The Impact of Multiple Risk Factors for Venous Thromboembolism and Its Implications for Management

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Abstract

Venous thromboembolism (VTE) is a rare multifactorial disorder in childhood with an annual incidence of about 0.07 to 0.14 per 10 000 children. A 15-year-old female with a body mass index of 48 kg/m^2 who endorsed oral contraceptive use presented with clinical findings consistent with deep venous thrombosis along with the presence of a pulmonary embolism. Further workup revealed that the patient was heterozygous for factor V Leiden and homozygous for prothrombin G20210A mutations. There are no current pediatric guidelines for the antithrombotic management of patients with multiple risk factors for VTE. Two such risk factors, obesity and the use of estrogen-containing hormone contraceptives, have been implicated in adult VTE cases but have not been clearly delineated in pediatric patients. The need for guidance regarding the VTE management of these patients has become more apparent given the increasing incidence of childhood obesity and the number of adolescents using oral contraceptives. Additionally, thrombophilia testing remains controversial though testing may be indicated in asymptomatic first-degree relatives and in families with antithrombin, protein C, or protein S deficiencies. Given the increased incidence of multiple risk factors for VTE, there is also a need to develop a comprehensive risk assessment tool for pediatric patients at high risk of VTE.

Keywords

venous thromboembolism, pulmonary embolism, thrombophilia, adolescence, obesity

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Case Report

Venous thromboembolism (VTE) is a rare multifactorial disorder in pediatrics with an annual incidence of about 0.07 to 0.14 per 10 000 children.[1-3] In contrast to adults, VTE in children is often associated with clinical risk factors. Chief among these risk factors is the presence of a central venous catheter that accounts for 90% of VTE in neonates and 50% in older children and adolescents.[4] Additional risk factors include congenital heart disease, malignancy, surgery, impaired mobility, medications such as asparaginase and estrogen-containing contraceptives, and inherited thrombophilia.[4] Several studies have developed risk-prediction models for VTE. To date, these studies have not looked into whether having multiple VTE risk factors should impact duration of anticoagulation and whether having multiple risk factors should be an indication for thrombophilia testing.

Thrombophilia testing continues to be a point of discussion in determining which patients benefit from testing and how these results affect their management. Some studies have reported that most pediatric patients have at least one acquired clinical risk factor for VTE and that a single thrombophilic defect alone is not enough to cause VTE.[4] Additionally, the efficacy of prophylactic anticoagulation in patients with a known history of thrombophilia has not been validated in pediatric studies. Also, there are potential negative psychosocial effects (knowing that one is a carrier, difficulty in obtaining health and life insurance) to thrombophilia testing.[4] Yet there is evidence that protein C, protein S, and antithrombin deficiencies and elevated factor VIII levels are

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present in 10% of pediatric patients with VTE and that this group of patients is a high risk of VTE.[5] Additionally, asymptomatic patients who have first-degree relatives with VTE may benefit from thrombophilia testing, which may help guide their choices for contraception or help in guiding health behaviors, such as obesity and smoking, which may place them at higher risk.[4] Given the increased diagnosis of VTE children, there is a need to investigate whether having multiple risk factors for thrombosis should affect duration of anticoagulation therapy and whether or not thrombophilia testing is indicated in this setting.

Ethical Approval and Informed Consent

According to the University of Illinois (UIC) Policy, "Determination Whether Activities Represent Human Subjects Research at UIC," the Office for the Protection of Research Subjects has determined that case reports pertaining to a single individual do not represent human subjects research and do not require submission of a determination application. As no patient identifiers or protected health information were utilized in this case report, informed consent was not needed.

Hospital Course

A 15-year-old previously asymptomatic Caucasian female presented with a 3-day history of right leg pain and right-sided chest pain. She endorsed oral contraceptive use for the last 9 months prior to presentation. Her family history was remarkable for her maternal grandmother having VTE during adolescence while taking oral contraceptive pills. Given her presenting symptoms and history, VTE and pulmonary embolism (PE) were suspected. On examination, her body mass index (BMI) was 48 kg/m^2, greater than the 99th percentile for age, gender, and height percentile. She was both tachycardic and tachypneic on presentation. Her diagnostic workup was significant for a chest computed tomography (CT) angiogram that showed pulmonary emboli in both the right and left pulmonary branch arteries and an infarct in the right lower lung lobe. Her electrocardiogram was significant for sinus tachycardia, and an echocardiogram performed did not show evidence of right ventricular hypertrophy. A right lower extremity Doppler was significant for a nonocclusive, subacute thrombus in the common femoral vein, and an occlusive, subacute thrombus in the femoral and popliteal veins. The patient was started on therapeutic anticoagulation with subcutaneous enoxaparin.

