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Case Report

Deep Vein Thrombosis as the Presenting Sign in an Adolescent With New-Onset Type 2 Diabetes

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Abstract

Prothrombin G20210A mutation occurs in only 2% to 3% of the population, but usually does not become apparent unless the individual exhibits another risk factor for clotting. A risk factor such as hyperglycemia in the setting of diabetes mellitus may accelerate this clotting process, even at a very young age. In this case report, we discuss a 15-year-old boy presenting with left calf swelling and pain, found to have extensive deep vein thrombosis in the setting of hyperglycemia and a newly discovered prothrombin *G20210A* mutation. Venous thromboembolism in the setting of type 2 diabetes mellitus has not been described in children.

Key Words: diabetes, deep vein thrombosis, pediatric, prothrombin mutation

Abbreviations: HbA_{1c}, glycated hemoglobin A_{1c}.

Introduction

While previous literature has described the connection between elevated blood sugar and blood clotting due to increased clotting factors and platelet reactivity during hyperglycemia-induced oxidative stress, this association is usually not apparent in pediatric patients [1-3]. The low rate of blood clots may be due to the absence of comorbidities like hyperlipidemia, hypertension, and insulin resistance in most pediatric patients. Although rare, patients younger than 18 years may develop thrombi after the perfect storm of a procoagulation mutation and elevated blood glucose, usually in the setting of diabetes mellitus.

Case Presentation

A previously healthy, obese (body mass index 34, >99th percentile) 15-year-old boy presented to the emergency room with a 2-day history of left hip pain radiating down to the left calf and 1 day of swelling of the left calf. He also endorsed purple discoloration of the left lower extremity after walking. The patient denied prolonged immobilization, recent infections, or vaccinations. Besides the pain, he denied other symptoms on review of systems such as polyuria, polydipsia, polyphagia, and nocturia. There was no known family history of deep vein thrombosis, pulmonary embolism, stroke, or early myocardial infarction. There was a strong family history of diabetes, likely type 2, in the boy's mother, maternal aunt, and maternal grandfather. Physical examination was remarkable for left lower-extremity swelling but no acanthosis nigricans.

Diagnostic Assessment

The differential diagnosis for lower-extremity pain and swelling in this patient included muscle sprain/tear and broken bones (which were ruled out with no history of trauma); soft tissue, muscle, joint, or bone infection (which were ruled out with no history of fever or recent infection); venous valvular insufficiency (unlikely due to age and acuteness of swelling); lymphedema (unlikely due to acuteness of swelling); and deep vein thrombosis. Ultrasound of both hips was negative for joint effusions, radiograph of the lower extremities was unremarkable, and an ultrasound of the veins of both lower extremities was negative. D-dimer was mildly elevated at 3.29 nmol/L (0.6 µg/mL; reference 0-2.74 nmol/L [0-0.5 µg/mL]). Other laboratory values were significant for serum glucose of 31.7 mmol/L (572 mg/dL; reference 4-6 mmol/L [54-117 mg/dL]). Glycated hemoglobin A_{1c} (HbA_{1c}) was 105.5 mmol/mol (11.8%; reference 13.7-37.7 mmol/mol [3.4%-5.6%]). The patient had a normal anion gap, serum osmolality, and bicarbonate, ruling out diabetic ketoacidosis and hyperosmolar hyperglycemic state. A local pediatric endocrinologist was contacted for an outpatient appointment. The pain in the patient's left lower extremity, however, increased and swelling persisted, so the patient returned to the hospital the following day. A computed tomography of the abdomen and pelvis with contrast revealed a filling defect in the inferior vena cava consistent with a thrombus (Fig. 1). The thrombus was also noted within the left common iliac, left external iliac, left internal iliac, and left common femoral veins (also shown in Fig. 1).

