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Factor XIII deficiency, a primer for anesthesiologist

Mary-Frances Scully, M.D.

* Profesora Asociada en el Departamento de Medicina de la Memorial University. Directora del Programa de Hemofilia Provincial de Adultos. Hematólogo / Oncólogo de adultos en el Centro de Ciencias de la Salud en St. John.

INTRODUCTION

Factor XIII is an unusual clotting factor for multiple reasons. First when the circulating zymogen is activated it becomes a transglutaminase and not a proteinase. Also unlike other coagulation factors, factor XIII circulates as a tetramer, consisting of two subunits A and two subunits B The part of the molecule which become activated includes the two A subunits and the B subunits are considered to be inhibitory, protective and possibly regulatory. In plasma the B subunits are present in excess and 50% circulate as a homodimer. Factor XIII subunit A is present intracellularly in platelets, monocytes and macrophages, also as a homodimer. Another unusual characteristic is that each subunit is coded for on a separate gene. The A subunit is coded on Chromosome 6 and this part of the molecule is synthesized in cells, which originate in the bone marrow. The B subunits just like most coagulation factors are synthesized by hepatocytes and the gene is located on chromosome 1. In the circulating zymogen, the activation peptide (AP) portion of the A subunit hold the two subunits together and occludes the active site cavity, preventing premature interaction with substrates. As for the proteases, activation by thrombin requires ionized calcium ions[1]. The free activation peptide (AP) factor XIII reduces further factor XIII activation and fibrin crosslinking locally. Again unlike other coagulation factors, which function by breaking peptide bonds, activated factor XIII functions by cross-linking fibrin γ-γ, γ-α and α-α chains. This strengthens the clot and allows it to become more compact. The antifibrinolytic effect of factor XIII is greatly amplified by cross-linking fibrinolysis inhibitors, which include α_2-antiplasmin and thrombin activatable fibrinolysis inhibitor (TAFI). Platelet retraction, which is a prerequisite for wound healing is dependent on factor XIII[2]. Recently Wolberg et al, have published data supporting the role of factor XIII in red blood cell retention, in whole blood clots in mice[3]. Their data is consistent with results published in 1970 describing a family with severe factor XIII deficiency. In addition to its role in hemostasis, factor XIII plays a role in cellular and innate immunity, in bone biology and in adipogenesis[4].

CLASSIFICATION OF FACTOR XIII DEFICIENCY

Severe congenital factor XIII subunit A deficiency is an extremely rare, autosomal recessive disorders affecting in the range of 2,000,000-5,000,000 people. However, in populations, where there has been a high rate of consanguineous marriage, either because of a religious or cultural preference or because of isolation, the disorder will be more common. In the province of Newfoundland and Labrador in Eastern Canada, where I practice, the prevalence is relatively high at 1 in 100,000 and is falling now as our demographics are rapidly changing. Patients with severe disease are either homozygotes or double heterozygotes. There is interest in, but a serious lack of data about whether or not heterozygotes are symptomatic. In the qualitative defect there appears to be a close correlation between the bleeding risk and the degree of deficiency. This also holds true for deficiencies of fibrinogen and factor X. However, this association does not hold true consistently for patients with deficiencies of factor V and VII and is not demonstrated at all for patients with factor XI deficiency, in whom there is minimal if any correlation, between factor levels and bleeding risk[5]. Although factor XIII subunit A deficiency is extremely rare in most populations, the bleeding tendency is so dramatic that it is very important, that the diagnosis not be delayed.

In undiagnosed and untreated patients, intracranial hemorrhage has been reported in from 10 -34% of patients and

frequently leads to death or disability. What is especially troubling being that serious bleeding episodes are unpredictable. Such episodes and can occur at any age and quite unexpectedly in untreated patients, even after a period of time, with few bleeding problems[5]. Type I deficiency is a quantitative defect resulting from decreased synthesis of the protein. As of November 2015, 111 mutations causing factor XIII subunit A deficiency had been registered on the Human Gene Mutation Database[1]. Type II deficiency is characterized by a normal or near normal Factor XIII subunit A level, which is functionally defective has been reported and is very likely to be underdiagnosed. Quantitative deficiencies of subunit B have been reported in a small number of patients. So far these patients appear to have a milder bleeding tendency consistent with the a more inhibitory and regulatory role for the B subunit[1].

