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Life-Threatening Contraceptive-Related Pulmonary Embolism in a 14-Year-Old Girl with Hereditary Thrombophilia

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Conflict of interest: None declared

Patient: Female, 14
Final Diagnosis: Pulmonary embolism
Symptoms: Chest pain • dyspnea • syncope
Medication: Combined oral contraceptives
Clinical Procedure: —
Specialty: Internal Medicine

Objective: Adverse events of drug therapy

Background: The prothrombotic effect of combined oral contraceptives (COCs) is well-established, with a 3–6-fold increased risk of VTE compared to non-users. When initiation of COCs is considered, it is therefore of paramount importance to carefully evaluate all other potential risk factors for VTE. Based on a case of life-threatening COC-associated pulmonary embolism in a girl heterozygous for the prothrombin G20210A mutation and with a family history of thrombotic disease, we discuss the importance of assessing not just the genotype but also the phenotype when considering initiation of COCs in patients with thrombophilia.

Case Report: A 14-year-old girl presented with acute onset of chest pain and dyspnea followed by syncope. She was hypoxic and hemodynamically compromised at admission. Computed tomography pulmonary angiography revealed a large central "saddle" pulmonary embolism causing nearly total occlusion of the right pulmonary artery, and several minor peripheral embolisms bilaterally. She was successfully treated with thrombolysis (alteplase) followed by aPTT-adjusted heparin infusion until adequate anticoagulation with warfarin was achieved.
Two years earlier, the patient had been found heterozygote for the prothrombin G20210A mutation, and 9 months before admission she had initiated use of second-generation COCs.

Conclusions: Hereditary thrombophilia and a family history of early-onset venous thromboembolism (VTE) each pose an increased risk of VTE and should be considered as separate, irreversible risk factors. Other contraceptive methods should be used when treatment with COCs is expected to result in an unacceptable high risk of VTE.

MeSH Keywords: Contraceptives, Oral, Hormonal • Thrombophilia • Venous Thrombosis

Full-text PDF: http://www.amjcaserep.com/abstract/index/idArt/894721

Background

Combined oral contraceptives (COCs) are associated with a 3-6 times higher risk of venous thromboembolism (VTE) compared to non-users [1,2]. Likewise, hereditary thrombophilia increases VTE risk, some more than other [3]. Persons heterozygous of the prothrombin G20210A mutation have a 3-fold increased risk of VTE [4]. Accordingly, this thrombophilia is generally classified as a minor risk factor for thrombosis [5] and, therefore, some consider this only as a relative, not absolute, contraindication for COC-use [6,7].

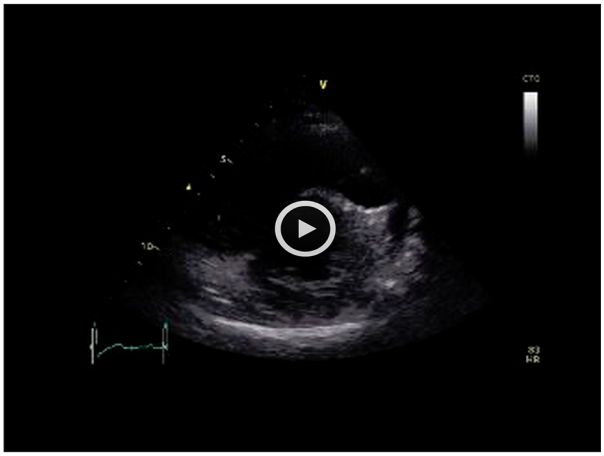
However, based on a case of massive pulmonary embolisms in a COC-using girl heterozygous for the prothrombin G20210A mutation and with familial disposition for thrombotic disease, we aim to emphasize the importance of assessing not just the genotype but also the phenotype when considering initiation of COCs in patients with thrombophilia.

Case Report

A 14-year-old, normal-weight, non-smoking, white girl presented with acute onset of chest pain and dyspnea followed by syncope. She was transported to the hospital by ambulance, where she was found hypoxic (saturation 87%), tachycardic (heart rate 125), and hypotensive (systolic BP <100 mmHg). Acute echocardiography was performed (Video 1) and revealed dilatation of the right ventricle ("D-configuration"), pulmonary hypertension (tricuspid regurgitation pressure gradient 50 mm Hg), and reduced pulmonary blood flow. A highly elevated D-dimer (16.1 mg/L) and a moderate increase in Troponin T (243 ng/L) was found. Computed tomography pulmonary angiography revealed a large central "saddle" pulmonary embolism causing nearly total occlusion of the right pulmonary artery (Figure 1), and several minor peripheral embolisms bilaterally. Physical examination was without clinical signs of deep venous thrombosis.