Treatment

The patient was given 10 mg/kg subcutaneous enoxaparin and transferred to our children's hospital. Once transferred, an unfractionated heparin infusion was begun. He was initially

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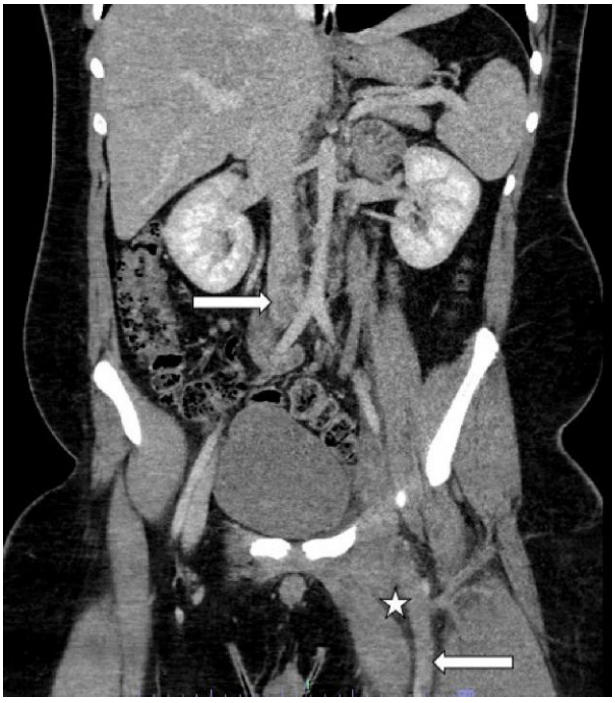

Figure 1. Computed tomography of the abdomen/pelvis demonstrating a clot extending from the left femoral vein into the inferior vena cava (arrows). Surrounding inflammatory changes/phlebitis in the left lower extremity (star), as demonstrated by fat stranding and increased attenuation, when compared with the right lower extremity.

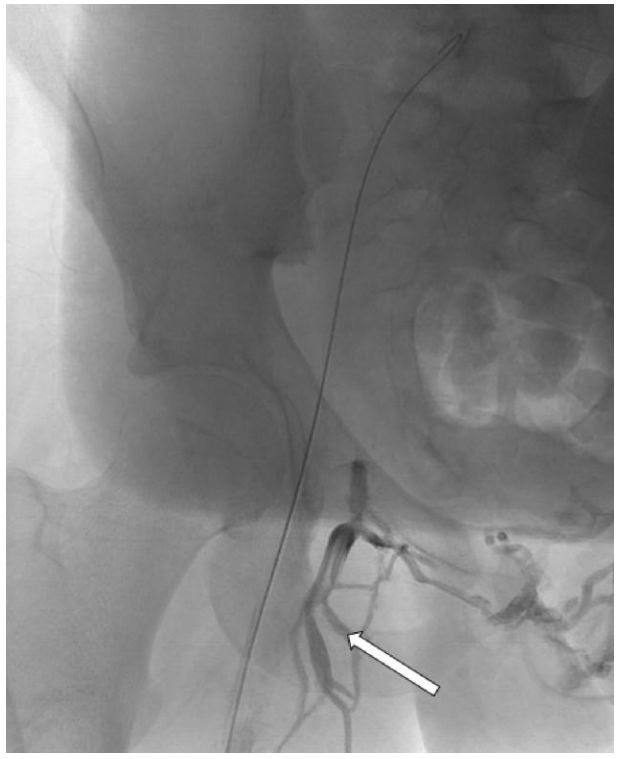

Figure 2. Angiogram demonstrating a guidewire traversing the completely occluded left iliac system prior to thrombectomy. Venogram through the left popliteal vascular sheath shows no contrast seen through the thrombosed and occluded iliac vessels where the wire was placed; instead, it flows through the contralateral collateral peritoneal vessels for venous drainage (arrow).

started on approximately 0.4 units/kg/day of insulin (glargine in the evenings and correction with lispro) while fasting in preparation of a possible procedure. Blood glucose readings were mostly in the low 200s. An echocardiogram was within normal limits, and there was no sign of pulmonary embolism or right heart strain. The following day, the patient underwent image-guided thrombolysis and thrombectomy (Fig. 2). Tissue plasminogen activator was instilled from the popliteal vein to the left iliac, leading to resolution of 50% of the thrombus. He received continuous heparin infusion into the left popliteal vein as well as tissue plasminogen activator after surgery. As the clot improved over the subsequent days, he underwent image-guided angioplasty and removal of the popliteal sheath. He was transitioned to enoxaparin with a goal anti-Xa level between 500 and 1000 IU/L (0.5 and 1.0 IU/mL). Laboratory tests showed a normal C-peptide (3.6 nmol/L [1.2 ng/mL], reference 3.3-13.3 nmol/L [1.1-4.4 ng/mL]) despite hyperglycemia, supporting the diagnosis of type 2 diabetes, in addition to negative antiglutamic acid decarboxylase 65, insulin, islet cell, and zinc transporter 8 antibody titers. Lipid panel was significant for hypertriglyceridemia of 1.83 mmol/L (162 mg/dL; reference 0-1.01 mmol/L [0-89 mg/dL]). Once able to eat after surgery, the regimen was increased to 0.5 units/kg/day of insulin, resulting in blood glucose readings mostly in the mid 100s.