CLINICAL FEATURES OF CONGENITAL DEFICIENCY

Undiagnosed and untreated severe factor XIII subunit A deficiency is likely the most severe of the reported hereditary bleeding disorders. Paradoxically when the diagnosis is made early in a child's life and prophylaxis with a factor XIII concentrate started and continued with appropriate dosing and monitoring, this is an incredibly rewarding disorder to treat as prophylaxis is associated with an excellent quality of life (personal experience). Umbilical cord bleeding after birth is pathognomonic for severe factor XIII deficiency. This finding should always trigger investigation for a defect in factor XIII and prompt treatment ideally with a factor XIII concentrate or if this is unavailable with either plasma or cryoprecipitate. In five different International registries this presenting feature was reported in from 56 to 83% of patients with severe factor XIII deficiency. Tragically late and misdiagnosis can lead to death for up to 20 % of patients, as reported from Iran. At our center, all four of our five adult patients have lost a sibling from intracranial bleeding in childhood and three out of five experienced intracranial hemorrhage before starting on prophylaxis (personal experience).

In a recent review, the authors compared data from five registries. One registry used a questionnaire to collect data form 104 patients living in 11 European countries, Iran and Morocco. The second reported data from a retrospective review of 42 patients in 11 European countries. This data was collected from 2007-2010. The third registry reported from India on retrospective data collected on 88 patients, from 1975-2008. A fourth, North American Registry also used a questionnaire to report on 32 patients. In addition, a group of 93 Iranian patients were surveyed using a questionnaire and a further 12 by reviewing a data-base from 2009 -2011. De Jager et al identified the studies reporting on these patients by searching Medline, Embase and Cochrane Databases. Umbilical cord bleeding was the most commonly reported symptom. This was reported by 56, 48.5, 83, 73 and 73%. After umbilical cord bleeding, subcutaneous bleeding was reported in 57, 56, 47 and 82%. Muscle hematomas were reported in 27-49% of patients in two of these registries. Hemarthroses (bleeding into joints) was reported in 36%, 55 and 36% respectively. Intracranial bleeding was reported in 34, 13, 10 and 11%. As previously mentioned Intracranial hemorrhage is the most dangerous type of bleeding leading either to death or disability, in this patient population. Mucosal bleeding such as gastro-intestinal (GI) bleeding has been reported in in 3-10%; epistaxis in 27-32% and oral bleeding in 25-48%[6]. As another comparator of severity, in the European network of rare bleeding disorders, treating physicians reported that 48.5% of bleeding events in the patients with severe factor XIII deficiency were spontaneous and severe, prior to initiation of regular replacement with factor concentrate XIII i.e. regular prophylaxis. This percentage can be compared with 42.3% for patients with deficiencies of fibrinogen and 3.2% for patients with deficiencies of factor XI[5]. Sharief et al reported on a series of 60 women who had 185 recorded pregnancies. Of these 125 or 67.5% resulted in a miscarriage. Two women had thirteen miscarriages with associated uncontrolled bleeding. Factor XIII subunit A contributes to the formation of the cytotrophoblastoid shell and fibrinoid layers and hence deficiency leads to separation of the placenta from the uterus and miscarriage. Women who experience recurrent miscarriage should be investigated for abnormalities in terms of quantity or function of their fibrinogen or factor XIII. Weekly replacement therapy with fresh, frozen plasma, cryoprecipitate or factor XIII concentrate will prevent this unfortunate complication. Curiously unlike the other procoagulant factors, Factor XIII levels fall during pregnancy[6].

