thrombophilia

Biological marker	Normal value	Result
ATIII (biological activity %)	50-150	95
PC (biological activity %)	50-150	90
PS (biological activity %)	50-150	75
LA screening	0-0	Negative
LA (sec.)	25-42	35
APA (SU)	0-20	3
Protrombin (biological activity %)	50-150	120
FVL G1691A	0	No mutation
FII PTB G20210A	0	Homozygous mutation
MTHFR C677T	0	No mutation
Homocysteine (µmol/L)	0-13.00	12.73

After one year the secondary thromboprophylaxis with rivaroxaban 20 mg/day was discontinued. Haemostatic screening tests and D-dimer level were in normal range as shown on Table 2.

Table 2. Coagulation test results before the first discontinuation of anticoagulation

Coagulation test	Normal value	Result
PT (sec)	9.8-14.4	12.29
APTT (sec)	27.9-37.7	31.22
TT (sec)	16.1-24.1	23.46
D-dimer (ng/ml)	0-500	170

The first control of haemostatic parameters and D-dimer which was performed after three months of discontinuation of anticoagulation revealed hypercoagulability of the blood. Rivaroxaban 20 mg/day was recommended but the patient agreed with 10 mg/day. Coagulation status monitoring in the period of 18 months showed hypercoagulability (APTT was 24-26 seconds) and increment of D-dimer (2100-2400 ng/ml) every time when rivaroxaban was discontinued and normal APTT (28-38 seconds) and D-dimer (< 500 ng/mL) when it was reintroduced as shown on Table 3.

Table 3. APTT and D-dimer results according to the anticoagulant thromboprophylaxis

Rivaroxaban 10 mg/day	Duration (months)	APTT (sec)	D-dimer (ng/ml)
No	3	26.5	2418
Yes	4	27.7	565
Yes	4	30.0	195
No	3	24.7	2144
Yes	4	28.3	366

The platelet count, PT and TT were always within the normal range. In the mean time, the two Doppler ultrasonography (Duplex ultrasound) investigations of the legs revealed only the presence of venous insufficiency, probably secondary, due to the thrombotic event in the past. Blood clots were not detected in the deep venous system.

According to the clinical (recurrent unprovoked deep vein thromboses and pulmonary embolism) and laboratory finding and also having in mind the history of thrombotic events, we continued the secondary thromboprophylaxis with rivaroxaban 20 mg/day.

3. DISCUSSION

Prothrombin G20210A gene mutation is the second most common coagulation abnormality

connected with thrombophilia, with a prevalence of heterozygotes in populations of Caucasian origin of 2–3%, which increases to 6% in patients with VTE. Homozygosity for the prothrombin gene mutation is much rarer and occurs in four out of 10,000 people with the prevalence of 0.02% in general population and < 1% in patients with VTE [2].

The Leiden Thrombophilia Study (LETS) demonstrated similar data with the prevalence of the G20210A allele among healthy carriers being 2.3% and 6.2% among venous thrombosis patients. A review of data from 11 centers in Europe found a range of 0.7 to 4.0 percent, with the prevalence in southern Europe being almost twice as high as northern Europe (3.0% versus 1.7%) [3].

The prothrombin gene mutation is shown to be extremely rare in the African and Asian population [4].

The thrombotic risk associated with inherited thrombophilia in Macedonian patients with VTE has been assessed in 2005. The prevalence of factor V Leiden, prothrombin G20210A polymorphism, ATIII, PC and PS deficiency was estimated to be 12.3 %, 6.3%, 2%, 16% and 14% respectively [5]. The prevalence of prothrombin G20210A mutation in our VTE patients is similar to the reported one in the literature. Yet, there are no studies performed to estimate the prevalence of the same mutation in the general population.

The absolute risk of thrombosis among patients with inherited thrombophilia was evaluated by Martinelli et al in 1998 in an Italian cohort study of 150 pedigrees consisting of 1213 individuals. The lifetime probability of developing thrombosis compared to those with no defect was 8.5 times higher for carriers of protein S deficiency, 8.1 for antithrombin deficiency, 7.3 for protein C deficiency, and 2.2 for factor V Leiden [6].

Linkage studies performed in 397 individuals from 21 Spanish families demonstrated that the presence of allele G20210A in the prothrombin gene influences prothrombin activity levels and susceptibility to thrombosis [7]. Heterozygous G20210A prothrombin mutation increases the risk of developing a first venous thromboembolic episode about 2 to 3 times, but it is not yet known how much the risk is increased in homozygous prothrombin mutations carriers [8]. Also few data are available about the risk of

recurrence and the need of lifelong secondary thromboprophylaxis after the first unprovoked thrombotic event [9]. Recently, Mannucci reported that homozygosity for the prothrombin gene mutation causes an approximately 30-fold increased VTE risk. The risk of VTE recurrence in patients with heterozygous prothrombin gene mutation is similar to that of factor V Leiden (1.4-fold) which remains not known yet for the VTE patients with homozygous prothrombin gene mutation [2].

