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## **Prednisolone treatment induced temporary Factor IX normalization in mild hemophilia B who required an epidural infiltration: a case report**

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The authors stated that they had no interests which might be perceived as posing a conflict or bias

### **Abstract**

A 31-year-old man with mild hemophilia B developed a herniated disc treated with prednisolone for back pain. Surprisingly, hemostasis result tests performed before epidural infiltration were a normal activated partial thrombin time at 36.1 s. (normal

range 27.9-37.7 s.) and factor IX (FIX) level 76% (normal range >70%), 13 days after prednisolone introduction. After a second control with a normal FIX level and a second genetic confirmation of hemophilia, no FIX concentrates was administered to perform the infiltration, which occurred without hemorrhagic complication. This new case of FIX normalization showed the necessity to have a perfect knowledge of patient's treatment to avoid misdiagnosis and a temporary normal hemostasis permit to perform epidural infiltration without replacement therapy.

## **INTRODUCTION**

Hemophilia B is an X-linked bleeding disorder due to *F9* gene variations. Hemorrhagic manifestations are the result of reduced levels, dysfunction or absence of liver synthesis of factor IX (FIX), whose function is to cleave and activate factor X (FX) [1]. According to FIX plasma level, hemophilia B is classified as severe (FIX < 1%) moderate (1-5%) or mild (5-40%). Hemophilia B treatment mostly consists of replacement therapy with FIX concentrates which can be used on demand or in prophylaxis considering bleeding manifestation and joint status [2].

We report a transitory factor IX increase in a patient with mild hemophilia B with low dose prednisolone treatment and an epidural infiltration without replacement therapy.

## **CASE REPORT**

A 31-year-old man presented to the local Hemophilia Care Center for management of epidural infiltration. He had a personal and family history of mild hemophilia B due to c.1346G > A (p.Arg449Gln) variation in *F9* gene exon 8 [3]. He was diagnosed at the age of 20 years after a diagnosis of carrier hemophilia in her sister. His mother and two sisters also carried the identified variation. Factor IX coagulant activity (FIX:C) was measured (Coagulation Factor IX Deficient plasma, Siemens Healthcare, Marburg) and fluctuated between 35 and 46% without inhibitor (normal level of FIX: >70 %). An activated partial thrombin time (APTT) (PTT automate®, Diagnostica Stago, Asnières sur Seine, France) was performed and measured at 43.95 and 40.3 s. (control: 32.8 s). This patient had previously received FIX concentrate for a tooth extraction.

No hemorrhagic manifestation was disclosed on clinical examination. The patient had a herniated disc and a history of oesophageal ulcers. His treatment consisted in

prednisolone (30 mg/day, 0.37 mg/kg/day), tramadol, pregabalin, paracetamol and esomeprazole. Surprisingly, 13 days after the introduction of prednisolone for relieving back pain, level of FIX:C was 76% and APTT was 36.1 s. Biological assays did not reveal any anomaly other than neutrophilia (13.15 G/L) induced by corticosteroids. Liver function tests were normal and no clinical or biological inflammatory syndrome was found (CRP < 5 mg/l, fibrinogen= 2.57 g/l).

Eleven days later, FIX:C was 89% and APTT was 33.2 s. One more time, no clinical or biological inflammatory syndrome was found (fibrinogen= 2.72 g/l). The only change in therapy was a decrease in prednisolone dosage (10 mg/day; 0.12 mg/kg/day). New molecular analysis was performed, confirming a unique c.1346G > A variation. As FIX:C level was normal, no FIX concentrates was administered to perform the infiltration, which occurred without hemorrhagic complication.

FIX:C was tested 5 months later, in the absence of corticoid treatment. The level had dropped to 51% and inhibitor screen was negative (Figure 1).

## **DISCUSSION**

We report the case of hemophilia B patient with transient normalization of factor IX, resulting in a temporary phenotypic recovery without administration of FIX concentrate.

To eliminate analytical interference, several control tests were performed on each sample. Each time, identical results were found. Also, expected low FIX:C levels plasma of other previously diagnosed hemophilia B patients were measured at the same time with no similar increase. A second assessment excluded an identity error.