Mild deficiencies may be underreported and little is known about the clinical outcome for these patients. At our center, the granddaughter of a patient who bled to death after dental work was referred to our clinic for management of a second pregnancy with a planned Caesarian section. At presentation she had a very mildly positive bleeding history. Her initial factor XIII subunit A level was 45% and it fell to 17% by 37 weeks. We treated her prophylactically with one vial i.e. 2,500 units of recombinant factor XIII subunit A. Her levels rose to 100% one-hour post infusion. She successfully underwent her second Caesarian Section with an excellent outcome for mother and baby. However, she also had a good outcome with her first Caesarian Section, for which she received no treatment, as her diagnosis was unknown. Impaired wound healing is another common challenge for these patients. One of our patients developed a significant umbilical hernia as an adult. We speculate if this might be a complication of his umbilical cord bleed, as a newborn. He successfully underwent a surgical repair after standard pretreatment with a plasma-derived factor XIII concentrate, fibrogammin P at 50 units/kg (unpublished personal experience).

LABORATORY DIAGNOSIS

Patients with even very severe deficiencies of factor XIII will have absolutely normal baseline coagulation tests including a normal complete blood count, blood smear, prothrombin time, activated partial thromboplastin time, fibrinogen and thrombin time. More specialized tests of platelet function are also normal. Traditionally the test used to screen for a deficiency of Factor XIII or α_2-antiplasmin deficiency has been the «the clot lysis» assay. This test measures the solubility of the fibrin clot in concentrated urea, acetic acid or monochloroacetic acid. However, the test is notoriously insensitive and may only detect levels as low as < 0.5% to 5% factor XIII activity[7]. Spontaneous intracranial hemorrhage has been reported in a patient with a factor level of 10%[5]. Hence this test is dangerously insensitive. The scientific subcommittee on factor XIII, for the International Society of Thrombosis and Hemostasis, recommends a quantitative functional FXIII activity assay as a «first-line» screening test. These assays include ammonia release assays, for which at least three commercial kits have been manufactured. Senior researchers in this field stress that for accuracy it is essential to also use a plasma blank, when performing the assay. An ammine incorporation assay is also commercially available. In research laboratories fibrin cross linking can be measured by SDS PAGE. The next recommended step is antigen testing of either the FXIII A2-B2 tetramer and/ or the subunits. Followed by fibrin cross-linking by SDS-PAGE and then detection of molecular defects[1].

Dorgaleh et al have published a suggested alternate laboratory algorithm, which recommends screening first for the known common mutations in well characterized populations such as in Iran, Pakistan, Finland and Tunisia. They still recommend the clot solubility test in countries with limited access to specialized tests[8]. In our laboratory we only have access to an automated latex enhanced immunoassay for the quantification of human factor XIII subunit A in citrated plasma samples. We find this a very reliable and robust assay. The limitation for us is cost and logistics as this assay cannot be run with other coagulations assays and hence ties up one of of our limited number of analyzers.

THERAPY

There is a consensus that patients with severe deficiency benefit from regular prophylaxis.

If factor concentrates are unavailable, patients will benefit from infusions of plasma and cryoprecipitate. The plasma –derived concentrate produced by CSL Behring has been safely and successfully used for more than two decades. The initial recommended dose in Canada was 10 units/kg infused every two– four weeks. Other countries used 15-30 Units /kg every 4-6 weeks. In studies focused on licensing requirements a dose of 40 Units/kg gave an average trough level of 15.3 (SD 3.4) at 28 days. This product is a purified, pasteurized, nanofiltered human plasma derived product and is available in two vial sizes of 250 units and 1,250 units. Currently the CSLBehring product used in Canada has the commercial name of Corifact. A recombinant Factor XIII subunit A has been produced in yeast cells by Novo Nordisk. This product has been successfully used as prophylaxis in patients known to have subunit A deficiency. In clinical trials a dose of 35 units/kg, given every 28 days, was chosen as the prophylactic dose. This product is available in one vial size of 2,500 units. It is currently licensed for the prophylactic treatment of patients with known subunit A deficiency only. Further clinical studies are needed to see if this product can effectively treat patients, with a defect in subunit B. The commercial name is Tretten. Due to the high costs of these therapies, currently at our center we give the minimum dose needed to produce a trough level of at least 10%.