Final Diagnosis

Given the family history of thrombosis, an inherited thrombophilia workup was performed and was notable for the patient being heterozygous for factor V Leiden (F5.0001, c.1691G>A, p.Arg506Gln located at 1q23) and homozygous for prothrombin G20210A (F2.0009; c.20210G>A located at 11p11-q12). The patient was discharged home to continue anticoagulation for a total duration of therapy of 6 months.

Discussion

Pulmonary embolism is less common in pediatric patients compared with adults, with an annual incidence of 0.12 to 0.9 per 100 000 in the general population.[6] Estrogen or combination estrogen-progesterone oral contraceptives are used in the management of different clinical scenarios including contraception, acne, hirsutism, dysmenorrhea, and menorrhagia. The risk for thrombosis in adolescent patients who take estrogen-containing oral contraceptive pills is 15 to 25 per 100 000 per year, compared with 5 per 100 000 who do not take oral contraceptives.[7] Children with multi-trait thrombophilia, such as our patient, have a 24-fold increase in recurrent VTE in comparison to children without inherited thrombophilia.[1-5]

Obesity has been reported as an independent risk factor for VTE. Obesity, in conjunction with oral contraceptive use, has also been reported as a risk factor for VTE among adolescents.[8,9] Currently, there are more than 31% of children from 2 to 19 years of age in the United States who are considered overweight (defined as BMI of 25-29.9 kg/m^2), almost 17% are considered obese (defined as BMI $\geq$30 kg/m^2), and each of these figures continues to rise.[5] The patient in our case was considered to be morbidly obese (BMI >40 kg/m^2) by this definition. A meta-analysis involving 8125 patients with VTE and 23 272 control patients indicated that the likelihood of first spontaneous VTE among obese patients was more than twice that of individuals with a normal BMI.[5] Additionally, a prospective cohort study of 87 226 women showed that the relative risk of unprovoked PE increased by approximately 8% per 1 kg/m^2 increase in BMI and approached a nearly 6-fold greater risk among individuals with a BMI $\geq$35 kg/m^2.[5] Obese women have twice the risk of VTE, with obese adult women who use oral contraceptives having a 10-fold increased VTE risk as compared with the general population.[8,9]

Obesity has been implicated in increasing procoagulant factors VII, VIII, XII, and fibrinogen.[3,8,9] Inherent differences exist between adolescents and adults with regard to concentrations of endogenous procoagulants

and anticoagulants.[3,10] Adolescents exhibit decreased procoagulants, increased endogenous anticoagulant inhibitors, and decreased endogenous anticoagulants as compared with adults.[3,10] These coagulation differences, in conjunction with decreased overall incidence in adolescence of acquired VTE risk factors such as tobacco use, type 2 diabetes mellitus, and cardiovascular disease might account for the decreased risk of oral contraceptive–associated risk of VTE in adolescents.[10] There remains a need to learn more about profile changes between children younger than 18 years of age and adult women who were taking oral contraceptives.[10]

The current recommendations by the US Medical Eligibility Criteria for Contraceptive Use for contraception for women with inherited thrombophilia and a personal history of VTE are that combination progesterone-estrogen oral contraceptives should be avoided.[11,12] A 2015 case-control study of 10 000 women with VTE reported a 3.64 to 4.28 increased risk of VTE in adult women taking combined oral contraceptives (COCs) containing desogestrel, gestodene, cyproterone, or drospirenone, and a 2.38 increased risk of VTE in women taking COCs with levonorgestrel.[11,12] The increased risk of VTE associated with COCs is highest in women with 2 or more inherited thrombophilia or patients who are homozygous for a single defect.[12] The contraceptive recommendation for women with inherited thrombophilia desiring a long-acting reversible contraceptive is a copper-releasing intrauterine device.[12] For women preferring a short-acting contraceptive and who accept a small increased risk in VTE, a levonorgestrel-releasing intrauterine device is recommended.[12]

