CASE REPORT

Multiple Combined Deficiency Factors II, X, and XII in a Young Female: A Case Study of Probable Congenital Origin

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ABSTRACT

Multiple combined deficiency of coagulation factors is presented as an extremely rare hemorrhagic disorder. The presence of this disorder is more likely to occur in communities with high rate of consanguineous marriages. Red Sea State is a province in Eastern Sudan with a high rate of consanguinity. I report here a rare case of multiple coagulation factors deficiency in an Eastern Sudanese 14-year-old young female. Normal reports of ultrasonography in association with endocrine analyses conducted to rule out any gynecological and endocrine causes of bleeding. Complete blood count, coagulation profiles, and simultaneous finding of prolonged prothrombin time and activated partial thromboplastin time, supported the diagnosed of multiple factors deficiency, confirmed by specific factor assay to reveal the combined deficiency of Factors II, X, and XII. Female with prolonged menstrual cycle (menorrhagia) and recurrent epistaxis without any other discernable causes needs proper assessment for coagulation factors. This abnormality seemed to be a congenital disorder of multiple coagulation factor deficiencies.

Key words: Menorrhagia, Combined Coagulation factor deficiency, Port Sudan

INTRODUCTION

Female with heavy menstruation might not ask medical advice due to lack of awareness; therefore, the objective evaluation of menstrual loss is a must using pictorial blood assessment chart (PBAC). PBAC is a semi-quantitative assessment of blood losses way adopted to evaluate and rule out the false menorrhagia. Globally, menstrual blood losses of >80 ml are deemed as heavy bleeding.[1] Congenital coagulation disorders are mostly yielded from reduced or defective production of one of the coagulation factors. Combined Vitamin K-dependent factor deficiency is a rare inherited coagulation defect which is considered a part of a wider group of seldom disorders called familial multiple coagulation factor deficiencies (FMCFDs). FMCFDs were proposed by Soff and Levin, 1981. FMCFDs are indicated by the simultaneous reduction in the concentration of two or more coagulation factors.[2] Vitamin K-dependent factor deficiency is a heterogeneous hemostatic disorder consisting of a deficiency of clotting Factors II, VII, IX, and X as well as protein C, protein S, and protein Z. The disorder leads to a bleeding tendency with varying clinical presentation.[3] Factor XII (Hageman factor) is one of the contact factors which start the intrinsic coagulation pathway. FXII deficiency causes of thrombotic tendency rather than a bleeding problem. Globally, there have little reports of FXII deficiency.[4] Management of patient with excessive bleeding includes a prompt evaluation for signs of hypovolemia and potential hemodynamic instability. If the patient still unstable or has signs of hypovolemia, intravenous access with a single or two large-bore intravenous lines should be started rapidly as well as preparation for blood transfusion and clotting factor replacements. The next step to identify the most likely causes so that the most appropriate and effective therapy plan to control the bleeding can be chosen.[5]

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CASE REPORT

A 14-year-old young Sudanese female complained with menstrual cycle disturbances for the past 2 years. She could not evaluate herself to be a heavy bleeder. Hence, she went to her family pediatrician and been referred to a gynecologist. The patient reported a history of recurrent epistaxis. The patient has been treated for bleeding episodes with fresh frozen plasma and 2 ampules of Vitamin K injections (20 mg) during the last hospitalization. As family history, all family members were normal except her father, he had a history of multiple interval bleeding episodes (epistaxis). The laboratory test findings included a normal complete blood count encompassing platelet count, prolonged prothrombin (PT) time/partial thromboplastin time (PTT) and normal thrombin time (TT), bleeding time, and D-Dimer level (Table 1). Liver function tests were also normal. In mixing studies, Step 1, the patient plasma with pooled normal plasma was observed full correction of PT and PTT. Findings consistent with factor deficiency. In mixing studies, Step 2, the patient plasma treated with aged and absorbed plasma was highlighted which factor was deficient. To emphasize more, we used a percent correction of prolongation of both PT and PTT in a 1:1 mix of patient plasma with citrated normal pooled plasma for the assessment of mixing studies. As in Chang index mixing studies,[6] >75% correction indicated the presence of a factor deficiency, whereas <75% correction indicated the presence of inhibitors. However, the patient finding showed 95.3% which strongly suggestive for factor deficiency.

