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A 12 Years Boy with Easy Bruisability and Bleeding Episodes Since Birth (A Case of Thrombasthenia)

M. AKBAR MALIK, SAJID MAQBOOL AND MOEEN-UD-DIN
Department of Pediatrics & Department of Haematology

HISTORY:

A 12-years old boy was admitted with presenting complaints of (1) easy bruisability since brith and (2) bleeding from gums for last 06 years.

The child was born with a few bruises all over the body which disappeared after one week. Then at the age of 11 days when he was circumcised he bled for 24 hours. This was stopped by pressure bandages but without any medication. After that he has been suffering from shin bruises quite frequently. At the age of six months there was an episode of mild haematura, which persisted for 03 days. When he was six years old, he was slapped by his father and started bleeding from the mouth which was so severe that a blood transfusion had to be given to stop it. Since then he has been having bleeding from gums of variable severity and duration. Upto now he has received 07 blood transfusions, out of these 04 were given over last one year with the diagnosis of haemophilia. Family history revealed a consanguinous marraige and bleeding disorder in other family members (as shown in family pedigree). Parents are alive and symptom fee. He is first child among five siblings. Second and third sisters are also suffering from the same sort of disorder. One male and one female among the siblings died at te age of 5 days and 07 days. There were bruises all over the body but exact cause for those is not known.

On physical examination his weight was 24 kg, thin and markedly pale but appropriately tall for his age. He was actively bleeding from gums and caries of teeth was marked. Multiple bruises were present on his left arm and right leg. No abnormality of nervous, cardiovascular or gastrointestinal system was detected.

Laboratory Data.

His laboratory data showed severe anaemia of hypochromic and microcytic nature with reticulocyte count of 5%. Platelet count was normal with prolonged bleeding time but normal Hess test and defective platelet aggregation. So the diagnosis of "thrombasthenia" (Glanzmans disease) was made and the entire family was screened for bleeding disorders. (Table–I)

REPORT:

Hb% = 5 Gm TLC = 10,500 P48% L 52%

Platelet count :– 2,70,000/cmm
(N-150000 to 450000/cmm)
(Bleeding time:- 33 minutes (N-! to 7 minutes)
(Clotting time:- 8.7 minutes (N-5-15 Minutes)
Activated Partial Thromboplastin Time:- 47 Sec. (N-32 to 46 Sec.)

CLOT RETRACTION

After 04 hour the clot that formed retracted very little. Therefore clot retraction was not normal.

PLATELET FACTOR. 3 AVAILABILITY:

Abnormal

Tube 1-Platelet-poor Plasma (PPP) of normal + Plateletrich plasma (PRP) of normal. Clotting time :- CT 51 sec.
Tube 2. PPP of patient + PRP of paitent CT 10 minutes
Tube 3-PRP of normal + PPP of patient CT. 53 sec.
Tube 4- PPP of patient + PPP of normal: CT 8.5 minutes.

FIBRIN STABILIZING FACTOR–Normal

EXAMINATION OF PERIPHERAL SMEAR : Made from finger prick did not show the presence of platelet clumps. Therefore platelet agregation is defective.

TABLE 1

Haematological Investigations of the Family.

Person	Age	Clotting Time	Bleeding Time	Aptt	Clot Retraction	platelet Count	Platelet Morphology	Platelet Aggregation
Index Patient (Male)	11yrs	4':15"	14'	26/31sec	Abnormal	210,000/cmm	Normal	No Aggregates
Sister	7yrs	6':45"	32':20"	36/40sec	Normal	220,000/cmm	Normal	Normal
Sister	5yrs	7':30"	25':45"	38/40sec	Abnormal	190/cmm	Normal	No Aggregates
Sister	2yrs	4':50"	15':40"	28/30sec	Abnormal	240,000/cmm	Normal	No Aggregates
Brother	5mo	3':20::	3':15"	32/36sec	Normal	230,000/cmm	Normal	Normal
Father	40yrs	4':15"	3':40"	37/30sec	Normal	220,000/cmm	Normal	Normal
Mother	30yrs	5':35"	4':50"	35/40sec	Normal	260,000/cmm	Normal	Normal
Control	30yrs	4':30"	3'	36/33sec	Normal	210,000/cmm	Normal	Normal

DISCUSSION

Physiological functions of platelets are shown in table 1, whereas laboratory tests for these functions are shown in table 3, There is a long list of qualitative disorders of platelets though these are rarely seen in clinical practice. The disorders can be congenital or acquired (table 4).

