CONGENITAL FACTOR XIII DEFICIENCY

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ABSTRACT

Clinical and hematological data of 9 cases with factor XIII deficiency is highlighted. The age at first bleed ranged from 3 days of life to 1 year. Seven of these 9 cases had bleeding from the umbilicus, 3 had recurrent subcutaneous and muscle hematomas, while 4 cases had CNS bleeds of which 3 expired. Routine coagulogram was normal, while clot solubility in 5 molar urea solution was abnormal in all cases. Factor XIII assay was not done in any. Patients were treated with plasma transfusion during episodes of bleeding. No patient received plasma transfusion as prophylactic therapy. The cumulative Indian data so far documented, inclusive of this series, shows a very high incidence of CNS bleeds (33%) in patients with this inherited coagulation disorder.

Key words: *Factor XIII deficiency, CNS bleeds, Clot solubility.*

Congenital deficiency of Factor XIII (fibrin stabilizing factor) was described by Duckert *et al.* in 1960, in a boy with a severe hemorrhagic disorder associated with defective wound healing(1). Since then, approximately 200 cases have been described(2). This rare deficiency is characterized biochemically by the absence of plasma factor XIII subunit A and diminished levels of subunit B protein(3). The homozygous deficient state results in a moderate to severe hemorrhagic diathesis and poor wound healing. In 1977 classification of factor XIII deficiency into two types was proposed: Type I, characterized by lack of both subunits A and B, and Type II, characterized by absence of subunit A but normal or near normal subunit B(4). In this report we present the data of 9 cases that we have encountered and in addition document data of 9 other cases collected from Indian literature(5-8), in order to characterize the clinical and hematological features of this disorder.

Material and Methods

Clinical and hematological data of 9 cases (from 1984 to 1991) were analysed from the records of the neonatology and

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Bleeding time (BT), clotting time (CT), prothrombin time (PT), activated partial thromboplastin time (PTT), fibrinogen levels and fibrin degradation products (FDP) were estimated in all cases using standard methods(9). Clot solubility was also tested in all cases either in a solution of 1% monochloroacetic acid or 5M urea as described(10).

All patients were treated with plasma transfusions during episodes of bleeding. No patients received regular plasma transfusions as prophylactic therapy.

Results

There were 7 males and 2 females (*Table I*). The age at first bleeding ranged from 3 days of life to 1 year and age at diagnosis varied from 10 days to 3 years. Seven patients had bleeding from the umbilical stump after the cord had fallen and 3 had subcutaneous or muscle hematomas either spontaneous or following trivial trauma. Three out of 4 patients who had CNS bleeds died. Gastrointestinal hemorrhage occurred in one. Other sites of bleeding included hyphema and epistaxis.

The coagulogram studies which included BT, CT, PT, PTT, fibrinogen level, clot retraction and platelet counts were normal in all 9 cases. Factor XIII screen was abnormal in all 9 patients with the clot dissolving in 5M urea solution within 50 minutes to 4 hours (n>24 hours). Factor XIII assay was not done in any case. Hb <9 g/dl was noted in 5 patients at diagnosis.

The mother (Case No. 8) of Cases Nos. 6 and 7 who were siblings, was asymptomatic, but was noted to have an abnormal clot solubility suggestive of Factor XIII deficiency.

CNS bleeds: Four patients had CNS bleeds. Three were documented on CT brainscan and one at autopsy. In all these

TABLE I—*Relevant Features of Nine Cases in Present Series*

Case No.	Age at first bleed	Age at diagnosis	Site of bleed				Course and outcome*
			Umbilical cord	Subcutaneous muscle	CNS	Others	
1	1 year	3 years	–	–	+	Hyphema Epistaxis	Died of CNS bleed (3 years)
2	8 days	6 months	+	–	+	–	Died of CNS bleed ($2^1/_4$ years)
3	3 days	4 months	+	+	–	–	Well (4 months)
4	5 days	2 months	+	–	+	–	Well (10 years)
5	6 days	10 days	+	–	+	GIT	Died of CNS bleed (12 days)
6	10 days	4 years	+	+	–	–	Well (4 years)
7	10 days	2 months	+	–	–	–	Well (3 months)
8	–	26 years	–	–	–	–	Well (26 years)
9	5 days	2 months	+	+	–	–	Well (5 years)

* = Age at last follow-up or death; GIT = Gastrointestinal tract.

cases the CNS bleed followed trivial head trauma. As two of these were not previously diagnosed to have Factor XIII deficiency, there was an initial difficulty and delay in determining the cause of their CNS manifestations. The clinical presentation of CNS bleed included acute onset headache, vomiting, convulsions and altered sensorium in 3 cases. One patient (Case No. 2) who had a cord bleed presented again at 6 months of age with progressive enlargement of head, delayed milestones, and severe anemia (Hb = 4.5 g/dl). CT brain scan of this patient revealed hemorrhagic cysts in both frontal lobes. These were drained under plasma coverage; however, at the age of 2 year 3 months this child expired following an acute CNS bleed.