Table 1: Patient laboratory findings

Parameters	Result	Reference interval
Platelet count/µl	262×10³/µl	150–400×10³/µl
Bleeding time/min		
Patient	4.10	2.0–7.0
Control	3.87	2.0–7.0
TT/sec		
Patient	12.9	8–15
Control	12.4	8–15
PT/sec		
Patient	27.05	10–16
Pooled normal plasma	13.0	10–16
Mixing studies (1:1)	13.05	10–16
PTT/sec		
Patient	185.2	23–40
Pooled normal plasma	30.0	23–40
Mixing studies (1:1)	45.8	23–40
Factor activities/%		
FII	5	69–140
FX	0.29	70–120
FVIII	55	50–180
FXII	22.3	50–150
D-Dimer/mg/l		
Patient	< 0.1	Up to 0.3

PTT: Partial thromboplastin time, TT: Thrombin time

DISCUSSION

The patient had liver profiles (laboratory test and ultrasonography) reported as normal acknowledging that the patient does not have any acquired condition causing combined factor deficiency. Furthermore, abnormal screening pro-TT test in association with severe prolonged PTT indicates Vitamin K deficiency and Vitamin K-dependent factor deficiencies. Thus, the severe prolongation of PTT also indicates too many factors deficiency along with the Vitamin K-dependent factor. The patient did not receive any treatment without prior diagnosis. The differential diagnosis encompasses dysfibrinogenemia, prothrombin deficiency, Factor V deficiency, combined deficiency of Factors V and VIII, Factor X deficiency, and congenital combined deficiency of Vitamin K-dependent clotting factors. The feature of these conditions is a prolongation of both PT and PTT.[7] Given the findings of mixed experimental studies followed by assessment of factor activities, vitamin K injection herapeutic dose, with fresh frozen plasma are infused to replace the defective clotting factors.

The results of this report regarding to the coagulation studies strongly suggested a diagnosis of multiple combined coagulation factor deficiency, because the activities of Factors II, X, and XII were markedly reduced. Coagulation is also characterized by homeostasis in the endometrium and more substantially during the first 2 -3 days of menstruation. Reports suggested a high prevalence of menorrhagia among female with coagulation disorders.[8] Factors II and X are Vitamin K-dependent glycoproteins, synthesized first by the liver hepatocyte as precursor proteins. Then, it undergoes extensive post-translational modification to become complete entire gamma carboxylated mature proenzyme and ultimately secreted into the blood.[1] This γ-carboxylation of the 10–12 amino-terminal glutamic acid residues is significant and needed for calcium ion binding for full proper enzymatic reactions. Hageman factor (FXII) is a plasma protein (zymogen) act on the intrinsic pathway. FXII deficiency is a rare disorder that is inherited in an autosomal recessive manner. FXII deficiency is totally asymptomatic and does not cause excessive hemorrhage. However, its deficiency is less to causes thrombosis. FXII is activated *in vivo* by foreign material such as valve prostheses or stance and may lead to thrombosis.[9] Menorrhagia is a hidden threatening disorder that could lead to acute or unanticipated congenital bleeding disorder with increased mortality rate if untreated.[5] It needs careful and precise screening of coagulation disorder. This

report demonstrated the method of evaluating heavy uterine bleeding.

CONCLUSION

As the findings, in case with suspected hereditary bleeding episodes associated with simultaneous prolongation of PT and PTT, the possibility of combined coagulation factor deficiency should be regarded. Menorrhagic females, irrespective of their ages, necessitate the investigation of bleeding tendency.

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