The results of one large meta-analysis of the literature suggest that FV Leiden patients are more likely to present with DVT than with isolated PE, whereas the presence of PTB mutation does not seem to influence VTE location at presentation. PTB mutation was present in 650 of the 7062 (9.2%) patients with DVT with or without concomitant VTE, and in 185 of the 2515 (7.4%) patients with isolated PE [10].

In individuals with combined genetic defects such as double heterozygotes for factor V Leiden and prothrombin G20210A mutation the risk for venous thrombosis is much higher. The data showed an odds ratio for venous thrombosis in double heterozygotes of 20.0 which is much higher than the odds ratios for thromboembolism of 4.9 for the factor V Leiden and 3.8 for the factor II G20210A mutation as single defects [11]. Carriers of both factor V Leiden and the G20210A prothrombin mutation have also an increased risk of recurrent deep venous thrombosis after a first episode and are candidates for lifelong anticoagulation [12].

Den Heijer and colleagues have demonstrated that hyperhomocysteinemia is an independent risk factor for venous thromboembolism [13]. Typically, a level less than 13 $\mu\text{mol/L}$ is considered normal. A level between 13 and 60 $\mu\text{mol/L}$ is considered moderately elevated, and a value greater than 60 to 100 $\mu\text{mol/L}$ is severely elevated [14].

It has also been shown that MTHFR C677T and MTHFR A1289C genotypes and haplotypes are connected with homocysteine plasma levels in Macedonian patients with occlusive artery disease and deep venous thrombosis [15].

There have been many pros and cons to testing for thrombophilia in terms who, when and to which extend to be tested because the results can often be confusing for the patient and of no use for the clinician to determine the duration of

anticoagulant therapy or thromboprophylaxis. Thrombophilia testing should not be performed in patients with VTE following a major provocation as extended anticoagulation is not indicated in these cases. Thrombophilia testing in a patient with unprovoked VTE should be done if the result would change the decision to stop anticoagulant therapy [16].

The absolute risk for recurrent VTE among patients with unprovoked thrombosis is higher than among those with provoked VTE, with 5-year risk approaching 30% unless extended-duration anticoagulant therapy is provided [17,18].

Current guidelines from the American College of Chest Physicians (ACCP) recommend extended anticoagulation (anticoagulation with no planned stop date) after unprovoked VTE unless the risk of bleeding is high. Therefore it would be desirable to offer extended anticoagulation only to those who would benefit from it. Thrombophilia testing has been suggested as a means to identify these patients who would otherwise stop anticoagulation [19].

In the past decade, many clinical and real life studies have proven the superiority of the direct acting oral anticoagulants (DOACs) such as rivaroxaban, dabigatran etc. over the vitamin K antagonists (VKAs) concerning their efficacy and safety in the treatment and prophylaxis of DVT and VTE [20]. DOACs are much more convenient for extended anticoagulation than VKAs not only because of the lower risk of bleeding, but also have many other advantages such as fixed dosage, no need for laboratory monitoring, less interference with drugs and food which makes the decision to extended anticoagulation where it is indicated to be easier.

Other factors, such as the degree of post-thrombotic symptoms, D-dimer levels after a minimum of 3 months of anticoagulant therapy, and residual vein thrombosis may also influence the risk of recurrence as well as the duration of anticoagulation [21,22].

As shown in the results, although clinically stable, laboratory parameters in our patient revealed hypercoagulability of the blood in the periods of discontinuation of the anticoagulant (screening hemostasis and D-dimer test were not performed to monitor the direct effect of rivaroxaban). Whether and to which extent this condition increases the risk of recurrence of the

thrombosis remains unknown. However, the laboratory findings, the homozygosity for PTB mutation, the fact that the first episode of DVT as well as the recurrence of VTE was not provoked in the absence of increased bleeding risk, contributed to the decision for a long term secondary thromboprophylaxis with rivaroxaban. We also find interesting that normal coagulability and normal D-dimer level was achieved with the dose of only 10 mg rivaroxaban daily in the period after it was reintroduced which is the proposed dose for certain indications for post-operative primary thromboprophylaxis such as the hip replacement. Further investigations are necessary to confirm this finding which may be of importance for the patients who are at risk of bleeding and still need extended anticoagulation. However, we continued with the extended, probably life-long anticoagulation with rivaroxaban 20 mg/day.

4. CONCLUSION

Thrombophilia testing should only be performed to assist the management of secondary prevention after a thrombotic event and to aid in primary prevention in relatives of affected patients.

Normal hemostasis, as well as normal level of D-dimer, should be one of the prerequisites to the decision to terminate anticoagulation therapy in thrombophilia patients which suffered thrombotic episode. Above mentioned tests should be performed in 3 to 6 months intervals in the first few years after the cessation of anticoagulation.

Although extended anticoagulant thromboprophylaxis, usually implies that it will be continued life-long, we consider worthwhile to apply the patient-oriented approach to the decision when and whether to terminate anticoagulation.

CONSENT

All authors declare that written informed consent was obtained from the patient for publication of this case report and accompanying images. The patient gave informed consent for publishing of this article.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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