Because the patient was hemodynamically compromised, thrombolytic treatment with alteplase was initiated and followed by aPTT-adjusted heparin infusion. After termination of the infusion, low molecular weight heparin was initiated and continued until adequate anticoagulation with warfarin was achieved. Clinical treatment effect was observed within a few hours, and echocardiography on day 2 confirmed that the pulmonary pressure was reduced. At discharge on day 3, the patient was hemodynamically stable (BP 120/70 mm Hg, HR 85, and saturation 98%) with only a minor sensation of respiratory distress.

Due to several cases of both arterial and venous thrombosis at young age in at least 2 generations of the family, the patient had been tested for hereditary thrombophilia 2 years earlier;



Video 1. Echocardiogram showing dilatation of the right ventricle.

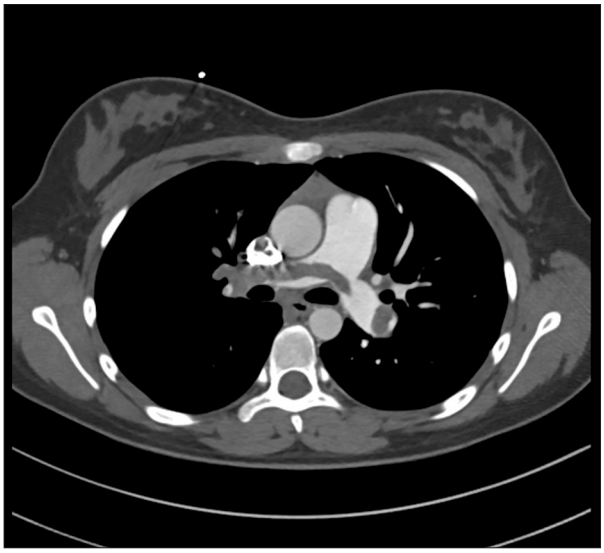


Figure 1. Computed tomography showing a large 'saddle' embolus occluding the right pulmonary artery.

she was heterozygote for the prothrombin G20210A mutation. Due to severe menstrual bleedings, she had initiated use of second-generation COCs containing 250 µg norgestimate and 35 µg ethinylestradiol once daily 9 months before admission. The use of this contraceptive was discontinued at admission, and she was strictly advised to never resume treatment.

Discussion

COC-users heterozygote for the prothrombin G20210A mutation have been found to have a 7–10-fold increased risk of VTE, with the risk being highest early in the course of COC use [8–10]. This combination thus results in an at least additive and maybe even a synergistic prothrombotic effect. Whether the risk is further increased in individuals who additionally have

a thrombophilic phenotype is not known. However, a positive family history, defined as a documented VTE in a first-degree relative, is an established individual risk factor for VTE (3-fold VTE risk) [9] and is therefore assumed to also be important in individuals with hereditary thrombophilia [5].

Current WHO guidelines advise against use of COCs in females with any known prothrombotic mutation [11]. However, several clinicians advocate that an individualized risk assessment where several risk factors, including the specific thrombophilia, age, and individual and family history of VTE, should be taken into consideration when counseling females with thrombophilia about contraceptive use [5,7,10]. Low-risk thrombophilia alone, such as the prothrombin G20210A mutation, is considered by some to be a relative, but not absolute, contraindication for COC use [6,7]. However, as emphasized by this case report, it is important to consider not just the inherited genotype but also the inherited phenotype when evaluating the risk of thrombosis. Since a prothrombotic genotype does not necessarily result in a prothrombotic phenotype, and vice versa, they should be considered as separate and potentially interacting risk factors [3,5,10]. Unprovoked venous thrombosis in a first-degree relative occurring before 50 years of age indicate a strongly thrombophilic phenotype, and should therefore be considered a relative contraindication for COC use, regardless of the patient´s genotype [5].

The family history of our patient indicated a strongly thrombophilic phenotype, which in combination with the prothrombotic effects of both the mutation and COCs resulted in a life-threatening major thrombotic event. Future treatment with COCs or other types of estrogen-containing hormonal preparations (i.e., hormone replacement therapy) is contraindicated. Non-hormonal methods or oral progestin-only contraceptives should be preferred in this patient and others where treatment with COCs is expected to impose an unacceptably high risk of VTE [11,12].

Current evidence does not support anticoagulant therapy of higher intensity or longer duration than normal when treating VTE patients with the prothrombin G20210A mutation [5]. Our patient was thus started on warfarin with target INR 2.0-3.0 and planned duration of 12 months [13]. A non-vitamin K antagonist oral anticoagulant (NOAC; dabigatran, rivaroxaban, or apixaban) might be an equally effective and safe treatment compared to warfarin in this patient [13,14]. However, patients with pulmonary embolism treated with thrombolysis were not included in phase III trials on NOACs, and data on long-term prophylaxis and treatment of VTE with NOACs are warranted.

Conclusions

Initiation of COCs should be based on individualized risk assessment with all potential risk factors for VTE, including both genotype (if available) and phenotype, taken into account. Other contraceptive methods should be considered in patients with an increased risk of VTE.

Conflicts of interest

None relevant to this manuscript.

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