Case Report: A patient with mild haemophilia A

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Case report
A plasma sample from a 40-year-old man was sent from a local hospital to our lab. The clinical bleeding history of the patient was unclear. In a pre-operative consultation, he told the anaesthesiologist he had once suffered from a mild bleeding of the ankle after falling from his bicycle. Because of the vague bleeding history, and additionally because the normal screening coagulation tests had been performed in the local lab, there was some reservation about sending the sample for further analysis.

The initial coagulation screening in the local lab showed a normal activated partial thromboplastin time (aPTT) 33.1 sec (reference value 26.3-34.8 seconds (s)), a normal prothrombin time, a normal closure time with Platelet Function Analyzer, a normal peripheral blood count and normal liver and renal parameters.

When we received the frozen plasma sample, we repeated the aPTT and found a slightly prolonged result of 43.8 sec (reference value 28-38.1 s). In the diagnostic work-up, we started with a mixing study of patient plasma and normal pooled plasma in a 1:1 proportion. The mixing study resulted in a correction of the aPTT (33.2 s) after one and two hours of incubation at 37°C. We concluded that there was a factor deficiency and performed a one-stage clotting assay (OSA) for (factor (F) IX and FXI, both of which were within the normal range. Von Willebrand antigen and activity were also normal. However, FVIII was decreased showing a result of 19%. The Bethesda assay could not demonstrate the presence of an inhibitor. We verified the sample quality by measuring FV, an unstable coagulation factor, that was 101% [1]. Based on these results we excluded a type I von Willebrand disease (VWD) [2] and an acquired haemophilia A [3]. At this point, the tentative diagnosis of mild haemophilia A was made.

Discussion
The severity of haemophilia is defined in three forms according to the factor level: the mild form has a factor level of >5%-40% of normal [4]. The proportion of patients with mild haemophilia within the haemophilia population varies (18%-54%) and depends on the resources available, family investigations and the awareness of haemophilia among physicians [5]. The diagnosis of mild haemophilia is often made as part of a family investigation, after a bleeding episode or prolonged bleeding after surgery. Bleedings are rarely spontaneous and over 90% of bleedings are associated with trauma [5].

The laboratory diagnosis of mild haemophilia in a first screening is made by a prolonged aPTT. However, the prolongation of the aPTT depends on the sensitivity of the reagent and on the deficient factor level [6]. The aPTT factor sensitivity depends on reagent composition comprising the type of contact activator as well as the origin and composition of phospholipids [7, 8]. Current guidelines recommend a prolongation of the aPTT when factor levels (FVIII, FIX, and FXI) are below 30% [9]. However, mild deficiencies above 30% can also imply a significant risk of bleeding [10, 11]. Therefore, a prolongation of the aPTT should preferably also be observed in mild factor deficiencies. Recommendations state that every laboratory should assess their own factor sensitivities in order correctly to interpret their routine coagulation tests. However, it is obvious that not all the labs are able to perform their local aPTT sensitivity, especially as it should be performed on patient-deficient plasmas not available in every lab. We studied the factor sensitivity in our daily practice by using two approaches: dilution experiments with normal pooled plasma and commercial factor deficient plasmas, and by the use of patient-deficient plasmas [12]. Sensitivity of the aPTT to FVIII deficiency varies with FVIII levels below 67.5%-33.5% [8] or 50% [12] resulting in a prolonged aPTT. For laboratory workers it is important to be aware of the sensitivity of the aPTT reagent used, and even with a normal aPTT and a suspected bleeding history, factor dosage should be performed.
The next step in the laboratory diagnosis of mild haemophilia is the measurement of FVIII. The most commonly used assay for the diagnosis of haemophilia is the automated one-stage clotting assay. The classical two-stage clotting assays are less frequently used. The chromogenic substrate FVIII assay (CSA) is a variant of the two-stage clotting assay and a suitable replacement for the more complex and more difficult to automate two-stage assay [13].

Both assays have advantages and limitations [13]. A main characteristic of the CSA is the extended incubation period needed to generate the optimum level of FXa, whereas in the OSA there is a rapid progression to thrombin and clot formation.

Although OSA and CSA can produce concordant results, discrepancies often occur in certain patients with mild haemophilia A [13, 14]. Discrepancy in FVIII measured by OSA and CSA occur in about 1/3 of mild haemophilia A patients [13].

Since the CSA requires an extended incubation time to generate optimum levels of FXa which is subsequently measured to indicate FVIII, we hypothesised that those abnormal forms of FVIII which have a less stable A1–A2–A3 interaction are more vulnerable to reduced FXa generation and therefore less FVIII is measured. In contrast, in the one-stage system, FXa generation is rapid and quickly progresses to thrombin and clot formation, and is not sensitive to the unstable FVIII intermediate [14]. In these patients the FVIII level measured by OSA is higher compared to the FVIII measured through a CSA. This implies the risk of missed diagnosis, as we know that in 5-10% of these patients the FVIII is within the normal range with a OSA. Another risk is mismanagement if the bleeding risk is underestimated [14].

The reverse phenomenon with higher levels in the CSA compared to the OSA is rarer and caused by other mutations, probably related to more efficient FVIII activation caused by the longer incubation time with thrombin in the CSA. Usually, these patients have an extremely mild phenotype [5, 14].

Identifying the mutation in the F8 gene can be useful for definitively classifying a patient with mild haemophilia A. In the patient described in this case report the FVIII measured with a CSA was 13%.

Mild haemophilia A has to be differentiated from VWD. In this case report, VWD type I was excluded on the basis that vWF antigen and activity were within the normal range, and there was a normal PFA closure time. However, VWD type 2 Normandy (N) has to be excluded, since typically these patients also present with moderately reduced FVIII levels between 5-30%, normal levels of VWF antigen and activity, and normal PFA [15]. In this type of VWD the capacity of vWF to bind to FVIII is reduced, and this can be measured. The vWF-FVIII binding capacity in the patient described in this case report was normal. Another differential diagnosis is combined deficiency of FV and FVIII, presenting typically with both FV and FVIII levels in the range of 5-20% [16]. The diagnosis is evidentially verified by measuring FV, but it was normal in this case.

The use of factor concentrates is essential in patients with mild haemophilia if there has been major surgery or trauma. The principles are the same as for patients with severe haemophilia with identical target levels. However, for patients with mild haemophilia there are additional treatment options.

For minor procedures in patients with factor levels in the upper range of mild haemophilia (approximately 20% FVIII), treatment with an inhibitor of fibrinolysis may be sufficient. This approach, for example with tranexamic acid should be used for any surgery involving mucosal membranes [5]. In mild haemophilia A, an important alternative to factor concentrates is desmopressin (DDAVP) [17].

Conclusion

Mild haemophilia is a neglected diagnosis. It is important to diagnose the disease early and to start an appropriate management. In a pre-operative setting, as described here, it is important to evaluate the most appropriate approach and for instance to evaluate the response to a test dose of DDAVP prior to surgery.

In the laboratory diagnosis, awareness of the sensitivity to reduced coagulation factor levels of the aPTT reagent used in daily practice is essential. A normal aPTT is not always an indication of normal haemostasis, and coagulation factor dosage may be needed even with a normal aPTT.

FVIII chromogenic assays and F8 gene mutation analysis may be necessary in order to confirm the diagnosis of mild haemophilia A.
References