Outcome and Follow-up

The patient received a staged thrombophilia workup including antithrombin III activity (normal), factor V Leiden polymerase chain reaction (normal), and prothrombin gene polymerase chain reaction. His factor II (prothrombin G20210A) DNA was heterozygous, consistent with a 2- to 4-fold increased risk of venous thromboembolism. The rest of the thrombophilia workup, including protein C and protein S, ended up being negative in the outpatient setting. The patient was discharged on enoxaparin, as well as insulin glargine and a sliding scale of insulin lispro due to difficulty with family understanding carbohydrate counting. Metformin extended-release 1000 mg daily with dinner was prescribed for home. He received extensive education regarding type 2 diabetes. He is being followed by the hematology/oncology and endocrinology departments.

After completing 20 weeks of enoxaparin, remnants of the clot remained, leading to starting on rivaroxaban. The clot dissolved over the next 8 months and rivaroxaban was stopped. The patient now follows up with his hematologist as needed. The family was informed of the need to notify the hematology department of any acute symptoms suggestive of the recurrence of a clot. The family was also encouraged to notify the hematology department of anticipated periods of prolonged immobility, as the patient may require thromboprophylaxis given his underlying proclotting gene mutation. Regarding the diabetes, the patient's blood glucose remained under satisfactory control. His most recent HbA_{1c} was 55.2 mmol/mol (7.2%; 14 months following hospitalization), and he wears a continuous glucose monitor.

Discussion

Several studies have investigated the association between hyperglycemia and thrombosis. Hyperglycemia activates platelet aldolase reductase and creates sorbitol, which