Thrombophilia testing in pediatric VTE remains controversial. In the presence of a provoked VTE, thrombophilia testing has limited implications on duration or intensity of anticoagulation therapy.[13] However thrombophilia testing in asymptomatic first-degree relatives may be useful in families with antithrombin, protein C, or protein S deficiency.[5] A meta-analysis of published observational studies from 1970 to 2007 revealed that inherited deficiencies of protein C, protein S, and antithrombin are present in 10% of patients with VTE.[5] Additionally, patients with these deficiency states are considered at higher risk for the first episode of VTE. These patients, along with patients with 2 or more inherited genetic traits, had an increased risk of recurrent VTE.[5] More studies are needed to determine the duration of anticoagulation in adolescents with multiple VTE risk factors, as current therapeutic recommendations are not modifiable based on thrombophilia, obesity, or oral contraceptive use.[4,10,11]

Thrombophilia testing is not cost-effective and therefore should not routinely be performed. Thrombophilia panel testing costs Medicare an estimated $300 million to $670 million annually.[14] Additionally, patients found to have an inherited thrombophilia report negative psychosocial effects including difficulty in obtaining health or life insurance.[15] It may be reasonable to postpone testing in asymptomatic children until they are old enough to decide for themselves after considering the benefits of testing.[14]

Given the increased incidence of obesity and the increased use of oral contraceptive treatment among adolescent patients, practitioners will continue to encounter patients who have multiple VTE risk factors. This increases to need to have screening tests that risk stratifies patients who are at high risk of VTE. Multiple scoring systems and algorithms have been utilized in the clinical setting. The Wells Scoring System is validated for use in the outpatient adult setting, but does not take into account obesity or oral contraceptive use in its criteria.[15] Using this scoring system, our patient would be at moderate risk of VTE given her lower extremity swelling and tenderness. Recently, evidence has emerged that the Wells Scoring System has a higher failure rate and a lower efficiency in the inpatient adult setting compared with that reported in the outpatient literature and is therefore not validated in the inpatient setting.[16]

Pediatric studies have shown that elevated factor VIII and D-dimer levels at VTE diagnosis may predict higher rates of recurrence and post-thrombotic syndrome, but more prospective studies are needed to determine which patient subset is at increased risk and whether higher risk patients would benefit from more aggressive anticoaguluation.[17,18] Our patient had elevated D-dimer levels (9 mg/mL, upper limit of normal is below 1 mg/mL), but did not have factor VIII levels measured. The Peds-Clot Clinical Decision Rule (PCDR) incorporates oral contraceptive use as a significant risk factor in VTE development, but does not include obesity or thrombophilia in its risk-prediction model.[19] Applying this tool to our patient's case, the patient would be defined as high-risk given her direct admission to the pediatric intensive care unit (0.5 points) and her oral contraceptive pill use (2 points), with a positive predictive value of VTE of 2.45%. While high BMI (BMI >30 kg/m^2) was not included in the final risk-prediction PCDR model, the prevalence of high BMI in hospitalized children with VTE is emerging especially in the adolescent and young adult populations.[19] The Lee et al group at Children's Hospital of Boston developed a risk-assessment tool to help guide CT angiography in pediatric patients suspected of having PE. The tool includes assessment of immobilization, hypercoagulability (thrombophilia or systemic disease such as malignancy), excess estrogen state (pregnancy or oral contraceptive pill use), presence

of an indwelling central venous catheter, and prior PE or DVT.[20] Utilizing this tool by the Lee et al group, our patient's VTE risk factors include her hypercoagulable state ($P = .003$) and her excess estrogen state ($P = .002$). Given the presence of these 2 risk factors as the clinical threshold, the sensitivity of a positive PE result on CT imaging is 89% and the specificity is 94%.[20] The risk factors assessed in this tool, coupled with inclusion of obesity assessment (especially for patients with BMI ≥ 30 kg/m^2), could serve as a comprehensive risk assessment tool for pediatric patients at high risk of VTE.

Conclusion

There are no current pediatric guidelines for the antithrombotic management of patients with multiple risk factors for VTE. The need for guidance regarding the VTE management of these patients is pertinent given the increasing incidence of childhood obesity and the number of adolescents and young adults using estrogen-containing oral contraceptives. Additionally, thrombophilia testing remains controversial though testing may be indicated in asymptomatic first-degree relatives with antithrombin, protein C, or protein S deficiencies or elevated factor VIII levels. Given the increased incidence of multiple risk factors for VTE, there is also a need to develop a comprehensive risk assessment tool for pediatric patients at high risk of VTE.

Author Contributions

APG: planning, research, manuscript development, editing, and manscript revision;
PK: planning, manuscript review, editing, and feedback.

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