FREQUENCY OF INHERITED PLATELET FUNCTION DISORDERS–ARMED FORCES INSTITUTE OF PATHOLOGY EXPERIENCE

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ABSTRACT

Objective: To determine the frequency and clinical features of inherited platelet function disorders diagnosed at Armed Forces Institute of Pathology.

Study Design: Cross sectional study.

Place and Duration of Study: Department of Haematology, Armed Forces Institute of Pathology, Rawalpindi, from Feb 2017 to Aug 2017.

Methodology: All patients with history of bleeding from multiple sites or requiring transfusion were selected. Initial tests performed included complete blood counts, peripheral film and bleeding time. When bleeding time was prolonged, prothrombin time and activated partial thromboplastin time were done to rule out Von Willebrand disease and Fibrinogen deficiency.

Results: A total of 172 patients were analyzed during study period.Inherited platelet function disorders were diagnosed in 24 (13.9%) patients, 111 (64.5%) patients had inherited coagulopathies. 3 (1.8%) patients showed inconclusive results while no inherited bleeding disorder was detected in 34 (19.8%) patients. Among platelet function disorders, Glanzmann thrombasthenia was diagnosed in 12 (50%) patients, Bernard soulier syndrome (BSS) in 11 (45.8%) patients and Storage pool disorder in 1 (4.1%) patient.

Conclusion: Glanzmann thrombasthenia was the most commonest inherited platelet function disorders. Diagnosis requires platelet aggregation studies.

Keywords: Bernard soulier syndrome, Glanzmann thrombasthenia, Inherited Platelet function disorders, Light transmission aggregometry.

INTRODUCTION

Inherited platelet function disorders are a heterogenous group of rare inherited bleeding disorders characterized by mild to moderate mucocutaneous bleeding[1]. These disorders are characterized by defects in platelet glycoproteins, in their receptors, in content or release of granules, in transcription factors, in signaling pathways and membrane phospholipids[2,3].

Bernard-Soulier syndrome and Glanzmann thrombasthenia are common platelet function disorders and are characterized by defects of glycoproteins Ib/IX/V and GP IIb/IIIa respectively. Platelet function defects due to impaired secretion and signal transduction are mild and include Gray platelet syndrome, Hermansky-Pudlak syndrome and Chediak-Higashi syndrome. Cytoskeletal defects include May-Hegglin anomaly and Wiskott-Aldrich syndrome. Scott syndrome is characterized by impaired platelet procoagulant activity[4,5].

The first step of laboratory diagnosis of Platelet function disorders includes examination of peripheral smear, light transmission aggregometry (LTA), measurement of granule release and flow cytometry for evaluation of surface glycoproteins GP IIb/IIIa and GP Ib/IX/V[6,7]. Bleeding time being invasive and is not reproducible, so no longer recommended but in developing countries like Pakistan, it is still a useful diagnostic tool[8]. If first step of tests fail to reach at a conclusive diagnosis, second set of laboratory tests are performed which include LTA with expanded range of agonists, flow cytometry with antibodies directed towards additional surface glycoproteins, granule content, clot retraction,

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serum TxB2, and transmission electron microscopy (TEM)[6,7]. Light transmission aggregometry (LTA) is the gold standard for detecting platelet function defects[9]. In LTA, change in light transmission is measured through a sample of platelet rich plasma when agonist is added[8,10].

Inherited platelet function disorders though rare in the West represent a significant proportion of bleeding disorders in our population due to consanguineous marriages, however, many of these remain undiagnosed due to lack of diagnostic facilities in various centres. The rationale of our study was to determine the frequency of inherited platelet function disorders and to study the clinical presentation of these disorders to guide clinicians for early diagnosis and to avoid unnecessary treatment and its potential harmful effects to the individual.

METHODOLOGY

This was a cross sectional study conducted in the department of Haematology, Armed Forces Institute of Pathology Rawalpindi, from February 2017 to August 2017.

All patients were selected by convenient non-probability sampling. Sample size was calculated by using WHO calculator. All patients with history of bleeding from two or more sites were included in the study. Patients with bleeding due to acquired causes and those taking anti antiplatelet drugs were excluded.

