# Clinical and laboratory features of congenital factor XIII deficiency

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## ABSTRACT

**Objective:** This is a retrospective analysis of the clinical and laboratory features of 17 cases of factor XIII deficiency that were followed in tertiary care hospitals in Riyadh, Kingdom of Saudi Arabia, over 20 years. Cases were referred to these hospitals from other health care centers in the country.

**Methods:** We performed a retrospective analysis of 17 cases of factor XIII deficiency comprising 11 males and 6 females, who were seen over a period of 20 years (1978-1998) in Riyadh, Kingdom of Saudi Arabia. Data variables including age, sex, origin, clinical presentation, bleeding time, prothrombin time, partial thromboplastin time, factor XIII screening and assay, hemoglobin, and platelet count were collected and analyzed. The diagnosis of factor XIII deficiency was made by urea clot lysis test alone in one patient and urea clot lysis test in combination with factor XIII quantitative assay in 16 patients.

**Results:** Eleven patients were males and 6 were females. Median age at the time of diagnosis was 9 years (3-29 years). Ten patients (59%) had a family history of excessive bleeding. Presenting symptoms included ecchymosis and recurrent hematomas in 12 patients (71%), bleeding after circumcision in 6 male patients (55%), umbilical stump bleeding in 7 (41%), poor wound healing and keloids in 3 patients (18%), and intracranial bleeding in 3 patients (18%). Other manifestations included cephalohematoma, abortion, abruptio placenta, and intraperitoneal bleeding (one patient each). Laboratory evaluation revealed a normal prothrombin time, partial thromboplastin time, bleeding time and platelet count in all patients. Factor XIII screening test was positive in all 17 patients tested and assay for factors XIII was <0.06 U/ml in 16 patients tested.

**Conclusion:** Our data confirms that factor XIII deficiency is a rare bleeding disorder characterized by variable bleeding manifestations but consistent laboratory findings. The occurrence of keloid in our patient group may reflect the poor quality of the clotting, associated with loss of tensile strength of fibrin polymers, caused by factor XIII deficiency and leading to abnormally large scar formation.

**Keywords:** Factor XIII, Factor XIII deficiency, bleeding.

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Blood coagulation factor XIII is the most recently discovered of the plasmatic coagulation factors. It has a pivotal role in stabilization of fibrin and its resistance against premature fibrinolysis.[1] This disorder was first discovered by Robbins[2] and was aptly named the fibrin-stabilizing factor (FSF).[2] It was described by Duckert et al,[3] when they reported on a case of a boy with severe bleeding diathesis, in whose clotting tests, the only abnormality was the solubility of the clots in 5M urea. Since that description, over 200 cases have been reported from all parts of the world, mostly in case reports and

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small series. The incidence of congenital factor XIII deficiency is reported to be in the range of one in 5 million in the United Kingdom and Japan, and most reports suggest that it is a rare disorder. Family studies have suggested that congenital factor XIII deficiency is inherited as an autosomal recessive trait.[4] The range of plasma factor XIII activity within the normal population is very wide. It has been recognized for many years, that low plasma factor XIII levels, less than 5% of normal, are sufficient to control bleeding. Factor XIII deficient patients completely lack plasma and platelet factor XIII and usually suffer from significant bleeding diathesis; however, some patients have only a mild bleeding tendency.[5] Due to the appropriate treatment, the severe bleeding complications associated with this deficiency are rarely seen nowadays. Patients with this disorder are at risk shortly after birth for severe and life-threatening bleeding from the umbilical cord stump, that may last for up to 3 weeks when treatment is not given. In infancy, persistent bleeding after injury or surgery, as well as hematoma formation and ecchymosis after minor trauma, can occur. Contrary to hemophilia, joint bleeding can be seen in only 20% of patients. Intracranial bleeding is a characteristic bleeding symptom of factor XIII deficiency, with an incidence of 23% and high mortality. In women, severe intra-abdominal hemorrhage from the ovaries after ovulation can occur. With or without prolonged menses, spontaneous abortions and bleeding complications after delivery are characteristic. We conducted a retrospective analysis of all cases of factor XIII deficiency that were seen and followed at tertiary care hospitals in a large city over 20 years. Seventeen cases were identified. The clinical and laboratory features of these cases will be summarized in this report.

