Original Articles

Platelet function disorders in north India

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ABSTRACT

Background. Platelet function disorders are a fairly common cause of bleeding manifestations. Although their relative types and incidence are well documented, data from India are lacking.

Methods. Between 1970 and 1991, we studied the clinical and laboratory features of 144 north Indian patients who presented to our hospital with a bleeding diathesis in whom coagulation disorders, von Willebrand's disease and a history of drug ingestion were absent.

Results. Isolated platelet factor 3 availability defect was the commonest (56 cases) followed by the thrombasthenias (49 cases), arachidonic acid pathway defect (26 cases), storage pool disease (8 cases) and the Bernard-Soulier syndrome (3 cases). Isolated platelet factor 3 deficiency was rare (2 cases). Two varieties of thrombasthenia were seen—the classical Glanzmann's (13 cases) and thrombopathic (36 cases). The latter was characterized by absent or sub-normal platelet aggregation with agonists along with a reduced (to less than 50% of normal) total platelet factor 3 content. This has not been reported from western countries. Patients with classical Glanzmann's thrombopathic thrombasthenia with absent platelet aggregation and isolated platelet factor 3 deficiency were severe bleeders. Their family history suggested an autosomal recessive transmission in Glanzmann's and thrombopathic thrombasthenia and a possible autosomal dominant transmission in isolated platelet factor 3 availability defect and isolated platelet factor 3 deficiency.

Conclusion. The frequency of various types of platelet function disorders in Indians is similar to that in western populations except that the incidence of thrombopathic thrombasthenias is higher in India.

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INTRODUCTION

Hereditary bleeding disorders due to platelet defects may be quantitative or qualitative.[1-3] While various platelet function disorders (PFDs) relating to adhesion, thromboxane synthesis, secretion and aggregation have been characterized, it is important to identify them in order to manage them properly. There is a paucity of literature regarding their relative frequency in India.[4-7]

PATIENTS AND METHODS

We studied the clinical and laboratory features of the various PFDs amongst patients seen at the All India Institute of Medical Sciences, New Delhi between 1970 and 1991. We included patients with a generalized bleeding diathesis in whom coagulation disorders, von Willebrand's disease (VWD) and drug ingestion were absent.

Blood samples were collected in trisodium citrate (1:9) and platelet rich and poor plasmas (PRP and PPP) prepared by centrifugation. Coagulation tests consisting of bleeding time (BT), platelet count, clot stability, activated partial thromboplastin time (APTT), plasma prothrombin time (PPT) and prothrombin consumption index (PCI) were performed by standard methods.[8] The Stypven calcium time with 10 μg/ml of Russell's viper venom (RVV) was done on PPP and PRP respectively. The Stypven calcium times with a higher concentration of RVV (25 μg/dl) with and without inositin (0.5 mg/ml) were also noted on PPP.[6] Platelet factor 3 (PF3) availability was determined by the method of Hardisty and Hutton.[9] The Stypven time was noted with an aliquot of PRP with a platelet count of 200 000/cmm and ADP 10 μg/ml at 0 time and after 20 minutes incubation at 37 °C in a water bath. A value more than 18.5 sec (at 20 minutes of incubation) was considered to be abnormal indicating reduced PF3 availability. Defective PF3 availability was differentiated from its absolute deficiency by assaying the total PF3 content of platelets. For this PRP was frozen and thawed three times and diluted serially with pooled normal PPP. Stypven calcium time was measured at each dilution and a standard curve was drawn. Total PF3 assay was expressed as a percentage of normal.[10] Patients with abnormal results in the tests for bleeding time (>5 minutes), PCI (>40%), Stypven calcium time (>28 seconds) and PF3 availability at 20 minutes (>18.5 seconds) with normal platelet count, APTT and PPT were suspected to have platelet function defects.[11] They were then subjected to platelet aggregation studies which were performed using a platelet aggregometer (Chronolog Corporation, Havertown, USA) with agonists ADP (0.6, 1.25 and 2.5 μg/ml), adrenaline (1 μg/ml), collagen (1 μg/ml), arachidonic acid (AA; 300 μg/ml) and ristocetin (2 μg/ml). Patients with coagulation defects in addition to platelet defects and unclassifiable PFDs were excluded.

