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The sudden and unexpected appearance of inhibitors in a previously treated severe haemophilia B patient after the switch to albutrepenonacog alpha

Inhibitor appearance in haemophilia B patients is very rare. The incidence of allo-antibodies against FIX is estimated around 1%-5%, but despite this low value, inhibitors in haemophilia B patients can be the cause of anaphylactic reaction in over than 60% of cases, that makes the treatment very difficult.[1,2] The inhibitors appearance is better documented in previous untreated patients (PUPs). In a recent review performed by Franchini et al[1] on 176 PUPs with severe haemophilia B, 18 of them (10.2%) developed inhibitors. The incidence

of these allo-antibodies was proven to be higher in patients treated with plasma-derived products (15.3%) than in those treated with recombinant ones (5.6%). Data concerning previous treated patients (PTPs) are however scarce and rarely described. Recently, Soto et al[3] reported a case of a young boy that developed a low-titre inhibitor after 10 years of treatment with replacement therapy with exogenous FIX.

Until now no cases of inhibitors were reported in patients treated with the FIX new extended half life (EHL) products.[4-7]

We report a case of a young man affected by severe haemophilia B who developed a low-titre inhibitor during prophylactic treatment with albutrepenonacog alpha. The description of this case follows the criteria indicated by the International Society in Thrombosis and Haemostasis Scientific and Standardization Committee (ISTH-SSC) on Factor VIII, Factor IX and Rare Disorders about the manuscripts reporting inhibitor cases developed in PTPs.[8,9]

Our patient was born in 1985 in Albania, where he was treated on demand only with plasma. The young man moved to Italy to continue his studies and in April 2007 he arrived at our Haemophilia Centre for a haemarthrosis on his right elbow. A diagnosis of severe haemophilia B was then performed, and the patient immediately started the on-demand treatment with nonacog alpha, a recombinant factor IX (rFIX). This regimen was maintained for about 4 years, from April 2007 to January 2011, when due to recurrent haemathroses to the right elbow, the patient was put on prophylaxis with rFIX 30 IU/Kg twice a week. During this prophylactic regimen, no major bleeding was reported by our patient.

Despite his young age, the patient suffers from haemophiliac arthropathy mainly because of a delay in the initiation of an adequate prophylactic treatment, and in May 2017 he was subjected to an arthroplasty of the right hip. The surgery was performed without complications, and under haemostatic coverage with rFIX. The inhibitor titre, periodically checked, was always negative.

In June 2017, the patient asked to the clinicians if it was possible to move to a long-acting concentrate in order to reduce the number of infusions. After a careful evaluation of the prolonged half-life marketed drugs, we decided to switch our patient to albutrepenonacog alpha. In order to determine the correct prophylaxis with this new drug, a pharmacokinetic profile was then performed using the Bayesian method provided by the Wapps-Hemo service, and after an administration of 50 IU/kg of albutrepenonacog alpha. The pharmacokinetics showed a half-life of 130.5 hours, and a FIX level on the 15th day of 5.7%. The patient then started a prophylaxis with this new EHL, 50 IU/kg every 14 days. This new treatment was effective for the next 5 months when, after 11 exposure days (ED), the patient developed spontaneous haematomas in the superior limbs, and the plasmatic FIX level assessed 1 week from the last infusion of albutrepenonacog alpha was below 7%, a result far from the estimated pharmacokinetics (FIX 16%). Four days after this determination, the patient came to our Haemophilia Centre due to a right lumbar pain suspected for an ileo-psoas haematoma, subsequently confirmed by a CT scan (Figure 1). Laboratory analyses performed