Methods. The medical records of 17 patients with congenital factor XIII deficiency who were followed in tertiary care hospitals in Riyadh, Kingdom, of Saudi Arabia between 1978 and 1998 were carefully reviewed for clinical and laboratory features. Additional data was also obtained by contacting the patients and their families. The data was fed into a flow sheet using Microsoft Excel program for analysis. Clinical variables included age at first presentation, sex, presenting symptoms and signs, disease course and family history. Laboratory data included prothrombin time (PT), partial thromboplastin time (PTT), bleeding time (BT), platelet count, urea clot lysis test, and factor XIII assay. In most cases, PT and PTT were carried out by using the standard methods. Bleeding time was performed by using the template method. Factor XIII screening test is based on the time it takes for a clot, formed in the presence of Factor XIII, to dissolve after adding 5M Urea. If the clot dissolves within the first 24 hours, it is considered abnormal and indicates factor XIII deficiency. Quantitative factor XIII was performed by adding an activator reagent to the plasma. This activator agent contains bovine thrombin, clot inhibitor which will inhibit the formed fibrin from forming a clot, calcium chloride and hexadimethrin bromide. This activator reagent will activate both factor XIII and fibrinogen. Factor XIII links a specific peptide substrate with glycine ethyl estor, thereby releasing ammonia. The ammonia released is determined in a parallel enzymatic reaction. The variable measured is the decrease in the reduced form of nicotinamide adenine dinucleotide (NADH) which is detected by monitoring its absorbance at 340nm.

Results. Among the 17 patients identified, 11 were males and 6 were females. The age range of the patients at the time of initial presentation was between 3 to 29 years, with a median age of 9 years. Five patients were under 5 years, 5 were between 6 and 11, 3 were between 11 and 15, and 4 were over 15 years. Bleeding manifestations observed at presentation included history of ecchymosis and recurrent hematomas in 12 (70.6%), bleeding after minor trauma in 11(65%), umbilical stump bleeding in 8 (47%), and excessive bleeding after circumcision in 6 of 11 male patients (54.5%). Three patients had poor wound healing and keloid formation. Another 3 presented with intracranial bleeding. Each of the following bleeding manifestations was observed in one of our patients: cephalohematoma, recurrent abortion, abruptio placenta, and intraperitoneal bleeding. Family history of excessive bleeding was present in the relatives of the 10 patients (59%). Laboratory evaluation revealed normal PT, PTT, and platelet count in all patients. Bleeding time was performed in 11 patients and was normal in all patients tested. Hemoglobin was normal in all patients, except in 2 females whose levels were less than 12 g/dl. Factor XIII screening test using urea clot lysis test was positive in 17 patients tested. Quantitative assay of factor XIII was available for 16 patients and was consistently low in all patients tested, with a value <0.06 U/ml. All our study patients responded appropriately to treatment with fresh frozen plasma or cryoprecipitate.

Discussion. Factor XIII deficiency can be a congenital disorder as well as acquired.[4] Acquired factor XIII deficiency is infrequently observed after major surgery, liver disorders, and various inflammatory and malignant diseases.[6,7] In this study, we considered the congenital type only. Seventeen cases of congenital factor XIII deficiency were identified, with an age range between 3-29 years, with 70% of the patients presenting at a pediatric age,

giving a median overall age at presentation of 9 years. This is consistent with previous studies that indicate that congenital factor XIII deficiency is usually diagnosed at a young age, hence the importance of early recognition of symptoms and correct diagnosis. Previous reports have indicated that congenital factor XIII deficiency affects both sexes equally.[1] The predominance of male patients in our study could be related to referral bias (more males are able to travel across the country to come to tertiary care centers). Factor XIII deficiency is known to be associated with significant and lifelong bleeding diathesis and this was confirmed in a retrospective study. Of interest is the occurrence of keloids in 3 patients, which to our knowledge has not been previously seen as a manifestation of factor XIII deficiency. The occurrence of keloid may reflect the poor quality of the clot, associated with loss of tensile strength of fibrin polymers, caused by factor XIII deficiency.[1] The standard laboratory clotting tests are normal in factor XIII deficiency. Laboratory diagnosis relies on the standard clot solubility test using monochloroacetic acid or 5M urea. The clot solubility test is a qualitative test and is positive if factor XIII activity in the patient's plasma is zero or very close to zero. It remains the standard screening test for inherited factor XIII deficiency in most routine laboratories due to its simplicity. Almost all patients with inherited factor XIII deficiency have zero factor XIII activity if untreated, and would be picked up by this test. If the diagnosis of factor XIII deficiency is suggested by the solubility test, it should be confirmed by estimation of factor XIII activity using one of several quantitative assays.[8-10] The concentration of the A and B sub-units could be determined by an immunological technique whenever possible.[11] Whole blood, fresh frozen plasma, stored plasma and cryoprecipitate have all been used successfully in the treatment of factor XIII deficiency and are adequate sources of factor XIII. As quite low levels of factor XIII in plasma are sufficient for control of bleeding[4,12] and the in vivo half-life of factor XIII after infusion of plasma or factor XIII concentrate is long (11-14 days), prophylaxis for high-risk patients is feasible.[13,14] Hoechst placental concentrate was successfully used for many years, initially in its non-pasteurized form and subsequently the pasteurized version marketed under the name of Fibrogammin-P.

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