TABLE 2

PLATELET FUNCTIONS

1. Plugs the gap in vessels
2. Surface for coagulation
3. Formation of heomostatic plug (Adhesion, aggregation consolidations)
4. Clot retraction
5. Secretory activities
   a) Adenosinetriphoshate (ATP)
   b) Serotonin
   c) Calcium
   d) Fibrinogen
   e) Factor V
   f) Platelet factor 3(PF+)
   g) PF 4 (Anti-heparin Factor)
   h) Beta thromboboglobin
   i) Beta Glucuronidase

TABLE 3

TEST FOR QUALITATIVE DISORDERS OF PLATLETS

1. Aggregation
2. Secretion
3. Retention in glass bead columns (Wrights Bulb Method)
4. Clot Retraction
5. Platelet factor 3 activities

THROMBASTHENIA

It is one of the rarest congenital platelet disorders characterised by-impaired or absent clot retraction. There is failure to aggregate to most of the substances. This disorder was described by Glanzman in 1918.

Some patients have normal bleeding time and platelet count, others may have reduced number of platelets. These are called atypical cases. About 170 cases have been reported from all over the world so far. Recently Khanduri reported 42 cases from S. india.

TABLE 4

QUALITTATIVE DISORDERS OF PLATELETS

A. CONGENITAL

1. Defects of Adhesion, or (Bernad-Souliers syndrome Gaint Platelets)
2. Absent VonWillebrands factor
3. Defects of primary aggregation (Thrombasthenia or Glanzmans Disease)
4. Abnormal secretions
   - (i) Primary effects in plts secretion
   - (ii) Primary defect in Plts secretion
   - (iii) Abnormal procoagulant activity (Platelet factor 3)
   - (iv) Platelet disorders with other congenital defects
   - (v) Cyclooxygenase Deficency
   - (vi) Thrombocytopathia with absent radius
   - (vii) May-hegglin anomaly
   - (viii) Connective Tissue Disorders
   - (ix) Ehlers-Danlos syndrome
5. Miscellaneous Disorders

B. ACQUIRED

- (i) Uraemia
- (ii) Myeloproliferative disorder
- (iii) Dysproteinemias
- (iv) Liver Disease
- (v) Idiopathic Thrombocyctopathic Purpura
- (vi) Storage pool deficiency
- (vii) Drug induced

ETIOLOGY AND PATHOGENESIS

There is normal adhesion to collagen ad sub-endothelial surface and normal ADP secretion when stimulated with collagen or thrombin but there is imparied aggregation by adenosine diphosphate (ADP) and other aggregating substances. There is impaired binding of fibrinogen to the Platelets membrane. Total and surface associated fibrinogen is decreased. Platelets do not bind fibrinogen in the absence or presence of ADP. Binding with calcium is also diminished. Since both Fibrinogen and Calcium are necessary for platelet aggregation by ADP, therefore ADP induced aggregation is impaired. Surface associated protiens, Glycoprotein I, is normal but two other membrane glycoprotiens (IIB, III a) are reduced both of which may be involved in platelets aggregation. Another evidence is its favour is the production of immunoglobulin G Antibodies in the thrombasthenic patients who recieve platelet transfusions. These antibodies are directed against the normal membrane-associated proteins and cause inhibition of the clot retraction as well as the platelet aggregation.

Other membrane proteins like alpha actin, Actomyosin and Platelet - specific alloantigen may or may not be abnormal. Metabolic abnormalities like decreased adenosine triphosphate (ATP) activity of pyruvate kinase, are also present in some of these patients. In some of the paitents are deficient in Glutathione reductase and peroxidase. Relation of these enzymes with platelet functions is not clear yet.

MODE OF INHERITANCE

This is one of the rarest of congenital bleeding disorder which is transmitted as autosomal recessive trait. Consanguinity has been reported on 10% of the cases. No aggregation abnormality in heterozygotes is found but a decreased amount of one of the membrane specific glycoprotiens

CLINICAL FEATURES

Bleeding usually begins early in life. Easy bruising and epistaxis is seen which sometimes may require blood transfusion. Fatal haemorrhages have been reported too. Excessive bleeding may occure during surgery whereas joint haemorrhages are rare. There is extreme variability in the clinical symptoms, even among paitent with similar degree of platelet abnormality and prolongation of bleeding time. The laboratory features of thrombasthemia are shown in table-6 There is no specific treatment for this disorder.

LAB FEATURES OF THROMBASTHENIA

1. Bleeding time markedly prolonged although rare exceptions are also met.
2. Platelet count and plasma clotting factors are present and normal.
3. No clot retraction in 04 hrs.
4. No abnormality on electron microscopy.
5. No aggregation of platelet with ADP, epinephrine, thrombin and collagen
6. With thrombin normal ATP consumption, pseudopodium formation, ADP release, degranulation and prostaglandins synthesis.
7. Platelet not retained by glass bead filters.

8. Platelet are aggregated by ristocetin and by bovine factor VIII in contrast to the impaired aggregation of platelets from patients with Bernard - Soulier syndrome & Von Willebrand disease.

9. Platelet factors abnormal in 80% of cases.

DIAGNOSTIC APPROACH TO BLEEDING DISORDER.

