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Factor XII deficiency: A rare case report and literature review

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ABSTRACT

Background: Factor XII is part of the intrinsic pathway. the activity of this pathway is assessed by measuring the activated partial thromboplastin time (aPTT). Deficiency of Factor XII is rare, often inherited as autosomal recessive, nevertheless autosomal dominant pattern has also been reported. congenital deficiency is associated with mutations in the F12 gene on chromosome 5. Here we report a patient with factor XII deficiency which is considered as a rare inherited coagulation disorder. **Case report:** we report the case of a 37 years old gentleman known to have Diabetes mellitus, hypertriglyceridemia, past history of pancreatitis and an episode of gingival bleeding a year prior to this presentation which was attributed to periodontitis. He presented to the emergency room complaining of epigastric pain radiating to the back as well as nonprojectile vomiting. He used to drink alcohol but stopped 6 years ago. physical examination showed epigastric tenderness, poor dental hygiene and periodontitis. investigations showed neutrophilic leucocytosis, high lipase and raised triglycerides level of 11.3 mmol/L. He was treated successfully for triglycerides induced pancreatitis with IV insulin, Dextrose 5% infusion and fenofibrates. Isolated prolonged aPTT was detected incidentally which was corrected with mixing study indicating a factor deficiency. Factor assays revealed factor XII deficiency (5.8%) with other factors being within normal ranges. Past records did not show any thrombotic event. No specific treatment was given for Factor XII deficiency. **Conclusion:** Factor XII deficiency is associated with an isolated prolonged aPTT without increasing risk of bleeding. patients with this condition should be offered regular follow up because of the increased rate of thromboembolic complications.

Keywords:
Factor XII deficiency, hypertriglyceridemia, thrombosis

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Background:

Factor XII is a protein which has a dual role in hemostasis. It functions as the enzyme which initiates the intrinsic pathway of the coagulation cascade by activating factor XI which in turn activates factor IX. Factor XII autoactivates when it comes in contact with negatively charged surfaces either biologic or artificial. However, this is considered to be its minor function. The main physiological function of activated factor XII is conversion of plasminogen to plasmin and initiation of fibrinolysis. In the human body these two processes are in a state of continuous dynamic equilibrium [1]. Deficiency of factor XII is considered very rare with a reported prevalence of one in a million [2]. The most common presentation of factor XII deficiency is asymptomatic prolongation of activated partial thromboplastin time (aPTT). Thrombotic complications of factor XII deficiency are more commonly reported than bleeding tendencies. Here we report a patient with factor XII deficiency diagnosed during his admission for treatment of acute pancreatitis related to hypertriglyceridemia.

Case Report:

We report a 37 years old gentleman who presented to the emergency room with one day history of abdominal pain mainly in the region of the epigastrium, moderate to severe in intensity and radiating to the back as well as one episode of non-projectile vomiting that did not contain any blood. He did not have any fever, diarrhoea, constipation, abdominal distention, weight loss or bleeding per rectum. He did not complain of any other symptoms regarding other body systems. His past medical history is significant only for pancreatitis one year ago the details of which are not available as well as an episode of gingival bleeding that was attributed to peri-odontitis due to poor oral hygiene. He is known to have diabetes mellitus managed only by dietary restriction of carbohydrates as well as hypertriglyceridemia. He doesn't smoke cigarettes, he used to drink alcohol but stopped 6 years ago. He had no family history of bleeding disorders or thrombosis. Physical examination showed epigastric tenderness without guarding or rebound tenderness. Oral cavity examination revealed poor oral hygiene with evidence of periodontitis. Skin examination showed some scaly lesions in both feet and on the knuckle area of the left hand. The rest of physical examination was unremarkable. Blood investigations showed neutrophilic leukocytosis, raised serum lipase, hyperglycemia, HbA1c of 9.4 % hypertriglyceridemia (11 mmol/l) and mild thrombocytopenia, however peripheral smear reported a normal platelet count. At this stage he was admitted as a case of hypertriglyceridemia induced pancreatitis and managed accordingly with paracetamol, IV fluids, esomeprazole, nil per-mouth for the first 48 hours as well as IV insulin infusion, Dextrose 5% infusion and fenofibrates. Serial clinical evaluations showed remarkable clinical improvement and reduction of triglycerides level to 2 mmol/l. Hematological investigations revealed a prolonged aPTT of 180 sec (25.1 to 36.5) with a normal Prothrombin time (PT) and International normalized ratio (INR). Mixing studies resulted in correction of the aPTT before and after two hours incubation indicating a factor deficiency. Factor assay revealed factor XII deficiency with a level of 5.8% with all other factors within the normal range. Careful interviewing of the patient and investigation of previous clinical records did not reveal any previous thrombotic events. The patient led a smooth recovery from pancreatitis and he was discharged on metformin, Insulin glargine and fenofibrate with follow up in Endocrine, dentistry and Hematology clinics. No specific treatment was provided with regard to factor XII deficiency.

Discussion:

Deficiency of factor XII is considered a rare condition. The congenital form of the disease is inherited as autosomal recessive, nevertheless autosomal dominant pattern has also been reported. Congenital deficiency is linked to mutations in the F12 gene on the long arm of chromosome 5. On the other hand, acquired

factor XII deficiency is found in patients with nephrotic syndrome, however the pathophysiological mechanism behind this is not well understood. Other conditions related to acquired factor XII deficiency include liver diseases, liver transplantation, autoimmune conditions, lupus anticoagulants, pre kallikrein and high molecular weight kininogen deficiency [3].

The most common reported presentation of factor XII deficiency is asymptomatic prolongation of activated partial thromboplastin time [4]. Literature describing bleeding as a manifestation of factor XII deficiency is very rare. On the contrary it is linked to thrombotic complications such as ischemic stroke [5,6] and recurrent miscarriages [7,8], therefore on detection of factor XII deficiency physicians should think about these associated risks rather than bleeding tendencies for a better risk assessment and patient's prognosis. Myocardial infarction and pulmonary embolism are frequent causes of death in patients with factor XII deficiency. Medical research is now focused on the thrombotic complications of factor XII deficiency [3]. With regard to our patient there is no literature describing any links between factor XII deficiency and pancreatitis or its complications so we believe the two conditions have no relation to each other.

As most of the patients diagnosed with factor XII deficiency are asymptomatic, treatment in general may not be needed. In fact, recent research showed that inhibition of factor XII can be considered a novel approach for therapeutic anti coagulation without additional risk of bleeding [9].

Conclusion:

Factor XII deficiency is associated with asymptomatic prolongation of aPTT without increased risk of bleeding. Recognition of the condition is important to prevent any unnecessary delays in surgical interventions as well as unnecessary administration of fresh frozen plasma in patients with isolated factor XII deficiency. Regular follow up is recommended for these patients due to the increased risk of thrombotic complications.

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