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Post infection Purpura Fulminans in a patient heterozygous for Factor V Leiden and transient protein S deficiency

الفرفرية المتفجرة بسبب الالتهابات عند مريض حامل لطفرة "لايدن" مع نقص مؤقت في عامل إس (S)

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Abstract:

Purpura fulminans usually consists of large, often symmetrical, spreading ecchymosis, which may later develop into extensive areas of skin necrosis and peripheral gangrene as well as intra abdominal thrombosis. Postinfectious purpura fulminans has been described in a few cases. The interaction and the contribution of the mutations such as factor V Leiden and prothrombin G20210A to the development and progression of postinfectious purpura fulminans and venous thrombosis is a rare occurrence. We describe a patient heterozygous for factor V Leiden mutation who developed purpura fulminans secondary to acquired protein S deficiency associated with recent varicella infection.

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ملخص:

الفرفرية المتفجرة(Purpura Fulminans) عادة تتكون من نزيف كبير تحت الجلد يصيب الأطراف بشكل متماثل قد يتطور فيما بعد إلى نخر في الجلد و إلى غرغرينا الأطراف بالإضافة إلى جلطات داخل البطن. الفرفرية المتفجرة المصاحبة للإلتهابات وصفت في عدة حالات لكن العلاقة أو المساهمة التي تقدمها طفرة "لايدن" الجينية في العامل الخامس و طفرة G20210A في العامل الثاني (بروثرومبين) في تكوين هذا المرض غير معروفة. نعرض في هذه المخطوطة حالة فرفرية متفجرة عند طفل يبلغ من العمر خمس سنوات بسبب

إعتلال وظيفي وراثي في العامل الخامس من عوامل التجلط مع نقص حاد مكتسب و مؤقت في بروتين إس ناتج عن التهاب حاد بـــ فيروس جدري الماء.

Introduction

Purpura fulminans is an acute, rapidly progressive hemorrhagic necrosis of the skin attributable to dermal vascular necrosis that is associated with disseminated intravascular coagulation. Purpura fulminans is a rare and occasionally life-threatening disorder that occurs most commonly in the setting of acute, severe bacterial or viral infection, or as a postinfectious syndrome after infections such as primary varicella or scarlet fever (1,2,3). Postinfectious purpura fulminans usually occurs 7 to 10 days after onset of symptoms of the acute infection (4,5). The ecchymotic lesions are most commonly distributed symmetrically on the lower extremities and buttocks, although the trunk and upper extremities can be involved. Visceral involvement is less frequent but can lead to hematuria or gastrointestinal hemorrhage.

Transient or congenital deficiencies of protein C or protein S have been documented in many cases of purpura fulminans in recent years. Protein C is the best known among the identified anticoagulant factors in the delicate molecular balance of homeostasis. Activated protein C degrades activated coagulation factors VIIIa and Va, attenuating their procoagulant activation of factors X and prothrombin. Protein S is a cofactor to activated protein C, which accounts for the increased risk of thrombosis associated with protein S deficiency states (6) .

Factor V Leiden, a factor V variant resulting from a single point mutation at nucleotide 1691 (guanine to adenine, resulting in arginine 506 to glutamine), has been recognized as a risk factor for thrombotic events in adults (7,8). The prevalence of factor V Leiden allele in the general population is 3% to 6%. (9,10) and around 13% in Arab population(11). Heterozygous for the mutation have a 7-fold increase in risk for venous thrombosis , and those who are homozygous for the mutation have a 80-fold increase in risk(12). Reported thromboses in children with factor V Leiden have included catheter-related thrombosis and renal vein and venous sinus thrombosis in a neonate (13). The

presence of factor V Leiden also heightens the risk for thrombotic events among adolescents and young women who use oral contraceptives (14).

The factor V Leiden mutation confers resistance to protein C activation and the subsequent degradation of factors Va and VIIIa. It therefore interferes with the natural inhibition of coagulation by activated protein C, predisposing to hypercoagulable states. Factor V Leiden appears to be the most common genetic cause of thrombophilia. At least one factor V Leiden alleles is present in 5.3% of white Americans, 2.2% of Hispanic Americans, 1.2% of African-Americans, and 0.4% of Asian Americans. The heterozygous state is a risk factor for thrombophilia.

We report here a child with varicella-associated purpura fulminans who had a transient deficiency of protein S and heterozygosity for factor V Leiden gene.

Case Report

A 5-year Arab boy developed pain and change in the color in his lower limbs and hands on the sixth day after eruption of varicella exanthem. The course was rapidly progressive to an extent that in matter of six hours the colour changed from dark red to almost black, and the lesion involved about half of both legs and parts of the dorsum of hands (fig 1 and 2). He had no fever, hematuria or gastrointestinal symptoms.