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RESULTS

One hundred and forty-four north Indian patients (male 69; female 75) whose ages ranged from 1 to 58 years had PFDs. The clinical features in these patients consisted of recurrent bleeding episodes from the skin, nose, gums, sites of minor injury as well as menorrhagia (Table I). Haemarthrosis occurred in 4 patients—3 with an arachidonic acid pathway defect and 1 with storage pool disease (SPD). The severity of the clinical manifestations varied with the most severe symptoms in patients who had Glanzmann's thrombasthenia. Based on the results of screening tests in the patients with PFDs (Table II) as well as the specific platelet function tests, the following platelet disorders were identified.

Isolated PF3 availability defect

This was seen in 56 (39%) patients with mild bleeding problems. It was characterized by poor PF3 availability with a normal amount of PF3 and normal platelet aggregation with ADP, adrenaline, collagen and AA. A similar history of mild bleeding was also observed in the mothers and siblings of 5 patients.

Glanzmann's thrombasthenia

This was detected in 13 (9%) patients with severe bleeding manifestations requiring administration of platelet concentrates. There was complete absence of platelet aggregation with ADP, adrenaline, collagen, thrombin and AA. The total PF3, however, was normal. There was a positive history of similar bleeding problems in siblings of 3 patients and a history of consanguinity in 1.

Thrombopathic thrombasthenia

This was diagnosed in 36 (25%) patients who had a reduced amount of total PF3 (less than 50% of normal). PF3 availability was poor in 34 patients. Platelet aggregation with ADP, adrenaline, collagen and AA was markedly reduced in 24 and absent in 12 patients. The latter had severe bleeding whereas the former had mild to moderate bleeding. A positive history of bleeding was present in the siblings of 7 cases (19%).

AA pathway defects

These occurred in 26 (18%) patients in whom the primary phase of platelet aggregation with ADP and collagen was normal but the secondary phase was reduced. AA induced aggregation was absent in 21 (80%) and minimal in 5 (19%).

Storage pool disease

This was seen in 8 patients and PF3 availability was reduced in 6. Primary platelet aggregation with ADP was normal in all but the secondary phase was absent. Aggregation with AA was normal in 5 patients and disaggregation followed initial aggregation in the remaining 3.

TABLE I. Clinical features in patients with platelet function defects

	Glanzmann's thrombasthenia $n=13$	Thrombopathic thrombasthenia $n=36$	AA pathway defect $n=26$	Isolated PF3 availability defect $n=56$	Bernard–Soulier syndrome $n=3$	Storage pool disease $n=8$
Ecchymosis	10	19	3	23	–	5
Epistaxis	7	10	6	31	–	–
Prolonged bleeding with minor injury	5	5	12	18	2	2
Gum bleeding	5	8	–	6	3	1
Menorrhagia	4	9	3	10	–	–
Gastrointestinal bleeding	2	4	–	8	–	–
Positive family history	3	7	–	5	–	–
Post-surgical bleeding	–	–	–	–	1	–
Haemarthrosis	–	–	3	–	–	1

AA arachidonic acid PF3 platelet factor 3

TABLE II. Abnormalities in screening tests in patients with platelet function defects

Test	Number of patients with abnormal results	AA pathway defect $n=26$	Isolated PF3 availability defect $n=56$	Thrombopathic thrombasthenia $n=36$	Storage pool disease $n=8$
1. Bleeding time	58	2	8	27	4
2. Platelet consumption index	105	20	29	31	8
3. Stypven calcium time	90	17	29	23	4
4. PF3 availability at 20 minutes	132	19	56	34	6
1+2	103	21	25	35	5
1+2+3	114	24	30	35	8
1+2+4	142	24	56	36	8
All 4 tests	142	24	56	36	8

All tests in patients with Glanzmann's thrombasthenia ($n=13$), Bernard–Soulier syndrome ($n=3$) and isolated PF3 deficiency ($n=2$) were abnormal.
AA arachidonic acid PF3 platelet factor 3

Bernard–Soulier syndrome

Mild thrombocytopenia (platelet count between 100 000 and 150 000 per cmm) with giant platelets of the size of small lymphocytes and a prolonged bleeding time was detected in 3 patients. Platelet aggregation was normal with ADP, adrenaline and collagen but was reduced or absent with ristocetin and could not be corrected after addition of normal plasma. PF3 availability was poor in all but PF3 assay was normal.

