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Case Report

Severe hematomas in an inherited FXIII deficiency successfully treated with Catridecacog (rFXIII-A)

Abstract.

A Pakistani boy with an inherited FXIII deficiency came at our attention with a suspect of compartment syndrome, and was successfully treated with recombinant r-FXIII-A replacement. We would like to emphasize the efficacy of rFXIII-A, compared with fresh frozen plasma and cryoprecipitates, which did not cause a significant increase in FXIII levels in our patient. In 2017, our experience had already showed that Catridecacog could be used safely and effectively not only for continued prophylaxis but also for on-demand treatment and adds to the limited body of evidence currently available on rFXIII-A for acute bleedings.

Keywords: inherited FXIII deficiency, FXIII, rFXIII-A, Catridecacog, hematomas, bleeding disorders

Introduction

Factor XIII (FXIII) is a protransglutaminase that, after activation by thrombin and in the presence of calcium, becomes transglutaminase, leading to increased stability of the fibrin clot. Plasma FXIII is a heterotetramer composed of 2 catalytic A-subunit and 2 carrier B-subunits linked by noncovalent bonds [1]. Inherited FXIII deficiency is a rare bleeding disorder caused by defects in both FXIIIA and FXIIIB genes; however, the majority of the cases are attributed to genetic variants of the FXIIIA gene. The clinical symptoms of FXIII deficiency include delayed wound healing, recurrent spontaneous miscarriage, bleeding of soft and subcutaneous tissue, and life-threatening spontaneous CNS bleeding, which is the primary cause of death in affected patients. The treatment of FXIII deficient patients consists of the use of fresh frozen plasma, cryoprecipitate, plasma derived concentrate or the recently developed recombinant FXIII (r-FXIII-A) for patients with FXIIIA subunit deficiency [2].

Report of the case

Here we report the case of a 14-year-old Pakistani boy with an inherited FXIII deficiency who came at our attention with a suspect of compartment syndrome, successfully treated with recombinant r-FXIII-A replacement. In 2017, he was referred to our Hospital because of a huge hematoma on the lower left limb and the suspicion of a compartment syndrome. In the familiar history, the consanguinity of his parents was noted. The boy had a history of bleeding after circumcision. At that time, he was transfused in his native country with HCV infected whole blood coming from his father. He was discharged with an undefined diagnosis of bleeding disorder. Other two severe bleeding episodes have been reported after traumatic events on the left hand and lips. When he was 10-year-old, he moved to Italy. During this period in Italy his father asked the paediatrician for a haematological counselling. However, as first level coagulation tests

treatment period. Unfortunately, two months after the suspension of the prophylaxis the patient had a contralateral post-traumatic intramuscular hematoma while he was playing soccer. Once again, he was treated with r-FXIII-A with excellent response. At the last follow-up, he was in good physical conditions the hematoma was undetectable, and he was still carrying on a secondary prophylaxis with r-FXIII-A at 2500 U ev every six weeks. this dosage is slightly different from that indicated in the technical data sheet but allows to avoid the waste of residual drug in the vial.

Discussion

Congenital FXIII deficiency is a rare autosomal recessive bleeding disorder whose diagnosis is challenging due to the rarity of the disease and because the standard clotting tests such as prothrombin time, activated partial thromboplastin time, fibrinogen level, platelets count and bleeding time result normal.

It is a disease difficult to manage, independently of the diagnosis because of a heterogeneous clinical presentation, as showed by the EN-RBD study [3]: patients with FXIII coagulant activity levels <30% might bleed with a heterogeneous clinical presentation. In particular, those with low activity levels developed spontaneous major bleeding and spontaneous minor or post traumatic bleeding. Then, a cut-off level of FXIII coagulant activity that could discriminate patients with severe bleeding manifestations from those with minor or no bleeding has been searched and The Prospective Rare Bleeding Disorders Database showed that a level of 15% FXIII clotting activity could be a good therapeutic target to maintain in patients with no bleeding [4].