He had been treated with amoxicillin, antihistamines and ibuprofen from the second to fifth day of his exanthem. He had no previous history of excessive bleeding even after circumcision, easy bruising, or thromboses and no previous hospitalizations or serious illnesses. He previously had not received varicella vaccine nor did he develop varicella infection. There was no family history of bleeding disorders, stroke, or thromboembolism.

He was admitted immediately to paediatric intensive care unit (PICU). He was alert and oriented. His temperature was 37°C, pulse 86 beats/minute, blood pressure 105/75 mmhg and weight 17kg. Scattered, crusted varicella lesions were present. Both lower limbs were symmetrically involved by necrotic dark purple lesions extending from tips of toes to the middle of his legs, they were dark in colour, swollen and very tender even to light touch and cold (fig 1) . Another necrotic,

dark purple lesion 6x5 cm in size, with well demarcated borders was present on the dorsum of the left hand and a smaller lesion on the right hand (fig 2) . Pulses in the dorsalis pedis arteries were not felt, while posterior tibial and popliteal arteries were normal.

His hemoglobin was 10.1g/dl and haematocrite 31%. Platelet count was

219 000/mm3 and the white blood cell (WBC) count was 15.500 mm3 with differential of 79% segmented neutrophils, 16% lymphocytes, 3% monocytes, 1% eosinophils and 1% basophils. Blood film showed moderate hypochromia and microcytosis, with mild polychromasia. Urine analysis, serum alanine aminotransferases were normal. His prothrombin time was 23.4 second (control 12 s), activated partial thromboplastin time 49.6 seconds (control 32 second) and INR 2.0. Fibrinogen level was 1.8 gm/l (Normal 2-4 gm/L) and D Dimer was 0.7 µg/ml (upper limit of normal was 0.5 µg/ml). Anti-thrombin levels were normal. Protein C activity was 1.2mg/l (Normal 1.08-3.9mg/l). Protein S activity and antigen levels (total and free) were undetectable. Tests for antiphospholipid antibodies were not done. The patient received heparin bolus injection (50U/kg) followed by infusion (30units/kg/hour) and Fresh frozen plasma (15ml/kg) six hourly on the day of admission then stopped. After twenty hours the standard unfractionated heparin was replaced by low molecular weight heparin Tinzaparin (Innohep) (175 U/kg) given once daily subcutaneously. Within 48 hours he had full correction of his prothrombin time and partial thromboplastin time but not his protein S activity. The patient was found to be heterozygous for factor V Leiden (by polymerase chain reaction amplification of the DNA fragment). He remained afebrile and the skin lesions started to regress in size (fig 3 and 4). He was discharged after six days with silver sulfadiazine 1% cream to be applied topically to the lesions, with no need for any skin grafts. His mother was found to be heterozygous for factor V Leiden. Protein S slowly returned to normal over a period of eight weeks.

Discussion

Post infection Purpura Fulminans is a well-recognized clinical presentation, mostly occurring in children, and the majority of cases preceded by infection, in particular, varicella and streptocci. The general body state is rarely altered. Fever is uncommon. Venous thromboebolic complications are frequent in this pathologic condition; lower limb deep vein thrombosis, renal vein thrombosis and pulmonary embolism have been reported(8,13). The histopathological features are those of widespread thrombosis of the dermal capillaries and venules with hemorrhagic infarction of the surrounding tissue. The disorder is often associated with laboratory evidence of a consumptive coagulopathy.

It is also well recognized to occur in neonates and infants with inherited homozygous protein S and protein C deficiency and in overwhelming sepsis. The occurrence of purpura fulminans in patients with meningococcal infection is so frequent that its presence is considered a cardinal feature of meningococcemia.

Acquired protein S deficiency could be consequent to disseminated intravascular coagulation or could result from the presence of an antibody against the protein.

There are few documented reports of Purpura Fulminans occurring after viral infection by causing acquired antibodies against protein S . Levine et al described five children with post infectious Purpura Fulminans due to acquired antibodies against protein S. In four of their patients the purpura fulminans followed varicella infection and one a non specific infection. In each of their patients, the disease began 7-10 days after the onset of the precipitating infection (16). In our patient there was a history of varicella infection about 7 days prior to presentation.

The protein S levels in our patient remained extremely low for four weeks after admission in the presence of normal protein C. The protein S levels (total and free) in the parents were normal and the fact that the protein S levels in our patient recovered to a normal level 8 weeks later, confirm that the event was a transient one and not a familial protein S deficiency.

Factor V Leiden, a variant of factor five resulting from a single point mutation at nucleotide 1691(Guanine to adenine, resulting in arginine

506 to glutamine) has been recognized as a risk factor for thrombotic events in adults . It has been reported as a cause of thrombosis in children with central venous catheters.

