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Case report

MTHFR C 677T Mutation and 4G/5G PAI-1 Polymorphism in Patient With Polycystic Ovarian Syndrome

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A B S T R A C T

Combined oral contraceptives (Ocs) are the most commonly used androgen supresors and the treatment of choice for menstrual dysfunction in women with polycystic ovarian syndrome (PCOs). Although OCs have remained popular due to their convenience and effectiveness, there have been continuing concerns about adverse effects. The OCs have long been known to incur and increased risk of venous thromboembolism especially in carriers of common inherited thromboembolic defects. Factor V Leiden, prothrombin factor G20210A polymorphism, MTHFR (C677T) mutation and 4G/5G polymorphism of the PAI-1 gene account for the majority of thromboembolic events in association with oral contraceptive use. The aim of the article is to present woman with unrecognized inherited thrombophilia who was treated with OCs due to PCOs signs.

***Key words**: MTHFR C 677T mutation, 4G/5G PAI-1 polymorphism, polycystic ovarian syndrome, oral contraceptives*

Introduction

Polycystic ovarian syndrome (PCOs) is the most common endocrinopathy in women. It is associated with both reproductive and metabolic disorders[1]. The therapeutic approaches to PCOs include lifestyle modifications, dietary-induced weight loss, insulin-senziting agents, antiandrogens and oral contraceptives (OCs), or by ovarian drilling procedure[2]. Combined OCs are frequently used androgen suppressors and the treatment of choice for menstrual dysfunction in PCOs patients. Although OCs have remained popular due to their convenience and effectiveness, there have been continuing concerns about adverse effects. The OCs has long been known to incur and increased risk of venous thromboembolism (VTE)[3]. The great problem in clinical practise is OCs-triggering of venous thromboembolic events in carriers of common inherited thromboembolic defects. Factor V Leiden, prothrombin factor G20210A polymorphism, methylene tetrahydrofolate reductase (MTHFR-C677T) mutation and 4G/5G polymorphism of the PAI-1 gene account for the majority of thromboembolic events, particularly in association with oral contraceptive use[4,5]. The aim of the article is to present woman with unrecognized inherited thrombophilia who was treated with OCs due to PCOs signs.

Case Report

A 30-year nouliparous with polycystic ovarian syndrome was treated by her general practitioner with combined oral contraceptive pills containing 35 μg of ethynil estradiol and 2 mg of cyproterone acetate for six months. She was admitted to the University Hospital Zagreb for care due to dysfunctional uterine bleeding during OCs use. Anamnestically, her mother died from cerebrovascular ischaemic stroke, and father has overcomed pulmonary embolism episode. An internal examination and ultrasound scan of the pelvis were unremarkable. According to a positive family history of venous thrombosis she was tested for eventually inherited coagulopathy. DNA analysis for mutation in factor V Leiden, prothrombin genes, MTHFR, 4G/5G PAI-1, F II 20210 A and FV R5 06Q was obtained. Plasma measurements of antithrombin, protein C, protein S, total homocysteine levels, and antiphospholipid antibodies were performed. Homozygous MTHFR–C 677 T using real time PCR/LC-PCR, hyperhomocysteinemia and 4G/5G PAI-1 polimorphysm using PCR-SSCP were determined. Total homocysteine plasma level was 25 μmol/L (5–15). F II 20210A (PCR) and FV R 5 06Q (PCR) mutation was not found in serume sample using PCR technique. Although the

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G20210A prothrombin mutation was not found, the prothrombin levels measured by a chromogenic assay was elevated (1.38, normal range 0.70–1.30) We found an increase in levels of procoagulant factors VII, X and XII. Antiphospholipide (LAC and anticardiolipin) antibodies were negative. Plasma level of D-dimers was estimated at 0.2 mg/L (normal range less than 0.3 mg/L). Plasma level of protein C (78%, normal range 75–125), protein S (65%, normal range 48–120) and antithrombin activity 95.8% (75–125) was within normal range.