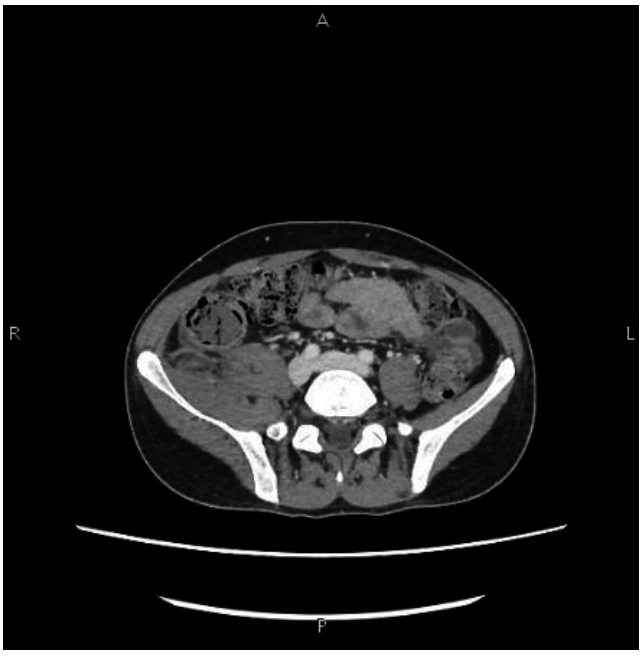

Figure 1. Ileo-psoas haematoma on the right side (11 × 3.5 cm) showed by a TC-Abdomen performed with iodinated contrast medium (ICM)

on samples collected during this visit revealed the presence of a low-titre inhibitor (0.9 BU/mL) and a plasmatic FIX level <0.25%, data confirmed analysing the samples collected and stored during the previous admission to our Centre, in which the inhibitor titre was 0.78 BU/mL. The patient was immediately treated with albutrepenonacog alpha 50 IU/kg, presenting a FIX recovery of 13.4%, and an incremental in vivo recovery (IVR) of 0.19. He refused further infusions of this concentrate, and a treatment with rFIX (nonacog alpha) 30 IU/kg/bid was then started. All FIX laboratory measurements were performed using the 1-stage assay (Actin Fs and FIX deficient plasma, Siemens, Germany; normal range 65%-150%); the inhibitor titre was detected by the Bethesda assay, Nijmegen modified (negative 0.4 BU/mL).[10] The use of the nonacog alpha in substitution of the albutrepenonacog alpha was also preferred because the patient had a severe ileo-psoas haematoma needing an high level of FIX in order to obtain a rapid resolution. In fact the postinfusion peak was 55.4% with a IVR of 0.81, and the ileo-psoas haematoma was resolved quickly without sequelae. Although the patient was able to self-infuse, we decided to treat him in the first time in hospital due to possible anaphylactic reaction given by inhibitor presence and the new switch to the previous concentrate, a risk always present in haemophilia B patients.

Six days later the inhibitor disappeared and the patient was reported to his previous prophylaxis with nonacog alpha 30 IU/Kg twice a week. Scheduled visits performed in the subsequent months recorded no haemorrhagic events and an inhibitor titre always negative.

Inhibitor development in haemophilia B patients is an extremely rare event, that involves especially the PUPs,[1] while only

few cases are reported in PTPs. Soto et al[3] reported the case of a PTP with severe haemophilia B who developed a low-titre inhibitor 10 years after the prophylaxis with rFIX was started. Even in our case the patient suffered from severe haemophilia B, but developed a low-titre inhibitor with an EHL product, after 11 exposure days (ED) with a new drug. No cases of allo-antibodies appearance in patients treated with FIX long-acting concentrates were recorded during the clinical trials[4-6] or during the limited experience in the real life. In our patient, despite the presence of a low-titre inhibitor, the clinical manifestations were important, in addition to haematomas on the superior limbs, he presented a severe haematoma to ileo-psoas muscle needing an immediate treatment with the FIX concentrate.

The occurrence of allergic or anaphylactic reactions related the development of inhibitors in haemophilia B patients can make it difficult to start any treatment, and especially an ITI to eradicate these allo-antibodies against the FIX. An Italian Survey performed by Castaman et al[7] reported 10 patients with inhibitors in the haemophilia B population (2.8%), among these, three patients developed an allergic reaction to the concentrate. Our patient was at high risk to develop an anaphylactic reaction. He refused further treatments with albutrepenonacog alpha, and an ITI was then started with nonacocog alpha, the product previously used on prophylaxis by our patient. The presence of allo-antibodies against the FIX associated to new switch increased the risk to allergic/anaphylactic reaction, even if the real causes of these reactions are still not clear; the patient was initially treated in hospital to limit this risky situation. The molecular structure of the nonacog alpha and albutrepenonacog alpha are the same concerning the FIX amino acid chain; the only difference is due to the binding between this protein and the albumin that gives rise to the albutrepenonacog alpha molecule. At this moment, to correlate this structural modification to the risk of inhibitor development is not possible, and hardly credible.

