Spontaneous disappearance of high titre factor VIII inhibitor 15 years after unsuccessful ITI

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Summary
The most serious complication of haemophilia A is development of a high titre factor VIII (FVIII) inhibitor which renders the patient unresponsive to FVIII replacement. Bleeding complications can only be controlled using FVIII-inhibitor bypassing agents but their effect is less certain. The ultimate goal is to eliminate the inhibitor by immune tolerance induction therapy (ITI) using daily high doses of FVIII. The success rate of ITI using various protocols is between 56 and 79% (1, 2). If ITI is unsuccessful, the inhibitor usually persists throughout life.

We report on a patient with a high titre FVIII inhibitor that persisted after ITI but spontaneously disappeared 15 years later.

The patient suffers from severe haemophilia A based on a large deletion in the factor VIII gene. Starting at 13 months of age, he received FVIII replacement on demand. Initial therapy was with low-purity non-virus-inactivated FVIII concentrates. During that time, the patient contracted hepatitis, later found to be due to hepatitis C virus (HCV) infection. Since testing became available, the patient has consistently been HCV antibody positive and HCV antigen negative. At three years of age, the patient was switched to an intermediate-purity pasteurized FVIII concentrate (Factor VIII HS®, Behring) which he has exclusively received since.

At 3.5 years of age, the patient developed a high-titre FVIII inhibitor. The time course of inhibitor titres is shown in the figure: Initial titre was 10.2 Bethesda units (BU)/ml corresponding to a FVIII recovery of 6%. The titre increased to a maximum of 68 BU/ml after six months, and slowly decreased to 10 BU/ml during the following five years. Average FVIII consumption per year is also shown in the figure 1: After inhibitor manifestation, the patient received ITI (200 units FVIII/kg body weight in two doses per day) for six months. Thereafter, ITI not continued for compliance reasons. Instead, the patient intermittently received FVIII therapy on demand. Frequent severe bleeding resulted in a FVIII consumption corresponding to an average of daily 38 to 156 units/kg body weight over the following years.

The boy developed severe arthropathy. When he was six years of age, activated prothrombin complex concentrate (APCC, FEIBA®) became available and used to control his bleedings (Fig. 1). During the following years, he usually received a combination of FVIII concentrate and APCC on demand which, in the patient’s perception, appeared to be more effective than APCC alone. Using this combination, several operations, including synovectomy, were performed without complications. After 10 years of age, inhibitor titres slowly decreased, fluctuating between 11 and 2 BU/ml until 19 years of age. However, at ages 13 and 16 years, FVIII recoveries were 7% and 4%, respectively, demonstrating still a functionally high-titre inhibitor.

Unexpectedly, at 19 years of age, the inhibitor became undetectable, confirmed by a FVIII recovery of 92% and a normal FVIII half-life of 12 hours. Consequently, therapy with APCC was discontinued. Shortly thereafter, the patient had his port-a-cath removed using solely FVIII replacement without bleeding complications. Since then, he receives FVIII replacement on demand in standard dose.

Discussion
This case of spontaneous disappearance of a high-titre FVIII inhibitor is the first reported
in the literature. Disappearance of FVIII inhibitors has been described in HIV-infected haemophiliacs as a result of immunodeficiency (3, 4), but not in immune-competent patients. A possible explanation for the disappearance of the inhibitor may be an altered immune response due to chronic HCV infection. However, the patient is HCV antigen negative, has no liver dysfunction, and normal immune parameters.

A more plausible explanation: After a relatively short course of formal ITI, long-term though intermittent FVIII exposure eventually induced immune tolerance. This observation is in contrast to the general conception that discontinuous FVIII exposure would booster inhibitor titres. The clinical course of our patient suggests that an extended low-dose ITI or even intermittent FVIII exposure may increase the chance of immune tolerance induction. In spite of initial high costs, such a regime would decrease morbidity and life-long costs compared to patients with persisting inhibitors.

References