

FREQUENCY OF BLEEDING DISORDERS DIAGNOSED AT ARMED FORCES INSTITUTE OF PATHOLOGY RAWALPINDI

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ABSTRACT

Introduction: Disorders of hemostasis can be divided into hereditary and acquired and can further be compartmentalized into deficiency of the procoagulant proteins and defects of the platelets and vasculature. There is scanty data on the frequency of bleeding disorders in Pakistan.

Objective: To determine the frequency of bleeding disorders diagnosed at Armed Forces Institute of Pathology, Rawalpindi (AFIP Rwp).

Study design: Descriptive study.

Setting and duration: Department of Hematology, AFIP Rwp from January 2006 to June 2009.

Materials and Methods: A total of 1836 patients of bleeding diathesis were included in the study. Hess test was done to investigate the vascular defects. Bleeding Time (BT) was done to screen platelet function defects. The 'clotting screen' and mixing studies were done to detect coagulation protein defects. Clot solubility test was performed to screen factor XIII deficiency.

Results: Out of 1836 patients of bleeding diathesis 435 (23.7%) were diagnosed as having haemostatic defects. Out of these 435 patients 273 (62.8%) had coagulation factor deficiency, 81 (18.6%) had platelet function defects and 81 (18.6%) had vWF deficiency. Among the 273 coagulation factor deficiency patients, factor VIII deficiency was 121 (44.3%), factor IX deficiency 32 (11.7%), factor V deficiency 18 (6.6%), factor XIII deficiency 15 (5.5%), factor VII deficiency 12 (4.4%), factor X deficiency 9 (3.3%), factor I deficiency 8 (2.9%) and factor II deficiency was 3 (1.1%). Multiple factor deficiency was 55 (20.1%). No defects of vasculature were identified.

Conclusion: Coagulation factor deficiencies with factor VIII deficiency being the commonest are the most frequent bleeding disorders. Platelet function defects and vWF deficiency also comprise significant proportion of the bleeding disorders.

Keywords: Bleeding disorders, clotting screen, mixing studies

INTRODUCTION

Disorders of hemostasis leading to bleeding are quite common. They can be divided into hereditary and acquired with the acquired defects being more common. All can further be compartmentalized into defects of the vasculature, defects of platelets or defects of the coagulation proteins. Although many are forthright still many particularly the acquired defects may be multifaceted and quite complex with respect to pathophysiology, diagnosis and management. Vasculature defects are common but often unappreciated causes of bleeding. Patients typically complain of mild to moderate mucosal membrane bleeding and dependent petechiae found on the extremities and usually absent from the torso. Platelet function defects

are mostly acquired and the patients usually have similar features to that of vasculature disorders except that the petechiae also involve the torso. In contrast the coagulation protein defects are more commonly inherited than acquired and are characterized by deep tissue bleeding including intraarticular, intramuscular and sometimes intracranial bleeding. VWD is an exception with characteristic "platelet type" bleeding however severe cases may have similar severe bleeding typical of classic coagulation factor deficiencies. Among the coagulation protein defects vWD is the most common affecting 1-4% of the population whereas the incidence of factor VIII deficiency is 1 in 10,000 and that of factor IX deficiency is 1 in 50,000.⁴ All other specific coagulation protein defects are rare with an incidence range of 1 in 500,000 for factor VII deficiency to 1 in 2 million for factor II.⁵ There is scanty data on the frequency of bleeding disorders in Pakistan.

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Therefore this study was carried out to determine the frequency of bleeding disorders.

MATERIALS AND METHODS

This descriptive study was carried out at Armed Forces Institute of Pathology (AFIP) Rawalpindi from Jan 2006 to June 2009. A total of 1836 patients of bleeding diathesis sent to AFIP for coagulation profile testing were included.

Hess test was done to investigate the vascular defects. Sphygmomanometer cuff was applied to the arm and inflated to 80 mm Hg pressure. The pressure was maintained for 5 minutes. Volar surface of the forearm was inspected for petechiae. Twenty or more petechiae were taken as positive.