Large delections or null mutations[11,12] were reported as associated to high risk of inhibitor development and could explain the appearance of these allo-antibodies also in cases of PTPs after multiple exposures to FIX concentrates. A nonsense mutation in FIX gene (p.Arg298Stop) was also related to an anaphylactic reaction as reported by Cugno et al.[13] In our patient, the gene mutation that caused his disease is a splice mutation at the exon 2 (intron 2), c.252+G>A. The splice genetic mutation can insert, delete or change a number of nucleotides in the specific site when the molecular splicing occurs and the precursor mRNA changes in mature mRNA. In case of deletion of the splicing site 1 or more introns remain included in the mature mRNA and cause a production of abnormal proteins. Usually, the information present in the intron sequences are not transcripted. The "Factor IX Mutation Database" recorded only nine cases of this splice mutation in the world. Among these haemophilia B patients, the majority had a severe phenotype, while none had ever developed inhibitors. In our case, therefore, there is no correlation between the inhibitor appearance and the present genetic mutation.

Our report shows that the inhibitor risk is always present also in haemophilia B previously treated patients, without a history of allo-antibodies development, and with a low-risk genetic mutation for inhibitors. Also the use of the new extended half-life products that during the clinical trials were found to be free of this serious side effect does not safeguard the patient from a possible inhibitor development. The explanation of why this could happen is still inexplicable. Molecular biology studies and case reports registrations are therefore important to understand the mechanisms underlying the development of inhibitors in patients with hemophilia B,

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Application of optimized nursing process to perioperative patients with haemophilic pseudotumours

A haemophilic pseudotumour is an encapsulated haematoma characterized by repeated episodes of bleeding.[1-3] Surgery is the preferred treatment for proximal pseudotumours.[4] To ensure patients' safety in the perioperative period, careful and individual management is required by haematologists, surgeons, physiotherapists, nurses and other members of the team who collaborate and participate in surgery.[5-9] Nurses are important members of the team and play an irreplaceable role in the management of perioperative patients.[10-13] Despite its clinical importance, few studies have focused on perioperative nursing. We herein present our experience with the optimized nursing process in perioperative patients with haemophilic pseudotumours.

We retrospectively reviewed the nursing and medical records of haemophilic patients cared for by our team. Sixteen patients with proximal pseudotumours underwent surgical treatment from 1990. All of them were men with a mean age of 31.1 years. Fourteen patients had haemophilia A (severe, n = 3; moderate, n = 6; and mild, n = 5), and two patients had moderate haemophilia B. The pseudotumour was confined to the muscles of the limb extremities, pathological fractures of the femur, and the abdomen or pelvis. Surgical methods include surgical excision, cyst cavity curettage and filling with a fibrin seal and cancellous bone graft, pseudotumour excision and reconstruction with an allogeneic bone graft, and amputation.

The basic outline of the optimized nursing process is shown in Figure 1. In general, the optimized nursing process consists of three consecutive periods (preoperative, intraoperative and postoperative phases) throughout the entire period of hospitalization. Except for regular nursing care, the optimized nursing process focuses on coagulation dysfunction and pseudotumour-related factors. The key points of nursing are as follows:

Haemophilia is a lifelong disease that often causes fear, pessimism and disappointment in affected patients. These emotions are usually amplified when they are admitted to a hospital for treatment of the pseudotumour. Therefore, mental nursing should continue throughout the hospitalization period. The Hospital Anxiety and Depression Scale (HADS)[14] was used to evaluate patients' mental states at the time of admission, in the preoperative period, and at discharge. At the time of hospitalization in our series, the patients were in a state of obvious anxiety with a mean HADS score of 16.3 ± 2.5. In particular, a high score for the item "I get sort of frightened as if something awful is about to happen" indicates obvious anxiety about operation and prognosis and a strong sense of uncertainty. For such patients, surgeons and nurses were asked to communicate with the patients to explain the disease, operation and postoperative-related matters in detail. After repeated explanation and careful perioperative nursing, patient's confidence in overcoming the disease was strengthened and the patient's trust in medical care was enhanced. The degree of anxiety was significantly lower before the operation, with a mean HADS score of 7.4 ± 3.2 (paired t test, $P < 0.001$). The mean HADS score was further decreased upon discharge (4.4 ± 3.1, $P = 0.021$) because of the satisfactory surgical results. Individualized intervention is necessary according to the degree of anxiety. The patients' anxiety can be obviously relieved through preoperative full communication, careful treatment and optimized nursing.

Attention to several details can prevent the patient from bleeding. Regular observation of oral, nasal and other sites of local haemorrhage is important. Patients should be guided to develop bleeding-prevention habits. Contact with and manipulation of the

Yaping Chen, Yu He and Xi Zhou authors are contributed equally to this work.