A detailed history and complete physical examination are very paying. History of spontaneous prolonged bleeding from multiple sites manifesting early in life and of recurrent nature points towards congenital hemorrhagic disorder. Complaints of mucosal and cutaneous bleeding with petechial spots and bruises favour platelet disorder or vascular abnormality. Excessive bleeding from wound, bleeding in to joints or deep tissues are more likely due to clotting dysfunction. Four basic tests for screening bleeding disorders are bleeding time, clotting time, prothrombin time and activaed partial thrombosplastin time (laboratory tests and their interpretations are shown in table 5,6,7.

TABLE 5

CLINICAL APPROACH TO BLEEDING DISORDER.

	ABNORMAL TEST.	DISORDER.
1.	Bleeding time	Platelets or blood ressels.
2.	Activated partial Thromboplastin time	Factors XII, XI, IX, VIII, X, V, II, I
3.	Prothrombin time (PT)	Factors VII, X, V, II, I.
4.	Thrombin g clotting time (TT)	Factor I Fibrinogen.

TABLE 6

CLINICAL APPROACH TO BLEEDING DISORDER

	TEST	RESULT	ABNORALITY.
1.	Hess Test	Positive	Blood Vessles.
2.	Platelet count	Decreased	Thrombocytopenia
3.	Platelet count	Normal	Functional abnormality of platelets.

TABLE 7

CLINICAL APPROACH TO PLATELET DISORDER.

	DISORDER	NUMBER	MORPHOLOGY	AGGREGATION
1.	Thrombcytopenia	decreased	Normal	Nomal
2.	Thrombasthenia	Normal	Normal	Ristocetin - Nortmal All others abnormal.
3.	Storage pool Disorder	Normal	Normal	Collegen-abnormal Adenosine-Normal diphosphate
4.	Cyclooxygenese (Aspirin)	Normal	Normal	Adrenaline-Normal Ristocetine abnormal All other abnormal.
5,	Bernard Soulier Syndrome	Normal	Giant Platelets	Adrenaline + ADP-Normal ADP + Collagen - Normal Ristocetin - Abnormal
6.	Vonwillebrands disease	Normal	Normal	Platelet factor 3 - Abnormal Ristocetin - Abnormal All other normal.

DR. MOEEN-UD-DIN. (*Haemotologist*)

Bleeding disorders are not common in clinical practice but when they do arise, they pose diagnostic and therapeutic problems. It is frist of all necessary to make a distinction between those who are bleeders and those in which bleeding episodes are associated with non-hemorrhagic systemic disorders. Before the diagnosis of bleeding diathesis is made, certain crieteria must be fulfilled.

There are:

1. Spontaneous bleeding.
2. Prolonged bleeding.
3. Bleeding from more than one site.
4. Recurrent bleeding.

Another important distinction to make is to separate bleeding disorders from coagulation disorders. Family history, personal history and history of any associated systemic illnesses can help considerably in making such a distinction. A very important feature which helps in this direction is bleeding from mucosal sites, mucocutaneous junctions or predominantly from the skin. In this instance the chances are that the defect is of the capillary type with or without associated platelet disorders. Large haemorrhages into soft tissues and organs are usually not associated with platelet disorder. Brain is one exception where it is common to have peticheal haemorrhages secondary to thrombocytopenia.

Another important feature to note is the recurrence of bleeding after it stops. It is known that the initial mechanisms of hemostasis are capillary contractility, platelet adhesion and aggregation followed by the platelet plus formation. The subsequent permanent hemostasis is effected by the coagulation mechanism. Therefore, in delayed bleeding, there is deficiency or perhaps functional abnormality of one of the clotting factors. When the platelet hemostatic plug fails and the initial bleeding continues then there is every possibility that an abnormality of blood vessels or platelet either quantative or qualitative is responsible for bleeding. The preliminary tests of coagulation which are done in bleeding disorders include PT, PTT, CT & BT in addition to the fibrin stabilizing factor test. B.T. is abnormal in thrombocytopenia if the platelet count is below 80,000/mm. It is prolonged in qualitative abnormalities of platelets and also in capillary defects.

Over the years the C.T. has been done as a secreeing test for hemostasis. Unfortunately this is not a reliable test. Even in haemophilics with factor VIII. levels less than 30%, there is good evidence that C.T. is normal in 25% of such patients. In minor hemostatic abnormalities, the C.T. may be normal but when these patients are subjected to surgical trauma like tooth extraction, they bleed. Now there are much better tests like PT & APTT to assess the efficacy of the hemostatic mechanism. Test for fibrin stabilizing factor (FSF) is an important but often ignored test of hemostasis. The deficiency of FSF causes delayed bleeding and poor wound healing. Therefore such patients are high surgical risk patients.

DR. SAJID MAQBOOl (*Pediatrician*)

Spontaneous prolonged bleeding or excessive bleeding after trivial injury points toward some congenital bleeding disorder. Any child suffering from excessive bleeding at the time of circumcision, teeth extraction or due to trauma should be fully investigated. A detailed hisotry and physical examination may distinguish between a bleeding and clotting disorder.

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