Bleeding Time using Ivy's method was done to test platelet function defects. Sphygmomanometer cuff was applied to the arm and inflated to 40 mm Hg pressure. Volar surface of the forearm was cleaned with a spirit swab and two separate punctures 5-10 cm apart using standard depth lancet were made. Stopwatch was started at the same time. Oozing blood was blotted using filter paper and the time when it stopped coming out was noted. A time of more than 11 minutes was taken as prolonged.

The 'clotting screen' was used to detect coagulation protein defects. Four ml blood was collected in trisodium citrate bottle. After centrifugation PT, APTT and TT and fibrinogen level (where indicated) were performed using Biopool (Ireland) and Weiner lab (Argentina) kits. A prolongation of more than 3 seconds as compared to control for PT, more than 7 seconds for APTT and more than 2 seconds for TT was taken as significant. Prolonged results were further tested by mixing studies using 50:50 mixture of patient plasma and control plasma, aged serum and adsorbed plasma respectively. For confirmation mixing studies with 50:50 mixture of patient plasma and specific factor deficient plasma and factor assays were done. Fibrinogen level was measured with Clauss technique.

Clot solubility test for factor XIII deficiency using 30% urea solution was also put up for

every patient. After clotting patient plasma 3 ml urea solution was added to the test tube and the clot dislodged. After 24 hours test tube was inspected for clot dissolution. Clot dissolution indicated factor XIII deficiency. Data had been analyzed using SPSS version 15. Descriptive statistics were used to describe the data i.e mean and Standard Deviation (SD) for quantitative variables and frequency along with percentage for qualitative variables.

RESULTS

Out of 1836 patients of bleeding diathesis 435 (23.7%) were diagnosed as having haemostatic defects (Table: 1). Average age was 6.13 ± 2.33 years, males were 304 (70%) and females were 131 (30%). Out of these 435 patients 273 (62.8%) had coagulation factor deficiency. There were 2 females among the 153 patients with X linked inheritance (Factors VIII and IX). Of the remaining 120 patients with autosomal inheritance there were 67 males and 53 females. Eighty one (18.6%) had platelet function defects. There were 45 males and 36 females among the patients. Another 81 (18.6%) had vWF deficiency. There were 41 males and 40 females among the patients. Among the 273 coagulation factor deficiency patients, inherited coagulation factor deficiencies including factor VIII deficiency was 121 (44.3%), factor IX deficiency 32 (11.7%), factor V deficiency 18 (6.6%), factor XIII deficiency 15 (5.5%), factor VII deficiency 12 (4.4%), factor X deficiency 9 (3.3%), factor I deficiency 8 (2.9%), factor II deficiency 3 (1.1%). Acquired deficiency in the form of multiple factor deficiency was 55 (20.1%) mainly due to vitamin K deficiency and liver disease (Table: 2). No defects of vasculature were identified.

DISCUSSION

Out of 1836 patients of bleeding diathesis haemostatic defects were identified in 435 (23.7%) patients. Out of these 435 patients coagulation factor deficiency was the most frequent with factor VIII deficiency being the commonest. The same has been documented by Yasmin et al. and, Sajid et al from Pakistan, Manisha et al and Gupta et al from India and Karimi et al. from Iran.⁶⁻¹⁰ The reduction in factor VIII activity secondary to vWD was not

ruled out by measuring the vWF:Ag and Ricof activity and since the BT may be normal in vWD we may have missed vWD in some instances. The under diagnosis of vWD has already been stressed by Salman et al.¹¹

vWD is the second most common bleeding disorder diagnosed at AFIP Rwp along with platelet function defects. El- Bostany et al documented vWD as the commonest bleeding disorder followed by factor VIII deficiency and platelet dysfunction.¹² Platelet function defects were also documented as the second most common bleeding disorders by Gupta et al and Karimi et al.^{9,10} Only the combination of increased BT and prolonged APTT were taken as evidence of vWF deficiency. In 34 patients the deficiency of vWF was later confirmed by getting ristocetin induced platelet aggregation on mixing patient plasma with control plasma. No attempt was made to subtype vWD and vWF:Ag and Ricof activity were not measured. Similarly vWF:F VIII binding assay was not done to rule out type 2N vWD. BT of more than 11 min was taken as evidence for platelet function defect. No distinction was made between inherited and acquired defects.

