Diagnosis and management of severe congenital factor XIII deficiency in the Emergency Department: lessons from a "model" family

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Introduction

Plasma factor XIII (FXIII) is a proenzyme (composed of 2α2β subunits), activated to XIIIa by calcium and thrombin in the final step of the coagulation cascade. FXIII stabilises the clot during the process of haemostasis by catalysing the cross-linking of fibrin, platelet membrane and matrix proteins. Moreover, FXIII prevents premature clot degradation by the fibrinolytic system. FXIII also plays an important role in wound healing and tissue repair.

Congenital FXIII deficiency is a rare genetic bleeding disorder that is inherited in an autosomal recessive manner with a frequency of one case per 2-3 million individuals in the human population. The genes involved in FXIII production are located on different chromosomes, namely subunit A on 6p25-p24 and subunit B on 1q31-q32.1. Genetic analyses have revealed that in most cases congenital FXIII deficiency is associated with deficiency of subunit A located on chromosome 6, while in a minority of cases it is found associated with deficiency of subunit B located on chromosome 1.

Affected subjects often have a positive history for consanguinity. Although rare, congenital FXIII deficiency is an important disorder because of the severity of its bleeding manifestations. In particular, the incidence of intracranial haemorrhage is 20-30%, which is significantly higher than that in any other bleeding disorder.

The clinical manifestations of congenital FXIII deficiency include a lifelong bleeding diathesis, in particular subcutaneous bleeding (57%), delayed umbilical cord bleeding (56%), muscle haematoma (49%), haemorrhage after surgery (40%), intracerebral bleeding (34%), and a high risk of miscarriage. Delayed bleeding (i.e., 12-36 hours) after trauma or surgery is pathognomonic of factor XIII deficiency.

Differently from all other congenital haemostatic protein deficiencies, in congenital FXIII deficiency typical coagulation screening tests and platelet function tests are absolutely normal; specific FXIII assays must, therefore, be performed. Indeed, factor XIII deficiency should be considered in patients with recurrent delayed bleeds and a normal coagulation profile.

Case report

C.S., a 1-year old boy, born after physiological delivery to non-consanguineous parents, was admitted to the emergency room for painful swelling of the right cheek subsequent to mild trauma that had occurred 5 days previously.

Laboratory tests revealed normal blood count, coagulation screening, and bleeding time. Ultrasound (US) examination of the lesion showed a large hypoechoic area with a "solid" internal portion below marked hyperechoic thickening of the subcutaneous layer.

The main differential diagnoses were infectious/inflammatory disease, tumour, non-accidental trauma/abuse and a bleeding diathesis. The patient had a history of significant recurrent umbilical stump haemorrhage that needed surgical treatment. Furthermore, during his first year of life, C.S. was admitted to the emergency room several times for soft tissue bleeding, both spontaneous and following mild trauma. Coagulation screening tests were repeatedly normal.

The differential diagnosis was narrowed down to recurrent non-accidental trauma and a bleeding diathesis, with the latter hypothesis being considered unlikely, since haemostatic tests were normal.

The patient's history did, however, lead the consultant haematologist to suggest a FXIII assay. This was done by experienced technicians using the clot lysis method with 1% monochloroacetic acid and sequential dilution of the proband's sample in a known thrombin content (Roche Diagnostics, Milan, Italy), which has been described as better suited for detecting severe deficiencies. FXIII activity was 0%; severe congenital FXIII deficiency was diagnosed and 20 IU/kg of plasma-derived FXIII concentrate (Fibrogammin, CSL-Behring, King of Prussia, PA, USA) was promptly infused. Subsequent molecular characterisation showed a heterozygous Gly562Arg mutation, which was previously found to be related (in homozygous form) to altered conformation and rapid degradation of the protein. The same mutation was found in heterozygous form in the mother, who had 37% FXIII activity but no history of bleeding. Based on the finding of 0% FXIII activity, a second mutation was anticipated but unsuccessfully searched for in C.S. by full gene sequencing. No mutation was found in the
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father, who presumably carries the second, unfound mutation. The family had already been included in a previous report. Figure 1 illustrates the family pedigree.

C.S. grew up regularly, with rare soft tissue bleeds (treated with on-demand therapy) and a reported good quality of life. At the age of 6 years, he complained of right groin pain the day after a short run, with progressive weakness of the right leg and difficulty in standing. He was therefore admitted to the emergency room; on physical examination the right hip was painful, even during passive mobilisation. There were no other pathological findings. US examination of the hip and right knee did not show any bleeding in the joints; the orthopaedic specialist suggested analgesic therapy. The haematologist suggested a more detailed US study of the ilio-psoas muscle which showed a deep haematoma, promptly treated with 20 IU/kg Fibrogammin infusion.

The patient was then scheduled to receive a regular regimen of prophylaxis, with monthly infusions of Fibrogammin at a dose of 20 IU/kg.

Five years later, his sister, C.E., was born by Caesarean section and was soon diagnosed with 0% FXIII activity by a modified Berichrom FXIII chromogenic assay on a Sysmex CA7000 coagulation analyser (Siemens Healthcare Diagnostics, Milan, Italy). A mutation search has not been performed yet.