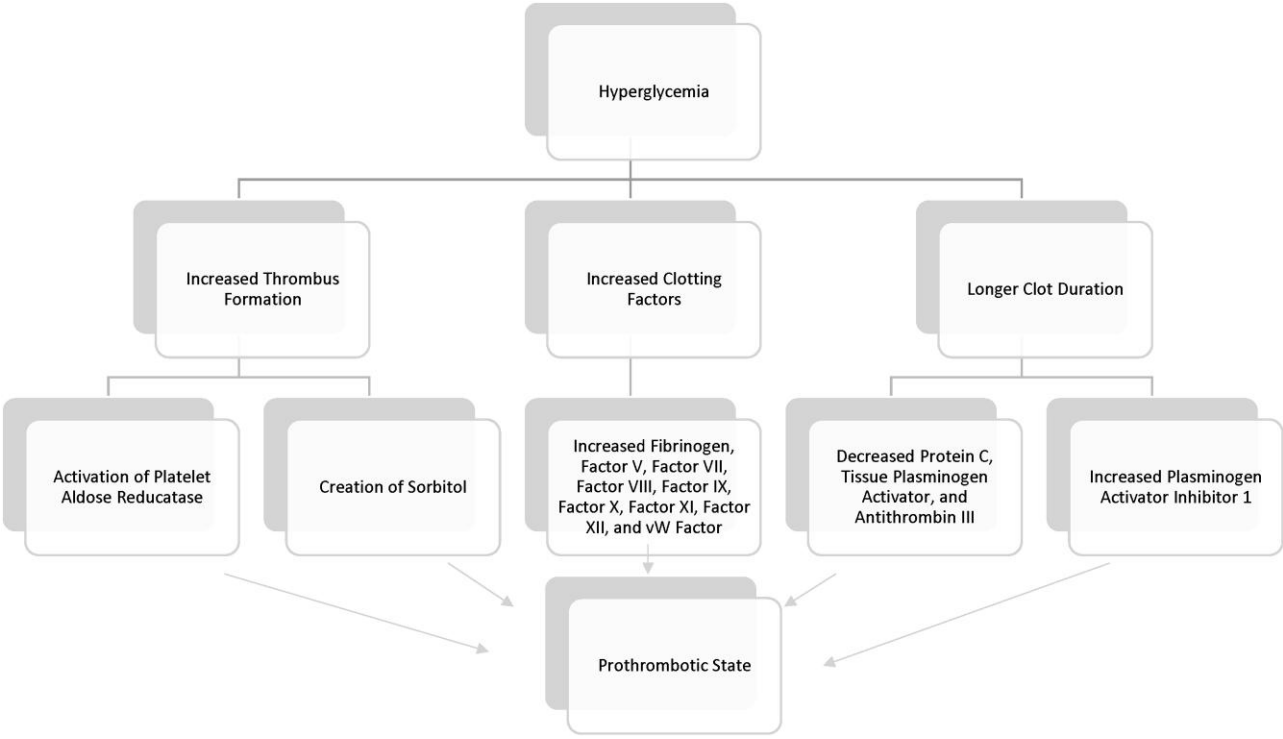

Figure 3. Flowchart summarizing the connection between hyperglycemia and increased clotting activity. vW, von Willebrand.

accelerates microtubule polymerization and thus increases platelet volume, platelet reactivity, and thrombin formation [1]. In addition to affecting platelets, hyperglycemia and insulin resistance may increase the presence of fibrinogen, factor V, factor VII, factor VIII, factor IX, factor X, factor XI, factor XII, and von Willebrand factor [2, 4], which also increases the risk of thrombosis. Sarkar and colleagues [5] studied infants of diabetic mothers and found decreased protein C activity compared with infants of euglycemic mothers. In addition to protein C, individuals with diabetes also have decreased antithrombin III, increased concentration of plasminogen activator inhibitor 1, and decreased concentration of tissue plasminogen activator, which all lead to longer duration of clots [4]. The connection between hyperglycemia and increased clotting activity is summarized in Fig. 3. Though other risk factors such as obesity, inflammation, and lifestyle factors (smoking, alcohol use, low exercise level) usually exist in patients with diabetes mellitus, especially type 2, Klein et al [2] adjusted the data for the aforementioned factors and found that insulin resistance was directly associated with hypercoagulability in young adults. Piazza and associates [6] also report similar results—diabetes was the only factor to be a significant independent predictor of recurrent deep vein thrombosis in their study of adults (adjusted odds ratio of 1.74).

The current data regarding clotting and diabetes are mostly among adults and, to date, there are limited data regarding mechanisms of clotting specifically in pediatric patients with type 2 diabetes. In their study of children with type 1 diabetes, Jasser-Nitsche et al [3] explain that high glucose levels damage the endothelium through oxidative stress, advanced glycation end products, and/or osmotic forces. This damage leads to a prothrombotic state, as the endothelium then releases activated tissue factor. Tissue factor is a membrane glycoprotein that forms atherosclerotic plaques [7]. Tissue-factor pathway inhibitor is synthesized by endothelial cells and megakaryocytes and regulates tissue factor-initiated coagulation [7]. The quantity of tissue factor inhibitor is, on average, lower in children than adults; however, Bratseth et al [7, 8] found that tissue-factor pathway inhibitor was significantly higher in children with type 1 diabetes. An increased insulin level raises tissue-factor procoagulant activity [9]. Additionally, hyperglycemia increases platelet-endothelial cell adhesion and coagulation factor release by affecting the glycocalyx (a layer of protective glycoproteins) in vessel walls [9]. Insulin usually stops platelet activation and aggregation in healthy individuals, but those with type 2 diabetes are resistant to the effects insulin has on the platelets [10]. Adult patients with type 1 and type 2 diabetes have a 1.4- to 2-fold increased risk of thromboembolism [10, 11]. Several case reports have also discussed an increased risk of thrombosis in diabetic pediatric patients with femoral venous catheters, which is another risk factor for clotting [12, 13].

In the White population, 2.7% of people are heterozygous for the 20210A allele of the common factor II polymorphism 20210G/A in the untranslated 3′ region of the prothrombin gene [14]. Individuals with this mutation usually have a slightly increased amount of factor II (also known as thrombin), which converts fibrinogen to fibrin to strengthen a clot [14]. Although there is no direct genetic link between single-nucleotide variation (formerly known as single-nucleotide polymorphism) in G20210A and the prothrombin genes with type 2 diabetes [15], the presence of this mutation increases the risk for thrombosis by 2- to 4-fold [16]. In the cohort study by Momot et al [16], the average age of acute venous thrombosis in women of reproductive age with this mutation was 30.7 ± 4.3 years. Compared with this finding, our patient was quite young at age 15 years to experience a

deep vein thrombosis, which raises the question of whether the age of presentation is affected by other factors such as patient sex or presence of other comorbidities like diabetes mellitus, obesity, hyperlipidemia, and hypertension. In addition to diabetes mellitus, our patient also exhibited obesity and hypertriglyceridemia.

