Letters to the Editor

Report on a disease-adapted treatment in a patient with severe factor X deficiency resulting from a homozygous factor X gene mutation

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Dear Sir,

Homozygous factor X deficiency (FXD) is a rare disease with an incidence of 1:1,000,000 in the general population (1), and diagnostic work-up is usually restricted to specialized centers. This is mainly due to the poor correlation between clinical manifestation of patients to laboratory assays and factor X coagulation activity. To therefore clearly identify the correct manifestation of severity in a homozygous factor X-deficient patient, a meticulous diagnostic screening has to be performed, involving the history, the classification of bleeding and genetic analysis of gene mutations, and control of treatment efficacy in the patient affected.

The gene of factor X is located on chromosome 13q34 involving eight exons. Homozygous factor X-deficient knockout mice die *in utero* or days after birth (1, 2), reflecting the severity of the mutation. Up to now, 102 cases of FXD have been identified world-wide (1, 3, 4), involving 28 homozygous, seven compound-heterozygous and 67 heterozygous patients presenting with 29 different mutations (1) plus one additional homozygous mutation (Cys364Arg), which has been described recently (5).

Clinical manifestations of FXD may occur at virtually any age, with more severely affected patients exhibiting more severe haemorrhage early in life. Less severely affected patients and "symptomatic" heterozygotes may bleed only after more severe challenge to the haemostatic system, as with trauma or surgery. Bleeding sites vary according to the severity of the deficiency. Mucocutaneous soft tissue haemorrhages, including menorrhagia in women, are common. Haemarthrosis, exsanguinating postoperative haemorrhage, pseudotumors, and haemorrhages of the central nervous system have been reported in severely affected patients. Mildly affected patients experience easy bruising and excessive bleeding after trauma or surgery.

In a recent publication by Herrmann et al. for the Greifswald Factor X Deficiency Study Group in Haemophilia (1), a detailed description of the world-wide identified factor X-deficient patients can be obtained. However, little information is available on the treatment options for these patients (1), which usually involve the administration of fresh frozen plasma or prothrombin complex concentrate (4). The disadvantages of fresh frozen plasma are the large infusion volume, potential viral transmission, and no standardized factor X content. These aspects, and in addition the potential prothrombotic risk (6), need to be addressed for the prothrombin complex concentrates. Factor IX P® (CSL Behring, meanwhile specified as Factor XP) a pasteurized factor IX/X concentrate, which is virus inactivated, contains almost equal amounts of factor IX (1,200 IU) and X (mean 1,800 IU) and is therefore also suited for the treatment of factor X deficiency.

We report on our experiences in the treatment of a patient with severe factor X deficiency caused by a homozygous factor X-mutation with Factor IX P (CSL Behring).

A 31-year-old male patient presented in our center with a severe FXD (<1%), caused by a homozygous Cys350Phe mutation in exon 8 on chromosome 13.

During the evaluation of the medical history, it appeared that this individual suffered from severe mucosal bleeding already shortly after birth. Adjacent bleeds manifested in the joints and the patient developed haemophilic arthropathy later on.

In the beginning, the patient was treated outside our department with fresh frozen plasma on demand, which was later on switched to prophylaxis using prothrombin complex concentrate, administered up to three times per week in dosages of 20–25 IU/kg body weight. Prothrombin complex concentrates do not contain equal amounts of factor IX and factor X. It is speculated that the administration of non-virus inactivated fresh frozen plasma up to the age of seven may cause infections by human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV).

As prothrombin complex concentrate contains additional plasmatic coagulation factors different to factor X, we switched the patient to a factor IX-factor X concentrate (Factor IX P) in order to reduce a potential prothrombotic risk, which has been reported in association with the use of prothrombin complex concentrate (5). The patient received Factor IX P two times weekly in dosages of 20 IU factor IX/kg body weight., equivalent to 30 IU factor X/kg body weight. With this treatment, the patient reached plasma trough levels of 20% of factor X-activity after 72 hours in contrast to plasma trough levels of 12% of factor X-activity 72 hours after the administration of prothrombin complex concentrate.

The patient experienced less episodes of joint pain while receiving Factor IX P. Whenever plasma levels of factor X activity

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fell below 20%, the patient complained about joint pain, which did not occur during the administration of Factor IX P. In analogy to that finding, excellent haemostatic efficacy without any adverse events was noted with Factor IX P concentrate during orthopedic and dental surgery.

In conclusion, Factor IX P is an alternative and potentially superior treatment option in this group of patients beside fresh frozen plasma and prothrombin complex concentrate. Despite a lower amount of factor X per week and a less frequent dosage interval, the patient showed higher trough levels of factor X-activity and experienced less joint pain using Factor IX P as compared to prothrombin complex concentrate. Factor IX P appears to be an effective and safe therapeutic option in prophylactic treatment in severe factor X-deficient patients.

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