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CASE REPORT

Venous thrombembolism, thrombophilic defects, combined oral contraception and anticoagulation

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Abstract
Background Several genetic polymorphisms increase the risk for venous thrombembolism (VTE). In particular, combined oral contraceptives (COCs) are known to enhance the risk for VTE and are therefore contraindicated.
Case We present here the case of a patient with protein S deficiency, who has used COCs together with anticoagulatory therapy (Phenprocoumon) after suffering from deep venous thromboses for 4 years. At the time of her first consultation at our clinic, the ultrasound examination showed a complete involution of her venous thrombosis.
Conclusion COCs can be used in patients with thrombogenic mutations and anticoagulatory therapy in individual cases.

Keywords Thrombembolism · Anticoagulation · Contraception · Protein S deficiency · Oral contraceptives

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Introduction

Venous thrombembolism (VTE) is associated with high rates of mortality and serious sequelae. Because there is a high prevalence of predisposing risk factors in the general population, research during the past decade has uncovered several genetic polymorphisms that substantially raise the risk for VTE, such as factor V Leiden mutation, prothrombin mutation, protein S and protein C deficiency [1]. VTE is rare in young people [2]. However, studies have shown that the use of combined oral contraceptives (COCs) can lead to an up to a sixfold increase in the risk for VTE [2]. The above mentioned genetic polymorphisms as well as a previous thrombembolic event are therefore relative or, depending on the circumstances, absolute contraindications for the use of COCs. For ethical reasons no studies have been carried out on the risk for VTE in patients with genetic mutations, anticoagulatory therapy and COCs. Although this is a rare combination of risk factors, it could assist in the prescribing of COCs or anticoagulatory therapy in women who use already one or the other type of medication. We report on a patient at risk for VTE, who has used COCs and anticoagulatory therapy for several years.

Case

In January 2008, a 28-year-old woman was referred to us for a hormonal check-up. At the time we saw her she was in good health; her BMI was 19.0, she denied the use of tobacco products, her blood pressure was within the normal range, and she showed no signs of cardiovascular disease. The results of her laboratory tests for glucose and triglycerides were also in the normal range.

An analysis of her medical records showed that she had taken COCs since 1999 (triphasic oral contraception: 50–70–100 µg gestoden +30–40–30 µg ethinylestradiol). In January 2004, she became aware of an increasing shortness of breath and pain in her left chest during exercise and sports activities. She also noticed a painful swelling in her left leg, which was subsequently diagnosed as deep venous thrombosis. Ultrasound examination of her left leg showed an extensive venous thrombosis: total occlusion of the left V. tibialis posterior and 50% occlusion of the left V. interossea. A chest radiograph showed indirect signs of a past peripheral pulmonary embolism. The suspected diagnosis was confirmed by computer tomography.

She mentioned that 2 weeks before she noticed the swelling in her left leg, she had changed jobs. The new job required her to stand up to 7 h a day.

She was screened for thrombophilic genetic defects before starting anticoagulatory treatment with vitamin k antagonists. However, she did not inform the medical doctors about her use of COCs, which were therefore not discontinued before the screening for thrombophilic genetic defects. The tests revealed a protein S deficiency (for details see Table 1). She was treated with low-molecular heparin and was prescribed Phenprocoumon for 6 months. However, her general practitioner placed her on long-time anticoagulatory treatment with Phenprocoumon. The decision was taken by him largely because of her family history. Her brother was known to be aPC-resistant and her father had suffered a deep venous thrombosis twice and had survived one central pulmonary embolism. In addition, one paternal aunt, one paternal grandaunt and one paternal granduncle had died from pulmonary embolisms.

Table 1 Results of blood examinations directly after deep venous thrombosis

Test	Result	Normal
aPC-resistance (ng/ml)	2.41	>1.9
Protein C activity (%)	96	70–140
Protein S activity (%)	46	60–140
Free protein S (immunologic) (%)	38	60–140
Plasminogen activator inhibitor (ng/ml)	<8	4–49
Antithrombin III activity (%)	91	70–120
Factor VIII activity (%)	175	60–230
Factor IX activity (%)	75	60–140
Factor XI activity (%)	80	60–140
Factor XII activity (%)	139	60–140
Prothrombin time (%)	81	80–140
Prothrombin-fragment F1,2 (nmol/l)	0.5	<1.9
aPTT (s)	31.0	27.0–41.0
Lupus anticoagulant (U/ml)	1.12	<1.3
Dilute Russel viper venom time (s)	40.1	30.0–48.0

The effectiveness of her therapy was checked regularly through monthly tests of her INR-levels during the first year of treatment and quarterly tests thereafter. The INR levels remained in the therapeutic range of 2–3.

It is noteworthy that she did not inform her gynecologist about her protein S deficiency. Her use of oral contraceptives was therefore continued. A follow-up ultrasound examination of her left leg in November 2006 revealed a complete involution of her earlier venous thrombosis. All venous valves were found to be intact and functioning properly.

Since the level of protein S was determined during the acute event and not a few months later as recommended [3], the tests were repeated; 38 months after the thrombotic event she discontinued the use of oral contraception for 1 month as well as the use of Phenprocoumon and was then reevaluated for thrombophilic defects. The initial finding of protein S deficiency was confirmed. Since she was not prepared to shift from oral contraception to another form of contraception or take, at least, a gestagen-only pill, she was advised to use a lower dose COCs.