Few case reports exist in the literature discussing pediatric patients with type 2 diabetes and risk of thrombosis. One describes a 26-year-old man with Klinefelter syndrome and type 2 diabetes who presented with a deep vein thrombosis of the lower extremity in the setting of heterozygosity of both factor V G1291A and prothrombin G20210A [17] and the other, a 10-year-old girl in diabetic ketoacidosis who developed sinus thrombosis in the setting of heterozygosity of prothrombin 20210A [14]. Our patient exhibited a clot in the setting of prothrombin G20210A mutation and diabetes like both patients, but he was aged 15 years (younger than the first patient and older than the second), and the clot appeared in his lower extremity (unlike the second patient). Haller and Rosenbloom both described children with type 1 diabetes, clots (lower-extremity arterial thrombus and cerebral infarction, respectively), and factor V Leiden mutation [18, 19]. The literature has also clearly demonstrated case reports of children developing blood clots in the setting of diabetic ketoacidosis in type 1 diabetes, further worsened by the presence of a central venous line [13, 20, 21]. In these papers, the diabetes and ketoacidosis were detected first and then the clots, which is different from our paper in which the thrombosis was the presenting sign and symptom. Our patient's extensive deep vein thrombosis extending from the inferior vena cava to the iliac and femoral veins (requiring thrombectomy and angioplasty) is also quite uncommon in a pediatric patient. Clots of this severity are rarely reported in the literature, which makes his genetic and clotting findings significant.

It will be essential for the patient to continue close outpatient care with endocrinology and hematology due to risk of recurrence. In their study of adults with deep vein thromboses, Piazza and colleagues [6] found that diabetic individuals had a 74% increase in the risk of recurrent deep vein thrombosis following an initial clot, with a median time of 94 days.

To our knowledge, this is the first reported case of deep vein thrombosis in a pediatric patient with type 2 diabetes. Our patient's hyperglycemia caused by his new-onset type 2 diabetes may have led to the onset of an extensive deep vein thrombosis at an unusually young age, since he had an underlying heterozygous prothrombin G20210A mutation. Our case also illustrates the need for a multidisciplinary approach (involving endocrinology, hematology/oncology, pediatric intensive care unit, and interventional radiology) for successful outcomes in these patients. Physicians should consider obtaining a serum glucose level or HbA_{1c} on their patients with deep vein thromboses to rule out diabetes mellitus, especially in children and adults with suspected metabolic syndrome (obesity, hyperlipidemia, etc). Genetic mutations affecting the clotting pathway should also be screened in pediatric patients with extensive deep vein thromboses.

Learning Points

- Hyperglycemia leads to an increased risk of thrombosis, especially in patients with known or unknown genetic mutations affecting clotting.
- Deep vein thrombosis may develop in pediatric patients with new-onset type 2 diabetes and may be the presenting symptom.
- When a pediatric patient is diagnosed with an extensive thrombosis, investigation into proclotting mutations and metabolic causes (such as checking blood glucose to screen for diabetes) should occur.

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Contributors

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Disclosures

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Informed Patient Consent for Publication

Signed informed consent obtained directly from the patient's relatives or guardians.

Data Availability Statement

Data sharing is not applicable to this article as no data sets were generated or analyzed during the current study.

References

1. Rusak T, Misztal T, Rusak M, Branska-Januszewska J, Tomasiak M. Involvement of hyperglycemia in the development of platelet procoagulant response: the role of aldose reductase and platelet swelling. *Blood Coagul Fibrinolysis*. 2017;28(6):443-451.
2. Klein OL, Okwuosa T, Chan C, *et al.* Changes in procoagulants track longitudinally with insulin resistance: findings from the coronary artery risk development in young adults (CARDIA) study. *Diabet Med*. 2014;31(4):462-465.
3. Jasser-Nitsche H, Haidl H, Cvirn G, *et al.* Increased tissue factor activity promotes thrombin generation at type 1 diabetes onset in children. *Pediatr Diabetes*. 2020;21(7):1210-1217.
4. Vojtková J, Motyková K, Bánovčin P. Possible association between haemostasis dysfunction and early onset of microvascular complications in patients with type 1 diabetes. *Pediatr Endocrinol Diabetes Metab*. 2020;26(2):89-96.
5. Sarkar S, Hagstrom NJ, Ingardia CJ, Lerer T, Herson VC. Prothrombotic risk factors in infants of diabetic mothers. *J Perinatol*. 2005;25(2):134-138.
6. Piazza G, Goldhaber SZ, Kroll A, Goldberg RJ, Emery C, Spencer FA. Venous thromboembolism in patients with diabetes mellitus. *Am J Med*. 2012;125(7):709-716.