Inflammation is a physical condition known to induce a global increase in coagulation factors. Indeed, FIX increase has been described in chronic inflammatory diseases such as metabolic syndrome [4] or inflammatory bowel disease [5]. However, this hypothesis was rejected on both clinical and biological grounds in this patient who had normal inflammatory markers. After the elimination of these hypotheses, particular attention was given to patient treatments. The only differences between the three assessments were the variations in dosages of prednisolone (Figure 1). High factor levels coincided with use of corticoids whereas a decrease in factor levels was observed after the end of treatment. Several studies have demonstrated the implication of glucocorticoids in the increase of clotting factors. A study conducted by Brotman *et al.* showed a modest rise of FVII, FVIII and FXI in 24 healthy men with a 5-day glucocorticoid treatment [6]. Nevertheless, factor IX levels were not tested. The increase of clotting factors in Cushing syndrome has also been explored, along with the hypercoagulability state in this pathology. A review conducted by Coelho *et al.* compiled data on the rise of coagulation factors in hypercortisolism, including four studies on FIX [7]. A study in Cushing syndrome demonstrated a higher mean FIX plasma level in patients compared [8] to healthy controls (147 % vs 104 %,  $p < 0.001$ ) and a non significant normalization after Cushing remission ( $171 \pm 47\%$  vs  $102 \pm 24\%$ ) [9]. No mechanism of up-regulation in Cushing syndrome is described in literature. In our case, the only suspected underlying mechanism is corticoids-induced up-regulation of mRNA transcription of factor IX.

FIX levels are also known to increase in hemophilia B Leyden, a rare subtype of hemophilia B in which phenotypic manifestations are observed during childhood [1] [10]. Point mutation or deletion of the *F9* promoter region reduces transcription factor

binding, inducing low FIX levels with variable degrees of severity. The proximal promoter mutation does not affect the androgen response element (ARE). Their ARE is intact and responsive to testosterone. Factor IX level increases with production of growth hormone and testosterone increases during puberty. To our knowledge, the c.1346G > A point mutation identified in our patient has never been previously described in Hemophilia B Leyden patient [11]. This mutation induces a catalytic modification, without FIX increase. Moreover, the progressive FIX level rising during childhood is lacking in our observation making this diagnosis unlikely. Furthermore, no study has demonstrated FIX normalization in hemophilia B with c.1346G > A variation yet.

Finally, based on this case report, diagnosis of mild hemophilia B should be performed with perfect knowledge of patient's treatment to avoid misdiagnosis. A temporary normal hemostasis permit to perform epidural infiltration without replacement therapy.

## **Disclosure**

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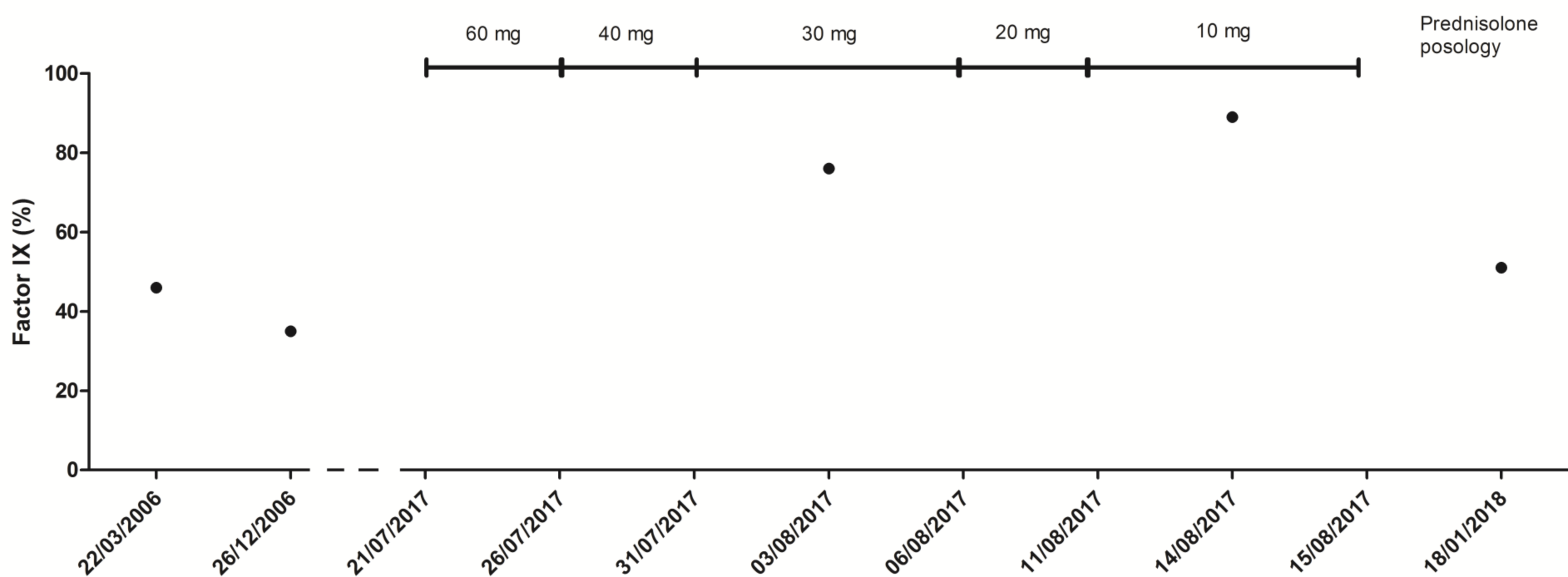


Figure 1. Factor IX variation under prednisolone treatment.