Discussion

Most studies on thrombogenic mutations and the use of COCs show an increased risk of VTE even in patients with no genetic risk factors. [1]. In patients with factor V Leiden mutation—the most common genetic risk factor for VTE—the use of COCs leads to a 30-fold increase in the incidence of VTE [4]. Similar results were found for prothrombin mutations and deficiencies in protein S, protein C and antithrombin, although the latter tend to be associated with smaller increases in the rate of VTEs [1]. The increased risk for VTE encompasses deep venous thrombosis of the lower extremities as well as cerebral vein thrombosis [5], although the latter happens less frequently but is associated with a higher mortality rate of up to 8% [6].

Thrombogenic mutations affect up to 16% of the population. Nevertheless general screening for thrombophilia does not seem to be cost-effective if fatal pulmonary embolism is considered as the clinical endpoint [7].

We found no studies dealing with the risk for VTE in patients with genetic mutations, who at the same time undergo anticoagulatory therapy and use COCs. Yet, physicians may find themselves in a situation where a patient, who is being treated with heparin, coumarins or other anticoagulatory drugs, asks for oral contraceptives.

Our experience with the patient we report here on may provide some guidance. In her case there was a complete remission with intact venous valves of the deep venous thrombosis in her left leg in spite of her ongoing use of COCs. However, it needs to be emphasized that her only

risk factors were her protein S deficiency and the use of oral contraceptives. When she was referred to our department, she was generally in good health and participated in sports activities without restrictions. Considering that she did not use tobacco products and generally complied with our recommendations, we decided to prescribe for her a low-dose COC.

Genetic testing of our patient showed that she had only the heterozygous form of protein S deficiency. Our patient has been re-evaluated for thrombophilic defects 1 month after stopping the use of COC. Since the recommended period is 2–3 months, following the stoppage of COC use, this somewhat weakens the conclusion of our case report.

Interestingly, screening for thrombophilic defects in her brother revealed aPC-resistance. Since PS deficiency is an autosomally inherited disease, this result is surprising. However, we have not been informed on what test has been used. Some tests are known to detect factor V Leiden mutation-related aPC-resistance only, whereas others additionally detect induced aPC-resistance [8]. No other members of her family have been screened for thrombophilic defects. Thus, aPC-resistance in her brother may be as well induced as related to factor V Leiden mutation.

Most patients, who are at genetic risk for VTE suffer from heterozygous forms of genetic mutations. They also tend to experience VTEs at an adult age [9]. For protein S deficient patients annual incidences of VTE range from 0.1 to 3.2% [10–15]. Regardless of whether a patient shows the heterozygous or the homozygous form of a thrombogenic mutation, the prescription of COCs is contraindicated when a thrombotic event has already occurred.

We believe, however, that COCs may be safely prescribed in patients with thrombogenic mutations and anticoagulatory therapy in individual cases. Still, patients should be advised to switch to other methods for contraception such as copper intrauterine devices or a gestagen-only pill. Until now, evidence suggests that there is no increased risk for VTE in women using a progestogen-only method [16, 17].

Our patient could not be convinced to use another contraceptive method in spite of explaining to her in detail all the risks of using COCs together with vitamin k antagonists. She had been prescribed Phenprocoumon by her general practitioner, because of her family history. It has been shown that patients with familial thrombophilia would benefit from long-term anticoagulation by means of recurrence-free survival. In patients without long-term anticoagulation, VTE recurrence rates of 5.0% per year have been reported. Long-term anticoagulation decreases the rate of recurrence by 80% [18]. However, a risk of severe hemorrhage of 1–3% has been reported [19, 20]. For patients with hereditary protein S deficiency a recurrence rate of 8.9% per year has been found [18]. However, prophylactic long-term anticoagulation is not a standard of care. In the recommendations to our patient, we stressed the need for regular checking of INR-levels.

In our view, preconditions for the prescription of COCs in such cases are (a) lack of other thrombotic risk factors such as the use of tobacco products or a high BMI, (b) a compliant and well-informed patient, (c) regular and frequent checks of the coagulatory status and, if necessary, adjustments in the anticoagulatory therapy and (d) informing the patient on what steps to take in the case of a thrombembolic event. It has not been investigated if COCs of the first, second or third-generation should be prescribed to women with thrombogenic mutations. However, as reviewed by Mohllajee et al., third-generation COCs are considered to be more thrombogenic than the first- or second-generation COCs [1].

Several other points have to be considered: since the pharmacodynamic interactions between oral contraceptives and anticoagulatory therapy are to a large extent known; the use of COCs changes the potency of Phenprocoumon and Acenocoumarol; the physician who manages the patients anticoagulatory therapy should be involved in the recommendation on the use of COCs [21, 22].

Furthermore, one has to keep in mind that acetylsalicylic acid does not provide sufficient protection from VTE. Therefore, patients with thrombogenic mutations should receive simultaneous anticoagulation with heparin and coumarins [23].

In conclusion, as of now there is no direct evidence that patients with genetic thrombophilic deficiencies can safely be placed on anticoagulatory therapy and prescribed COCs. However, the contraindication of COCs in such patients is not absolute. There is a reasonably widespread agreement among experts that oral contraceptives can be prescribed to women with a history of thrombosis, when they are under anticoagulatory treatment. However, further research, maybe in the form of retrospective studies since prospective studies could not be carried out for ethical reasons, is necessary to answer these questions.

Conflict of interest statement None.

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