The factor V mutation confers resistance to protein C activation and the subsequent degradation of factors Va. It therefore interferes with the natural inhibition of coagulation by activated protein C, predisposing to hypercoagulable state. Factor V Leiden appears to be the most common genetic cause of thrombophilia (15). Heterozygous state of factor V Leiden affects about 5.3% of white Americans 1.2% of African Americans and about 13% of Arabs (11).

The finding of a heterozygous state for factor V Leiden in our patient may have contributed to the increased thrombotic risk, but is likely that the acquired protein S deficiency may have been the main underlying cause for the development of Purpura Fulminans.

The rare but potentially serious occurrences of thrombotic events associated with varicella infection further support recommendations for universal vaccination of individuals identified as having the factor V Leiden mutation, if they have not yet had primary varicella infection.

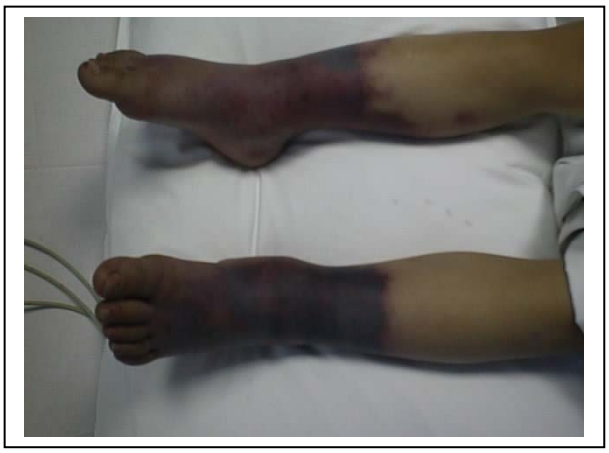

Figure 1

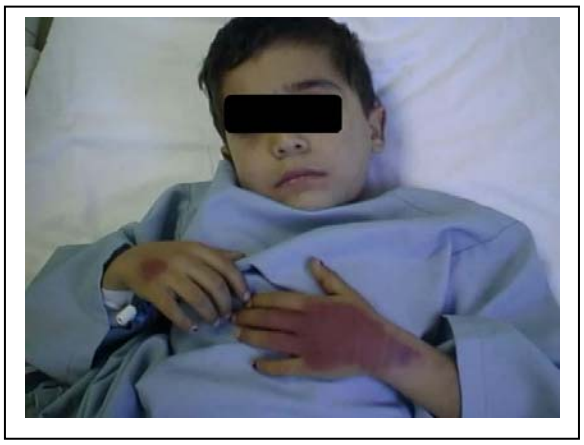

Figure 2

Hands and feet as seen on second day of admission

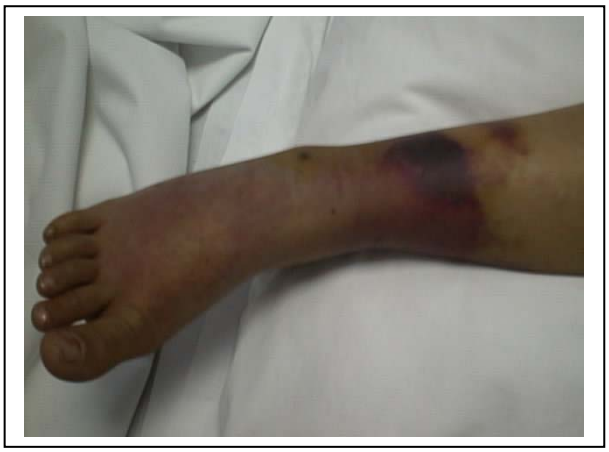

Figure 3

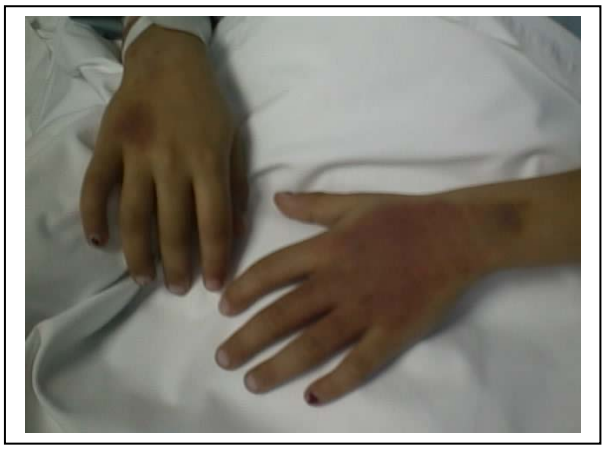

Figure 4

Improvement seen six days later

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