Study was started after the approval of the institutional review board. Informed consent was taken from adult participants and parents or guardians of younger patients. Detailed history was taken and physical examination was carried out and findings were recorded in predesigned performa.

Venous sample was taken in trisodium citrate bottle. The initial baseline investigations performed included complete blood count, evaluation of peripheral film and bleeding time (BT) done by Ivy's method. When bleeding time was prolonged, prothrombin time (PT) and activated partial thromboplastin time (APTT) were done to rule out Von Willebrand disease and Fibrinogen deficiency. In case of normal PT and APTT, Platelet aggregation studies were carried out when BT was more than 7 minutes with normal or low platelet count or when there was a strong suspicion of platelet function disorder. For Platelet aggregation disorders, sample was taken in conical tube with trisodium citrate anticoagulant. Platelet aggregation studies were done by Chrono-Log corporation Model 700 aggregometer using platelet rich plasma (PRP). Commercially prepared agonists from central scientific company which included Collagen (1ul), epinephrine (5ul), ADP (5ul) and ristocetin (5ul) were used to assess response. Statistical analysis was done by using SPSS 24. Quantitative variables were presented by mean and SD while qualitative variables have been presented by frequency and percentage.

RESULTS

A total of 172 patients were analyzed during study period. Inherited platelet function disorders were diagnosed in 24 (13.9%) patients, 111 (64.5%) patients had inherited coagulopathies. 3 (1.8%) patients showed inconclusive results while no inherited bleeding disorder was detected in 34

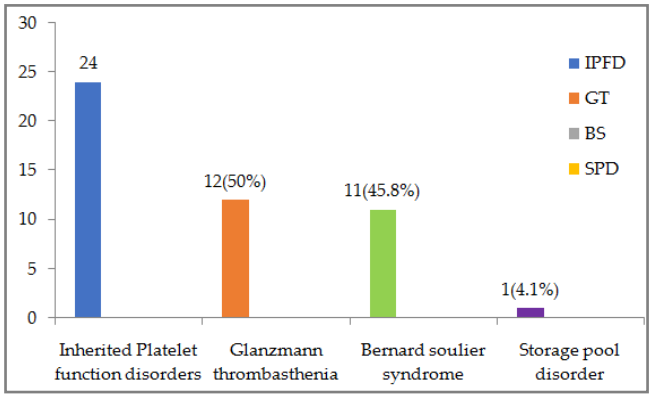

Figure: Distribution of inherited platelet function disorders.

(19.8%) patients. Among platelet function disorders, Glanzmann thrombasthenia was diagnosed in 12 (50%) patients, Bernard soulier syndrome in 11 (45.8%) patients and Storage pool disorder in 1 (4.1%) patient (figure). Mean age of patients with Glanzmann thrombasthenia was 7 ±

8.8 years. Out of 12 patients with GT, 10 (83%) were female and 2 (17%) were male. All patients with GT had normal PT, APTT and prolonged bleeding time. Platelet aggregation studies showed no response with collagen, epinephrine and ADP but showed normal response with ristocetin. While mean age of patients with Bernard soulier syndrome was 10 ± 8.7 years and it also showed female predilection, 8 (73%) females and 3 (27%) males. Patients with BSS also had normal PT, APTT and prolonged bleeding time. Platelet aggregation studies showed normal response with collagen, epinephrine and ADP but no response with ristocetin and response was not seen even after mixing of normal plasma. Patient with storage pool disorder was male child and showed impaired response to ADP, epinephrine, ristocetin and collagen but showed normal response with arachidonic acid (figure).

Table-I: Clinical features of Glanzmann thrombasthenia and Bernard soulier syndrome.

Clinical features	Glanzmann Thrombasthenia (n=12)		Bernard Soulier Syndrome (n=11)	
	Frequency	Percentage	Frequency	Percentage
Epistaxis	10	83.3	5	45.4
Bruising	9	75	7	63.6
Prolonged bleeding after trauma	6	50	5	45.4
Melena	4	33.3	2	18.2
Gum bleeding	2	16.7	4	36.3
Menorrhagia	1	8.3	1	9
Hemoptysis	1	8.3	-	-
Hematuria	-	-	1	9
Hematemesis	-	-	1	9

Table-II: Haematological Parameters of Glanzmann thrombasthenia and Bernard soulier syndrome.

