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Case Report Open Access

Elevated aPTT and factor XII Deficiency After Complicating Meningioma Resection – What Is The Role of factor XII?

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Summary

A 45 year-old Asian female presented with new onset of progressive ataxia and underwent resection of a ponto-cerebellar meningioma. A catastrophic intracranial hemorrhage complicated recovery. Her preoperative coagulation tests were within reference limits. Detailed analysis revealed a very low factor XII level concomitant with prolonged aPTT, but no other coagulation abnormalities were detected. In the discussion, the role of factor XII is described with special emphasize on the novel understanding of the coagulation pathway.

Introduction

Factor XII (Hageman's factor) belongs to the vast group of kinins [1-3]. A deficit of factor XII is usually serendipitously discovered as a prolonged aPTT [4]. The prevalence of this factor deficiency is seen in about one in one million individuals, with a higher prevalence in the Asian population [4]. Classically, factor XII is involved in initiating the intrinsic coagulation cascade and one may expect that abnormally low levels would result in a coagulopathy [3,4]. However, almost all these patients remain asymptomatic. Oddly enough, factor XII deficiency is linked to a higher prevalence of thrombotic events, defying the aforementioned classical understanding of factor XII's role in initiation of the coagulation cascade [1,2,4,5]. Herein, we present the case of a patient who developed a catastrophic coagulopathy with a prolongation of the aPTT and abnormally low serum levels of factor XII.

Case Report

A 45 year-old Asian female (45 kg) developed new onset of ataxia and gait disturbances. Subsequently, she was diagnosed with a large right pontine angle mass resulting in compression of the brainstem and the right cerebellum. Pre-anesthetic assessment was significant for a history of chronic anemia. Her preoperative coagulation parameters (PTT=27 [sec], INR=1.1) were normal. Her anesthetic and surgical course was uneventful, with pathology revealing a meningioma. After admission to the intensive care unit, standard deep venous thrombosis prophylaxis was implemented (compressible stocking and 5,000 IU of generic, non-fragmented heparin administered subcutaneously). However, she soon became obtunded and hypotensive (~within 1 hour after admission), with blood pressure decreasing from 134 / 83 mmHg to 92 / 34 mmHg. An emergent ventriculostomy was placed with temporary improvement, followed by steep decline in neurological function. A subsequent imaging study revealed multiple intracranial hemorrhages, resulting in an emergent craniotomy. As the operating team suggested consideration of possible coagulopathy, an activated clotting time (ACT) was performed, resulting is a value of 250 [sec] (normal ≅ 70 [sec]). Empirically, 100 mg of intravenous protamine sulfate and 2 units of fresh frozen plasma (FFP) were given after sending coagulation studies. This resulted in a decline of the ACT to 100 sec. The patient's coagulation studies before administration of the protamine and FFP were: PTT = 64 [sec], INR = 1.0, platelets = 160 [x10^3cells / mL], fibrinogen = 419 [mg/dL], and an unfractionated serum heparin level = 0.25[IU/mL]. That tests were performed under 2 hours after admission to the unit. Additional tests were conducted after completion of surgical procedure and showed PTT =29 [sec], INR=1,1, and serum fibrinogen= 418 [mg/dL]. Thromboelastogram study was not available to us.

Hematology was consulted. A thorough investigation revealed a factor XII level measuring 20% of normal, while factors VII, IX, and XI, as well as thrombin time, were within reference limits. The aPTT normalized over next three days and DVT prophylaxis was restarted as described above, which was again accompanied by prolongation of the aPTT. Repeated coagulation studies showed exclusively low levels of factor XII. Subsequently, the patient's DVT prophylaxis was limited to compressible stockings. Unfortunately the patient expired after 12 days of ICU due to the cardiovascular instability and deteriorating neurological function.

Discussion

Factor XII is traditionally considered as the initial step in the intrinsic coagulation cascade [1,3,5]. It propels the enzymatic conversion of factor XI to Xia [1,4,5]. Stabilization of thrombin, release of bradykinin, and local inflammatory reaction ensue [1,3,6]. Deficiency of factor XII is inherited in an autosomal recessive fashion, with the majority of cases seeming to be a result of a spontaneous mutation [6]. Deficit of factor XII is usually accidentally recognized during routine coagulation analysis and is signified by an abnormal aPTT, with normal PT and INR [2,4,5]. Since aPTT can be prolonged in the presence of heparin, antiphospholipid syndrome, some forms of von Willebrand disease, and deficiency of IX, XI, XII, a mixing study should be performed. Further, prolongation of aPTT in vitro may not be related to the increased risk of coagulopathy *in vivo*, since other coagulation factors make up for lack of this factor [4,5,7]. Direct assessment of factor XII is done by immunoassay.

Our patient did not report any pre-existing symptoms suggestive of a coagulation diathesis. Initial testing showed no laboratory value

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abnormalities. Hence, the observed prolongation of aPTT was an acquired deficit. Initially, overdose of heparin was suspected secondary to a drug error. Since the serum level of heparin was low, this seems not to be a culprit here. Interestingly, some authors reported increased risk of intracranial hemorrhage in patient with intracranial pathologies if the DVT prophylaxis is instituted [8]. Since the overall risk : benefit ratio supported the use of heparin in this case, not much attention was given to this observation but it is possible that such increase in hemorrhage results from medical errors or relative overdose of heparin comparing to body mass [8]. Alternatively, the commercially available preparations of heparin may catalyze activation of Hageman factor resulting in prolongation of aPTT, hypotension, and anaphylactic shock [9]. This depletion of factor XII results from contamination of heparin by oversulfated chondroin sulfates (OSCS) [9]. Additionally, exposed brain tissue may further augment consumption of factor XII leading to abnormally low levels and subsequent prolongation of aPTT [3,9]. Despite the observed prolongation in the aPTT, it is unlikely that this abnormality resulted in profound bleeding. A prolonged aPTT represents an *in vitro* phenomenon with unknown relevance to clinical practice [2,4,10].

In the classical thinking of hemostasis, the absence of factor XII prevents activation of the intrinsic pathway, as proposed in the waterfall cascade hypothesis of coagulation [11]. In that model, negatively charged surfaces trigger transformation of factor XII into the active enzyme that in turn activates factor XI. However, a clinically significant deficit of factor XII is very rare, suggesting that the proposed waterfall coagulation cascade does not reflect haemostatic events in vivo [3,4,12,13]. Published case reports suggest that factor XII deficiency is related to the pro-coagulation propensity triggering both venous and arterial thrombosis [1,2,4,5]. It is speculated that this may result in a higher prevalence of myocardial infarction and miscarriages or extension of stroke [2,14,15]. The only suggested bleeding diathesis that may be linked to low level of factor XII is chronic subdural hematoma but the etiology is related to increased vascular permeability rather than a coagulation deficit [7]. Factor XII has been shown to stimulate the complement system as well as bradykinin production [9,10,16]. It is also important in recognition of denatured / misfolded proteins in serum and regulation of the function of the endothelial cells [3]. However, due to the rarity of this disorder and great variability of the presenting clinical symptoms, caution is advised before definitively associating low serum levels of factor XII with any coagulation abnormality. One has to take into account that thrombin can be generated without activation of factor XII and instrinic and extrinsic coagulation pathways are complementary and mutually redundant in their roles of hemostasis [12].

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