7. Bratseth V, Margeirsdottir HD, Heier M, *et al*. Procoagulant activity in children and adolescents on intensive insulin therapy. *Pediatr Diabetes*. 2020;21(3):496-504.
8. Achey MA, Nag UP, Robinson VL, *et al*. The developing balance of thrombosis and hemorrhage in pediatric surgery: clinical implications of age-related changes in hemostasis. *Clin Appl Thromb Hemost*. 2020;26:1076029620929092.
9. Lemkes BA, Hermanides J, Devries JH, Holleman F, Meijers JC, Hoekstra JBL. Hyperglycemia: a prothrombotic factor? *J Thromb Haemost*. 2010;8(8):1663-1669.
10. Petrauskiene V, Falk M, Waernbaum I, Norberg M, Eriksson JW. The risk of venous thromboembolism is markedly elevated in patients with diabetes. *Diabetologia*. 2005;48(5):1017-1021.
11. Ageno W, Becattini C, Brighton T, Selby R, Kamphuisen PW. Cardiovascular risk factors and venous thromboembolism: a meta-analysis. *Circulation*. 2008;117(1):93-102.
12. Gutierrez JA, Bagatell R, Samson MP, Theodorou AA, Berg RA. Femoral central venous catheter-associated deep venous thrombosis in children with diabetic ketoacidosis. *Crit Care Med*. 2003;31(1):80-83.
13. Worly JM, Fortenberry JD, Hansen I, Chambliss CR, Stockwell J. Deep venous thrombosis in children with diabetic ketoacidosis and femoral central venous catheters. *Pediatrics*. 2004;113(1):e57-e60.
14. Zerah M, Patterson R, Hansen I, Briones M, Dion J, Renfroe B. Resolution of severe sinus vein thrombosis with super selective thrombolysis in a pre-adolescent with diabetic ketoacidosis and a prothrombin gene mutation. *J Pediatr Endocrinol Metab*. 2007;20(6):725-731.
15. Wakim-Ghorayeb SF, Keleshian SH, Timson G, *et al*. Factor V G1261A (Leiden) and prothrombin G20210A single-nucleotide polymorphisms in type 2 diabetes mellitus. *Am J Hematol*. 2005;80(1):84-86.
16. Momot AP, Nikolaeva MG, Yasafova NN, Zainulina MS, Momot KA, Taranenko IA. Clinical and laboratory manifestations of the prothrombin gene mutation in women of reproductive age. *J Blood Med*. 2019;10:255-263.
17. Ayli M, Ertek S. Serious venous thromboembolism, heterozygous factor V Leiden and prothrombin G20210A mutations in a patient with Klinefelter syndrome and type 2 diabetes. *Intern Med*. 2009;48(18):1681-1685.
18. Haller MJ, Valladares A, Rosenbloom AL. Arterial thrombosis resulting in amputation in a child with poorly controlled type 1 diabetes and heterozygous factor V Leiden mutation. *Pediatr Diabetes*. 2006;7(4):229-231.
19. Rosenbloom AL. Fatal cerebral infarctions in diabetic ketoacidosis in a child with previously unknown heterozygosity for factor V Leiden deficiency. *J Pediatr*. 2004;145(4):561-562.
20. Davis J, Surendran T, Thompson S, Corkey C. DKA, CVL and DVT. Increased risk of deep venous thrombosis in children with diabetic ketoacidosis and femoral central venous lines. *Ir Med J*. 2007;100(1):344.
21. Cherian SV, Khara L, Das S, Hamarneh WA, Garcha AS, Frechette V. Diabetic ketoacidosis complicated by generalized venous thrombosis: a case report and review. *Blood Coagul Fibrinolysis*. 2012;23(3):238-240.