Discussion

Factor XIII is a zymogen which acts in the final stages of coagulation after thrombin converts fibrinogen to fibrin. In its active form it functions as a transglutaminase to stabilize fibrin clots by catalysing the formation of E-(r-glutamyl)-lysyl cross-links(11). The disorder appears to be inherited as an autosomal recessive trait(12), but sex-linked inheritance has also been postulated(13). Acquired deficiency of this factor has been described with INH therapy, liver disease and some malignancies(14,15). None of our cases had any of the above risk factors.

Features of the 9 cases in this series and relevant data of the other 9 cases reported in Indian literature are described in *Tables I & II*, respectively. Most patients with this deficiency have bleeding from the umbilical cord during the first few days of life. Cord bleeds were seen in 7 out of 9 patients in this series and in 4 out of the other 9 cases documented(5-8), *i.e.*, 11 of 18 reported cases (61%) have had cord bleeds. There follows in severely afflicted patients a life long bleeding disorder characterized by ecchymoses, hematomas, and prolonged bleeding following trauma. This has been accompanied in a few instances, by poor wound healing(16). Three of our cases developed recurrent subcutaneous or muscle hematomas following trivial trauma, whereas most of the other reported cases have had subcutaneous and/or muscle bleeds (*Table II*). In some patients, the bleeding may be delayed for 12-36 hours following injury. The high incidence of intracranial hemorrhage in this bleeding disorder makes the prognosis worse than with most other inherited bleeding disorders(17). The CNS bleed may often be the presenting manifestation as in 2 of our cases (Case No. 1 and 5). It may be acute or chronic (Case 2) and is often catastrophic. Three of our patients died due to an acute CNS bleed. In the absence of proper imaging technique such as the CT brain scan, the diagnosis of a CNS bleed may be initially overlooked, as in Case No. 1. In all, 6 of 18 cases (33%) recorded so far, have had CNS bleeds, of these 4 were from present series and 2 cumulative Indian data.

Routine coagulation tests are normal except for the friable clot formation which is soluble in 5M urea solution or in 1% solution of monochloroacetic acid. Abnormal clot solubility was noted in all our cases. The time lag between the age of first presentation and the diagnosis in our series was due to non-performance of the clot solubility as a routine test. Hence, we have now included 5M urea clot solubility as a routine screening test in all patients with bleeding disorders.

The diagnosis can be confirmed by specific biochemical or immunologic assays,

TABLE II—*Cumulative Data of the Other Nine Cases Reported in Indian Literature*

Authors	Sr. No.	Age at first bleed	Age at diagnosis	Site of bleed				Treatment	Course and outcome
				Umbilical cord	Subcutaneous muscle	CNS	Others		
Prakash *et al.*(5)	1	7 days	4 years	+	+	–	–	Plasma 4-weekly	Not recorded
	2	Not described	12 years	–	+*	+	–	Blood	-do-
	3	-do-	9 years	–	+	–	–	Blood	-do-
Nitsure *et al.*(6)	4	10 days	18 years	+	+*	+	Joints	Plasma 3-weekly	Died of CNS bleed (18 years)
	5	Pregnancy	not mentioned	–	–	–	Threatened abortion	Plasma 3-weekly	Delivered safely a baby 9 years later
	6	1½ years	4 years	–	+*	–	–	Blood 3-weekly	Not recorded
Dekate *et al.*(7)	7	8 days	13 years	+	+*	–	–	Not mentioned	Not recorded
Pati *et al.*(8)	8	Not described	7 years	–	+	–	Joints	FFP	Well
	9	Birth	22 years	+	+	–	–	FFP	Well

* = Excessive bleeding from trivial trauma, FFP = Fresh frozen plasma.

which are needed to detect carriers(18). These are not available to us. Genetic, biochemical and immunologic studies have revealed considerable heterogeneity of both the Factor XIII molecule and its disorders(19). Hence, the extreme variability of clinical severity among the patients. The disorder must be differentiated from other inherited disorders of blood coagulation especially dysfibrinogenemia and afibrinogenemia, in which there may be similar manifestations but an overtly abnormal coagulation profile(20).

Replacement therapy in Factor XIII deficiency is highly satisfactory because of the small quantities needed for effective hemostasis and the long half life (upto 19 days) of this factor(21). Transfusion of only 2 to 3 ml of plasma per kg body weight will induce effective hemostasis for periods of upto 4 weeks(22). Prophylactic therapy using infusions of plasma or cryoprecipitate every 3-4 weeks has been successful(23). Placental Factor XIII may be useful in prophylaxis(24), but commercial preparations contain several active components some of which have a short half life(25). Replacement therapy is useful in preventing hemorrhage in patients undergoing surgery and in terminating hemorrhage occurring spontaneously or after trauma. Patients receiving prophylactic transfusion therapy may be able to live a normal life.

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NOTES AND NEWS

CME PROGRAMME ON PREVENTION AND CONTROL OF NOSOCOMIAL INFECTION IN HOSPITALIZED PATIENTS

Under the scheme for Continuing Medical Education with the Medical Council of India, approved by the Ministry of Health and Family Welfare, Government of India, a Continuing Medical Education Programme on 'Prevention and Control of Nosocomial Infection in Hospitalized Patients' is to be held at Christian Medical College, Vellore from *October 29-31, 1992*, in collaboration with American Association of Physicians from India and USA.

The Organizing Secretary is Dr. M.K. Lalitha, Professor of Microbiology, Christian Medical College, Vellore.