Haematological Parameter	Glanzmann Thrombasthenia	Bernard Soulier Syndrome
Haemoglobin (g/dl)	8.3 ± 2.59	11.07 ± 1.6
Platelets (x10^9/L)	254 ± 98	56 ± 20
White blood cell count (x10^9/L)	9.64 ± 4.82	7.53 ± 2.7

Glanzmann thrombasthenia and Bernard soulier syndrome being the most common disorder we studied. The clinical features of these two groups are shown in table-I.

Haematological parameters of Glanzmann thrombasthenia and Bernard Soulier syndrome were listed in table-II. Anaemia was more commonly seen in GT. All patients with GT presented with normal platelet counts. While patients with BSS had low platelet counts and giant platelets were seen on peripheral film examination of these patients.

DISCUSSION

Inherited platelet function disorders comprises a large group of inherited bleeding disorders and involve a wide range of genetic defects that can lead to bleeding symptoms of varying severity. These disorders are more common in areas with high consanguinity rate. In developing countries like Pakistan, diagnostic facilities for detection of platelet function disorders are not available in most laboratories, so these disorders remain undiagnosed and mismanaged[11-13]. Armed Forces Institute of Pathology, Rawalpindi is tertiary care institute so patients from different parts of the country are referred to AFIP for diagnosis of these disorders as facility of LTA is available at our institute. Even though flow cytometry is a useful diagnostic tool but in developing countries, due to resource and cost constraints, it is not routinely used for the diagnosis of platelet function disorders, however, in selected cases, it is still used for confirmation of diagnosis.

In our study inherited platelet function disorders were detected in 13.9% of patients.

Borhanyetal from Karachi have reported an almost similar frequency of 12.8%. Total 376 patients were included in their study and platelet function disorders were diagnosed in 48 (12.8%) patients. Of platelet function disorders, GT was diagnosed in 12, BSS in 4, ADP receptor defect in 11, collagen receptor defect in 3 and epinephrine receptor defect in 11 patients while in 7 patients, platelet function disorder could not be classified into specific group[14]. In a study conducted by Sajid *et al* in Lahore, platelet function disorders were detected in 11.7% patients and GT was the most common platelet function disorder[15]. Lower frequency of platelet function disorders have been reported by Mansouritorghabeh *et al*, their study conducted in Iran and included 552 patients, they have reported platelet function disorders in 6.9% of the Iranian population[16]. Manishaet alfrom India also reported low frequency 5.03% of these disorders, thirty two out of 630 patients had platelet function disorders and GT was the most common disorder[17]. However a study conducted by Gupta *et al* from India reported high frequency (39.4%) of platelet function disorders, but this study included large number of patients and secondly isolated PF3 availabilty defect was seen as the most common platelet function disorder, In our institute we did not have the facility to diagnose these disorders[18].

The mean age of patients with inherited platelet function disorders in our study was 10 years. Mean age of 10.6 years has also been reported by Gupta *et al*[18] Although clinical presentation of these disorders start in early age but lack of awareness and poor diagnostic facilities in various parts of our country result in delay of diagnosis. Our study revealed that predominant clinical features were epistaxis, bruising and prolonged bleeding, similar results have also been reported by Borhany *et al*[10].

Diagnosing these rare disorders is important because misdiagnosis can lead to unnecessary treatment like platelet transfusions. As these disorders can be managed with supportive measures and platelet transfusions are only given in life threatening bleeds because frequent platelet transfusions can result in platelet refractoriness as a result of antibody formation.

CONCLUSION

Glanzmann thrombasthenia was the most common platelet function disorder detected and diagnosis requires platelet aggregation studies. Although rare but these disorders comprise a large group of inherited bleeding disorders and a high index of suspicion should be kept while dealing with bleeding disorders because accurate diagnosis is essential to provide unnecessary treatment and its potential harmful effects to individuals.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any authors.

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