The severity of bleeding symptoms in congenital FXIII deficiency is the main reason for regular replacement therapy. Prophylaxis is highly efficient and successful because of the long half-life of FXIII. Fresh frozen plasma, cryoprecipitate, and a plasma-derived, virally inactivated FXIII concentrate have been available for prophylaxis. Moreover, the new recombinant FXIII manufactured in Saccharomyces cerevisiae is now available. The r-FXIII-A links in plasma with the endogenous FXIII-B subunit to form stable FXIII heterotetramer. FXIII-B-subunit deficiency is associated with a much more reduced half-life of the administered pharmacologically active A-subunit.

The efficacy and safety of the new rFXIII-A was shown in 2012 in a multinational prophylaxis trial demonstrating that a single dose of 35 UI/kg r-FXIII-A maintained plasma FXIII levels above 10% in patients aged ≥ 6 years and with FXIII A deficiency.

In our case, given the unavailability of plasma-derived FXIII and the low levels of FXIII after cryoprecipitates, r-FXIII-A was administered as treatment and then every 4 weeks as prophylaxis during physiotherapy, monitoring his trough levels closely, in order to maintain it higher than 30%.

This strategy allowed to resolve the acute bleeding and prevent invalidity due to muscular damage related to bleeding.

The subunits A and B were not tested before the use of r-FXIII-A, but retrospectively we can say that the boy has an A defect, because of the improvement in FXIII activity measured after r-FXIII-A replacement.

It remains unclear if our patient, that is still carrying on a secondary prophylaxis with r-FXIII-A, will need a long-term prophylaxis.

In 2017, recombinant FXIII-A was indicated only for the long-term prophylaxis of bleeding in patients with type A subunit defect, but this case shows the successful use of recombinant FXIII-A as treatment of acute hemorrhagic episodes in an inherited FXIII deficiency.

The on-demand treatment has not been studied in the clinical development programme but, recently, the on-demand use has been reported in the drug data sheet of Catridecacog.

In this report, we would like to emphasize the efficacy of rFXIII-A, compared with fresh frozen plasma and cryoprecipitates, which did not cause a significant increase in FXIII levels in our patient.

In 2017, our experience had already showed that Catridecacog could be used safely and effectively not only for continued prophylaxis but also for on-demand treatment and adds to the very limited body of evidence currently available on rFXIII-A for acute bleedings.

were found normal, the paediatrician considered any further investigation unnecessary. In October 2017, the patient was referred to a peripheral hospital because of a painful swelling on his lower left limb after a trauma on the bike. Knee radiography was normal, while a hematoma in gastrocnemius muscle of 4 cm diameter was detected on a Doppler ultrasound. After hematological consultation, FXIII dosage was requested. However, almost a week passed between sample collection and results availability; during this period the hematoma progressively enlarged because no specific treatment was started in the absence of a diagnosis. On the physical examination the patient showed hyperpyrexia (TC 39,5 °C), painful swelling on the left knee, leg and proximal calf with red and hot skin. A severe functional limitation in the dorsal flexion of the foot with a tendency to equinism was noted. Increased inflammation and muscle lysis indexes (RCP 15.4 mg/dL, CPK 1243 U/L) were also detected. As soon as the result of FXIII dosage was available (10,7%), the patient was treated with fresh frozen plasma (FFP) at the dosage of 20 ml/kg, as the FXIII concentrate was at that time not available, and then he was referred to our hospital.

At our examination he was still feverish. The left calf circumference was 37 cm. Obliged decubitus with left limb in flexion was noted. Sensibility was not impaired and peripheral pulses were detectable. An echocolordoppler showed a regular arterial flow. A multidisciplinary team including an orthopaedic, a physiotherapist, an infectious disease specialist and a hematologist took care of him in order to avoid the development of a compartment syndrome. On October 20th, 2017, after infusion of FFP the result of FXIII dosage was 17,6% (2:30 p.m.)

