ECAT Newsletter

Case Report:
Prekallikrein deficiency

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Introduction

A 34-year-old woman, G2P1, with a 14-week period of amenorrhea, presented to the gynaecologist with heavy vaginal bleeding. The patient had no history of other bleeding problems, was not taking any medication, and had never undergone surgery. The gynaecologist confirmed an intact pregnancy by ultrasound and found no evidence of other gynaecological sources of bleeding. After a short observation period of a few hours, no active bleeding was detected, but the patient was still concerned. The following laboratory tests were therefore requested to investigate the possibility of an increased bleeding tendency: platelet count, INR, Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT) and fibrinogen.

Laboratory results

In the delivery room, blood was drawn for the previously mentioned basic coagulation tests. These revealed a slightly elevated fibrinogen level of 5.7 g/L (reference range: 2.0-4.0 g/L) and a significantly prolonged APTT of 83 seconds (reference range: 26-36 seconds). Since the patient was pregnant, further diagnostic tests (after exclusion of heparin contamination) were initiated simultaneously, including mixing studies, assessment of intrinsic pathway factors and von Willebrand parameters. Factors VIII, IX ,XI and XII were found to be normal, as were the von Willebrand parameters. However, in the mixing study, APTT showed a different value for the patient's undiluted APTT: 34 seconds compared to the initial APTT result.

The full results of the mixing study were as follows (see table)

APTT Mixing study	Direct	60 minutes 37 degrees Celsius
Patient plasma (PP)	34 sec	95 sec
Normal pooled plasma (NP)	30 sec	30 sec
PP: NP (1:1)	28 sec	29 sec

A new sample was collected, but the results showed a similar pattern: the APTT results varied widely (ranging from normal to significantly prolonged) between different samples and between different APTT reagents (STA®-C.K. Prest®, kaolin activator, STA ®-Cephascreen ®, polyphenolic activator, PTT-LA®, silica activator, Diagnostica Stago).

Interpretation and consultation

This patient presented with clinical and biochemical findings that did not provide a clear explanation for her bleeding complaint. However, variable APTT results ranging from 34 to 83 seconds were observed. In fact, despite normal activities of FVIII, FIX, FXI and FXII as well as normal von Willebrand parameters, big differences in APTT prolongation were observed using different reagents and incubation times, all of which were fully corrected in the mixing studies. This full correction ruled out inhibitors against clotting factors or lupus anticoagulant and indicated coagulation factor deficiency.

This case description may indicate a contact activation disorder. APTT measurement is based on the activation of the intrinsic pathway by contact activation1. In vitro contact activation involves Factor XII, prekallikrein (PK) and high-molecular-weight kininogen (HMWK). In a contact activation disorder, the rate at which contact activation occurs can vary, resulting in different APTT prolongations . Since factor XII deficiency had already been ruled out, PK activity was determined using PK-deficient plasma, which showed <3% activity, strongly suggesting a contact activation disorder based on PK deficiency.

Background

PK is a glycoprotein synthesised in the liver and it circulates in the plasma bound to HMWK with only 20% in free form. PK is the zymogen of the serine protease plasma kallikrein, which, together with factors XII, XI and HK, participates in the initiation of the intrinsic coagulation pathway. PK deficiency was first reported in the Fletcher family in Kentucky in 1965; it is an autosomal recessive genetic disorder caused by KLKB1 mutations with a

prevalence of 1 in 150,000 in the Caucasian population. The deficiency is not associated with bleeding disorders and has been classified as type I (deficiency in activity and antigen) and type II (deficiency of activity and normal antigen levels). Diagnostic tests to confirm PK deficiency are based on the normalisation of APTT after prolonged pre-incubation prior to recalcification, low PK activity (< 15%), and the presence of KLKB1 mutations.

Conclusion

If an APTT prolongation is observed and common explanations are ruled out by standard coagulation tests, it may still be worthwhile investigating further. This also applies to disorders without clinical consequences, such as contact activation disorders. In the case of the patient described above, although her bleeding history was somewhat equivocal, her concern persisted, and a conclusive diagnosis was sufficient to reassure her. In addition, the diagnosis may be relevant to related family members, mainly to avoid time-consuming investigation of a possible APTT prolongation. Recommendations on the use of coagulation tests should be included in the report when low PK activity is observed. When an APTT test is indicated, for example, for monitoring unfractionated heparin, alternative approaches such as anti-Xa measurement should be advised by the specialist in laboratory medicine.

References

1. Barco S, Sollfrank S, Trinchero A, Adenaeuer A, Abolghasemi H, Conti L, Häuser F, Kremer Hovinga JA, Lackner KJ, Loewecke F, Miloni E, Vazifeh Shiran N, Tomao L, Wuillemin WA, Zieger B, Lämmle B, Rossmann H. Severe plasma prekallikrein deficiency: Clinical characteristics, novel KLKB1 mutations, and estimated prevalence. J Thromb Haemost. 2020 Jul;18(7):1598-1617.
2. Schmaier AH. The contact activation and kallikrein/kinin systems: pathophysiologic and physiologic activities. J Thromb Haemost. 2016 Jan;14(1):28-39.In Spring 2023 a small pilot study was performed on testing for Fibrin(ogen) Degradation Products (FDP). The meaning of this pilot study was to investigate the feasibility of an external quality assessment survey for FDP. In total 14 laboratories took part in this pilot study, 9 of which have returned results.