Life threatening bleeding after circumcision has been reported. When undiagnosed and hence untreated, bleeding after surgery was reported in 40% of patients registered in a European data-base[5]. 84% of 32 Iranian patients who underwent surgery experienced a surgical bleed[6]. Hence for surgery the recommended dose is 50 units of plasma derived Factor XIII. This regime is usually very effective and safe. Often one dose is quite adequate due to the long half-life. In an emergency situation such as a head injury again the dose is 50 units/kg in patients who are not receiving prophylaxis. 25-35 units/kg is sufficient for patients on regular prophylaxis, provided their last infusion has been within one to two weeks. Intravenous tranexamic acid is recommended as an adjunct to therapy[9].

ACQUIRED FACTOR XIII DEFICIENCY

There is limited data available with regards to the optimal levels of factor XIII required for the prevention of peri-and post-operative bleeding and for wound healing. However, there is accumulating data, which suggests that factor XIII may decrease due to consumption in some surgical populations, including patients undergoing cardiac bypass, orthopedic surgery, neurosurgery and gastric cancer surgery. In a study of 1,264 patients who underwent intracranial surgery, 34 patients bled extensively more than expected, using a standardized assessment tool. All 8 patients with significantly lower factor XIII levels experienced a major post-operative hemorrhage, in contrast to only 3 out of 26, who had normal levels. A much smaller study reported on 226 consecutive patients, who underwent elective surgery and were evaluated for parameters connected with the final steps of fibrin clot formation. The 8.8% of patients, who bled were found to have lower levels of factor XIII. A small number of patients have been enrolled in placebo-controlled

randomized clinical trials of factor XIII supplementation peri-operatively. One such trial showed a positive result for high risk patients undergoing elective surgery for gastric cancer. A small randomized trial of 75 patients undergoing cardiac bypass surgery, demonstrated decrease blood loss and transfusion requirements when factor XIII levels were maintained above 70%[4]. However, in a randomized controlled trial including 409 patients, supplementation with either 17.5 or 35 U/kg had no effect on transfusion requirements or reoperative rates in moderate risk patients. There was no increase in thrombo-embolic events in the patients who received supplementation. This trial was not tailored to treat patients with lower levels[10]. So there is a need for further studies focused on supplementing patients who have significantly lower factor XIII levels. In medical patients, acquired factor XIII deficiency likely due to consumption can occur in disseminated intravascular coagulation and levels around 40% may contribute to bleeding in patients with both acute myeloid and lymphoid leukemia and in patients undergoing stem cell transplantation. Symptomatic acquired deficiency has been reported in case reports of patients with Henoch-Schönlein purpura. Patients with ulcerative colitis are another patient population, who may have may have decreased levels of factor XIII[1]. Very preliminary studies suggest a possible role in the treatment of patients with systemic sclerosis, bacterial sepsis and for wound healing[4].

ALLO AND AUTOANTIBODIES AGAINST FACTOR XIII

Alloantibody formation, while potentially very serious and even fatal occurs extremely rarely, in patients with congenital deficiency treated with replacement therapy. A very recently published review reported on four patients, who developed antibodies to subunit A and one whose antibodies were against subunit B. All reported cases against subunit A exhibited a very serious bleeding pattern and in one case bleeding was fatal. The patient with the alloantibody to subunit B had moderate bleeding. Autoantibodies also occur rarely and are associated with a very severe bleeding pattern, somewhat similar to the patients with a congenital deficiency. A majority occur in patients aged over 60. The mortality rate in a predominantly caucasian population was 29% and in the Japanese population was 22%. Several presumably were drug-induced and a few cases have been reported in association with malignancy. 20% occur as part of an autoimmune disorder. The most effective reported therapies are with immunosuppression with cyclophosphamide and prednisone and rituximab and cyclosporine have been successfully used in some patients to eradicate the antibody. Regular infusions at high doses are useful to prevent bleeding. However, some patients with high titer antibodies will not respond and managing bleeding is very challenging[1].

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