Considering the high risk of intracranial haemorrhage (ICH), two brain US scans were performed on the second and third day of the girl's life: the findings were normal in both cases. Predictably, on the fifth day of life, C.E. developed a significant stump haemorrhage, which was successfully treated with Fibrogammin.

When she was 2 months old, she developed vomiting followed by transitory shivering. The general paediatrician excluded pathological findings. Fifteen days later, a new episode of protracted, right-sided shivering was reported. The general paediatrician, suspecting epilepsy, requested a neurological evaluation. The parents called the haemophilia centre; the haematologist suspected ICH and immediately referred the infant to the emergency room. On admission, 40 IU/kg Fibrogammin was promptly administered. Subsequent brain US showed a vast hypocho Gegic parietal area, probably due to a sub-acute hematoma. Urgent brain computed tomography confirmed the diagnosis of ICH. Magnetic resonance imaging was performed 2 days later to define the extension of the brain lesion better (Figure 2).

Replacement therapy with high-dose Fibrogammin (40 IU/kg) was started and then adjusted with the goal of maintaining FXIII activity above 20%.

C.E. was discharged after 2 weeks, on regular Fibrogammin infusions every 2 weeks; at 3 months after the ICH, she is receiving 40 IU/kg Fibrogammin every 3 weeks and the last US examination of the brain showed progressive reduction of the haematoma.

Discussion

The diagnosis of congenital FXIII deficiency is a challenge in the field of rare bleeding disorders and is often still missed all over the world with potentially fatal consequences from severe bleeding complications.

Although congenital FXIII deficiency is a rare genetic disorder, it should be considered in children with

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**Figure 1** - Family pedigree.

FXIII: factor XIII.
a history of bruising and prolonged umbilical bleeding, with a normal coagulation screen despite a negative family history of bleeding and consanguinity.

The mainstay of treatment is the replacement of the defective factor with plasma, cryoprecipitate, and FXIII concentrates. The treatment of choice is Fibrogammin, a plasma-derived FXIII concentrate that is pasteurised to provide virological safety and is less likely than plasma to cause systemic reactions'. Due to some regulatory issues, this product is imported into Italy on special request from physicians. Recombinant FXIII concentrates have been evaluated in clinical trials and will be available in the near future.

Levels of FXIII above 3-5% are usually sufficient to prevent spontaneous bleeding; this fact, together with the long plasma half-life of FXIII (7-12 days), makes prophylaxis highly feasible. Thus, a dose of 10-20 U/kg every 4-6 weeks provides adequate plasma levels in most patients. The dose and frequency should be tailored to plasma levels and clinical efficacy for each patient. However, unlike in severe haemophilia, regular prophylaxis has not become the standard of care in congenital FXIII deficiency, because of the heterogeneous availability of the plasma-derived concentrate.

Ilio-psoas haematoma is a serious complication of severe bleeding disorders; it is considered a potentially life-threatening event and is significantly associated with morbidity. The symptoms may mimic acute appendicitis, including a positive Blumberg's sign. Retroperitoneal haemorrhage in the psoas muscle can be severe enough to cause a significant drop in haemoglobin. For this reason, ilio-psoas hematoma is a well-known serious complication in patients with bleeding diseases, but it often remains undiagnosed in the emergency room.

Severe congenital FXIII deficiency is associated with a significant risk of spontaneous ICH; indeed, this risk is much higher than that in other congenital clotting defects. For this reason, in patients with severe congenital FXIII deficiency, ICH must be considered as the cause of every neurological symptom until it is ruled out by instrumental examination. Nearly 80% of deaths in these patients have been ascribed to ICH. Indeed, neurological symptoms in patients with severe bleeding disease should always lead to urgent FXIII concentrate infusion until exclusion of ICH, even in the absence of head injury.

Patient C.E. experienced ICH at 2 months of age. Ever since her diagnosis at birth, the haematologist had been able to suspect bleeding and organise urgent admission to the emergency room with immediate FXIII treatment. If her condition had not been diagnosed at birth, as had happened to her brother, she could have experienced severe consequences such as rapid deterioration of brain function, associated brain swelling, herniation of the brainstem, and perhaps death.

Both ICH (or its suspicion) and psoas haematoma are considered emergencies in the management of patients with haemophilia or other congenital bleeding diseases. Common clinical experience teaches that significant life-threatening complications can occur when the clotting defect is not corrected. Nevertheless, it has been reported that there is often a substantial delay in starting replacement therapy in patients with known congenital bleeding diseases on admission to the emergency room; the main cause of this delay is the long period between triage and administration of therapy.

Our patients' histories highlight several significant issues about the complexity of diagnosis and management of severe congenital FXIII deficiency and other severe congenital bleeding disorders.

There is a need for better knowledge of these conditions and dedicated emergency policies that could speed up the procedures, thereby reducing the risk of severe and long-term complications.

This article is aimed at improving the diagnostic approach to this rare defect and therefore the management and treatment of congenital FXIII deficiency and other bleeding diseases. As a consequence, patients with severe congenital clotting defects will receive prompt treatment for their bleeding in emergency departments and this will reduce the development of serious complications. With the future widespread availability of recombinant factor XIII concentrate, prophylaxis should become standard care in all patients with severe congenital FXIII deficiency.
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**Keywords:** factor XIII deficiency, intracranial haemorrhage, stump haemorrhage, ilio-psoas haematoma, abuse.

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