Isolated PF3 deficiency

Two patients (a father and son) with this deficiency had ecchymoses as well as prolonged severe bleeding from cuts. Platelet aggregation with adrenaline, collagen and AA was normal. PF3 availability was low and PF3 assay was reduced considerably (48% and 12% of normal respectively).

DISCUSSION

There is little information regarding the prevalence of various congenital platelet function defects[2] in north India. Glanzmann's thrombasthenia, considered to be a rare platelet function disorder,[2,12] was observed in 8.3% cases. This incidence was lower than that reported from south India,[4] possibly because of a lower incidence of consanguinity in the north. Thrombopathic thrombasthenia, however, occurred much more commonly (26%). This was initially reported in 1982[5] and is characterized by features of normal platelet aggregation with a reduced PF3 content. Subsequently, two subgroups with distinct clinical and laboratory features have been identified: one, with absent platelet aggregation, and the other with subnormal platelet aggregation. This disease needs to be further characterized in terms of changes in platelet membrane glycoproteins and lipoproteins and has not been reported from western countries.

Isolated PF3 availability defect is the most common defect in our series (39%). Earlier, this had been considered to be a common cause for mild bleeding disorders.[2] AA pathway defects were seen in 26 (18%) cases. In 7 of them, the addition of normal aspirinated platelets to the patients' platelets did not correct the platelet aggregation and suggested a possible defect in cyclo-oxygenase. In others, the exact nature of the defect remains speculative as no further studies were done. We may hypothesize that there are defects in the liberation of AA from phospholipids, deficiency of thromboxane synthesis and platelet secretion defects due to impaired responsiveness to thromboxane A2. The proportion of SPD (5.5%) was comparable to that in other studies where it was observed in less than 10% of cases with congenital platelet secretion defects.[2] Isolated PF3 deficiency, seen in two of our patients, is a rare disorder with only a few cases described.[7]

Patients with PFDs may have bleeding which varies in severity. Those with Glanzmann's thrombasthenia may present with mild bruising and epistaxis or severe life-threatening bleeding which requires blood transfusions.[13] Our patients with both Glanzmann's and thrombopathic thrombasthenia with absent aggregation had severe bleeding requiring repeated platelet transfusions. Patients with thrombopathic thrombasthenia with reduced aggregation, however, had only mild to moderate bleeding. Patients with an isolated PF3 availability defect, the Bernard–Soulier syndrome, storage pool disease and AA deficiency had mild bleeding manifestations as has been reported earlier.[2] Haemarthrosis, considered to be distinctly uncommon, was observed in 4 patients with PFD. Patients with isolated PF3 deficiency had severe bleeding.

A positive family history in the patient's mother and siblings in cases with isolated PF3 availability defects suggests a possible autosomal dominant transmission and this may also have occurred in isolated PF3 deficiencies as it was seen in a father and son. In contrast, a positive sibling history in Glanzmann's (3 cases) and thrombopathic thrombasthenia (7 cases) suggests a possible autosomal recessive transmission in both of them. However, there was no family history in the other patient with PFD.

Earlier reports have observed PF3 availability to be normal in the Bernard–Soulier syndrome. We found reduced PF3 availability in all the 3 cases studied. In 3 of the 8 patients with SPD, disaggregation occurred with AA suggesting that intensive ADP release may be partly responsible for AA induced platelet aggregation. In 2 cases with thrombopathic thrombasthenia who had reduced PF3, its availability was normal suggesting that mobilization of phospholipid onto the platelet surface on stimulation with agonists may be normal even when its total content is reduced.

The management was mainly conservative. The use of antiplatelet drugs was prohibited and platelet concentrates were given when severe bleeding occurred. We have found that patients with PFDs present with a variable severity of disease and those with Glanzmann's thrombasthenia, thrombopathic thrombasthenia (with absent aggregation) and isolated PF3 deficiency have severe bleeding manifestations.

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