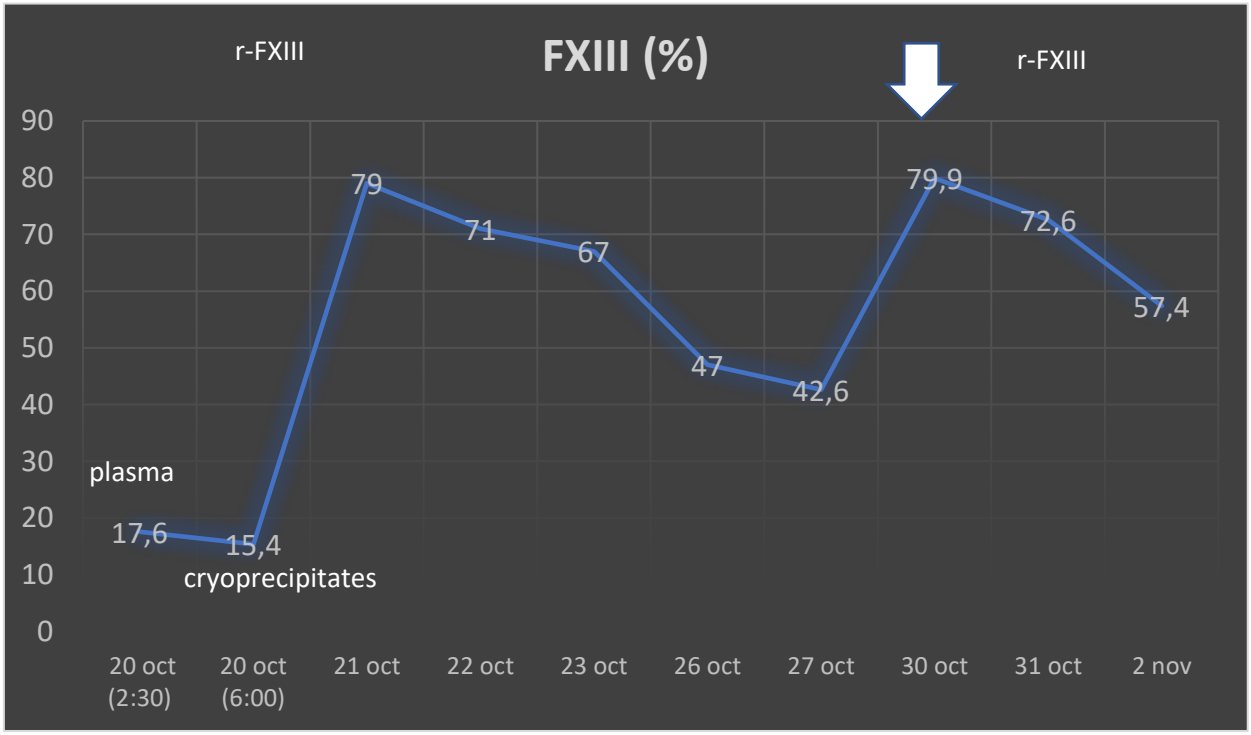

Figure 1: Dosage of FXIII levels (%) after infusion of fresh frozen plasma, cryoprecipitates

The patient was at first treated with cryoprecipitate (4 bags) and then, because of persistent low levels of FXIII (15,4% on October 20th, 2017 at 6 p.m.), with r-FXIII-A replacement at the dosage of 50 U/kg.

FXIII levels were near 80% immediately after r-FXIII-A replacement and they still remained > 60 % in the following 48 hours (figure 1). Ten days later the clinical conditions of the patient were definitely better: he was afebrile, the inflammatory indexes were almost normalized and no more pain at rest was reported. The calf circumference was 32 cm (the other calf measured 29 cm) with normal skin. He had almost recovered the mobility of the leg. The hematoma measured 15 x 8 mm. In order to keep FXIII levels higher than 30%, a secondary prophylaxis with r-FXIII-A was administered monthly for 6 months during the physiokinesitherapy

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