Discussion

VTE events represent a serious complication related to hormonal contraception[3,6]. Presence of inherited thrombophilia increases the risk for VTE due to oral contraceptive use up to an absolute risk of 3 per 1000 person-years, in comparison with the baseline risk of 3 to 6 per 10 000 person-years[7,8]. The risk is further increased by first usage, the use of preparations containing third- generation progestins, and thrombophilia due to antithrombin, protein C and S deficiency as well as homozygous factor V (Leiden) and combined defects. The most likely mechanism explaining the increased risk of VTE is the changes provoked by the Ocs on the hemostatic and fibrinolytic systems. There is an increase in levels of procoagulant factors such as factors VII, X, XII and XIII associated with estrogen use, as well as reductions in anticoagulant factors including protein S and antithrombin[5,6]. There is also an increase in fibrinolysis, which is thought to reflect a reduction in levels of PAI-1 combined with an increase in plasminogen[5,6]. There is significant interaction between the use of the oral contraceptive pill and heritable thrombophilia. The best studied example is the interaction between factor V Leiden and OCs, showing that the risk for VTE events was increased more than 30-fold for women with factor V Leiden who used combined pill[7]. Bloemenkamp et al. reported a 50-fold increased risk of VTE for carriers of factor V Leiden using third generation OCs, compared with non-users without the factor V mutation[8]. Legnani et al. found that elevated prothrombin levels, even in women without G20210A prothrombin mutation, are associated with an increased risk for venous thromboembolism and that oral contraceptive use potentiates such association[9]. Although the G20210A prothrombin mutation was not found in our patient, the prothrombin level measured by a chromogenic assay was elevated what could display a strong interaction with OCs use. Diamanti-Kandaraksi et al. concluded the PCOs patients had significantly higher fre- quency of 4G/5G and 4G/4G PAI-1 polymorphism[10]. Also, patients with PCOs have higher levels of PAI-1. The presence of the 4G allele in PAI-1 promoter region of the gene further increases the PAI-1 levels. It is known that PAI-1 is a key negative regulator of the fibrinolytic system. The PAI-1 gene 4G/5G polymorphism may modulate the inhibitor's synthesis thus influence PAI-1 expression and thrombotic risk in patients with inherited thrombophilia[11]. The odds ratio of bearing a mutation on the MTHFR gene is 1.2-fold higher in women with PCOs than in women without PCOs[12]. Homozygous genotype of C677T *MTHFR* mutation is associated with hyperhomocysteinaemia in the presence of low folate concentration[12,13]. Prevalence of homozygous persons in different races is 13.9%[12]. The high frequency of the C677T mutation worldwide is surprising if homozygotes have an increased risk of atherosclerosis and venous thrombosis. However, although a range adverse events are associated with hyperhomocysteinaemia it is unclear whether screening for this condition should be added to the list of inherited thrombophilias likely to be associated with thrombosis. Oral contraceptive pill use is associated with exponentially higher VTE relative risks when used by women who carry an inherited hypercoagulable state. According to currently lack of reliable screening tools, we recommended to avoid oral contraceptive use not only among non-PCOs women, but also in PCOs patients with either a personal history of VTE or a strong family history until evaluated for hemostatic abnormalities, and perhaps limiting the use of desogestrel or gestodene containing oral contraceptives[3,6]. Women with PCOs and no inherited thrombophilia seem to be able to follow hormonal therapy without having increased risk for thromboembolic complications when the same principles as in non-PCOs women are applied[14]. However, inherited thrombophilia could complicated treatment modalities in patients with PCOs[15]. Therefore, other treatment modalities should be considered for women with PCOs and inherited thrombophilia such as inzulin senziting agents, antiandrogens or ovarian drilling procedure.

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MUTACIJA MTHFR C677T I 4G/5G PAI-1 POLIMORFIZAM U PACIJENTICE S POLICISTIČNIM OVARIJSKIM SINDROMOM

S A Ž E T A K

Kombinirani oralni kontraceptivi su najčešće korišteni supresori androgena, i lijek izbora u terapiji poremećaja menstruacijskog ciklusa u žena s policističnim ovarijskim sindromom. Iako su kombinirani oralni kontraceptivi popularni zbog praktičnosti i učinkovitosti, postoji kontinuirana zabrinutost zbog neželjenih učinaka. Poznato je da kombinirani oralni kontraceptivi potiču i povećavaju rizik nastanka venskog tromboembolizma, posebice u nositeljica nasljednih tromboembolijskih defekata. Faktor V Leiden, polimorfizam protrombinskog faktora G20210A, mutacija MTHFR (C677T) i polimorfizam 4G/5G PAI-1gena povezani su s većinom tromboembolijskih dogadjaja u žena koje koriste oralnu hormonsku kontracepciju. Cilj ovog rada je prikazati ženu s neprepoznatom nasljednom trombofilijom, koja je liječena oralnim kontraceptivima zbog znakova policističnog ovarijskog sindroma.