Multiple factor deficiency was the next most common cause of bleeding diathesis. As inherited combined factor deficiencies are quite rare, it probably represents the acquired deficiencies secondary to vitamin K deficiency especially in the newborns or liver disease mainly in the adults. No attempt was made to identify the underlying cause.

Among other coagulation factor deficiencies factor IX deficiency was the second most common after factor VIII deficiency. Next in frequency was deficiency of factor V, factor XIII, factor VII, factor X and factor I. Least frequent bleeding disorder was factor II deficiency. No patient with factor XI deficiency was detected indicating extremely low incidence. In contrast factor XI deficiency has the highest frequency other than hemophilia A and B excluding vWD in UK and Italy.¹³ Rare inherited coagulopathies other than factor VIII and IX deficiencies found in our population by Khalid S et al include deficiency of factor VII,

factor X, factor XIII, factor V, factor I, factor II and factor XII in the descending order of frequency.¹⁴ Rare inherited coagulation disorders in Southern Iran include factor X, factor VII, factor XIII, factor I and factor XI deficiency in the descending order of frequency whereas from India it is factor X deficiency followed by factor XIII, I, VII and V in the same order.^{15,16} The non sex linked bleeding disorders also demonstrate a slight male predominance.

Three clinical patterns of bleeding were identified and related to the underlying deficiencies. Deep tissue bleeding involving particularly joints in factor VIII, IX and X deficiency and the intracranial site in factor XIII deficiency. Mucosal only bleeding with platelet function defects and combined deep tissue and mucosal bleeding with vWD and factor I, II, V and VII deficiency.

No inhibitor was detected as causing factor deficiency. Hence the acquired coagulation protein defects are quite rare.

Possible explanations for bleeding with normal coagulation profile in the remaining 1401 (76.3%) patients include local causes, heterozygosity of inherited coagulation factor deficiency, vWD, some forms of dysfibrinogenemias, platelet function defects like release reaction abnormalities, hereditary haemorrhagic telangiectasia, allergic and other vascular purpuras, α 2 antiplasmin deficiency, elevated levels of plasminogen activator, testing at inappropriate time post transfusion, high levels of one factor masking deficiency of the other and result fluctuation from time to time.

We recommend that bleeding patients be investigated based on clinical patterns. VWD disease workup needs to be improved so that more cases can be identified and accurately subtyped. Causes of multiple factor deficiency and acquired causes of platelet function defects should be identified so that they can be adequately corrected.

CONCLUSION

Frequency of bleeding disorder was 23.7%. Coagulation factor deficiencies with factor VIII deficiency being the commonest are the most

frequent bleeding disorders. Platelet function defects and vWF deficiency also comprise significant proportion of the bleeding disorders.

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Table: 1 Frequency of various bleeding disorders (n=435)

| Bleeding disorder | Frequency | Percentage |
|----------------------------------|------------------|-------------------|
| Coagulation factor deficiency | 273 | 62.8% |
| Platelet function defects | 81 | 18.6% |
| Von willibrand factor deficiency | 81 | 18.6% |

Table: 2 Frequency of various coagulation factor deficiencies (n=273)

| Bleeding disorder | Frequency | Percentage |
|----------------------------|------------------|-------------------|
| Factor VIII deficiency | 121 | 44.3% |
| Factor IX deficiency | 32 | 11.7% |
| Factor V deficiency | 18 | 6.6% |
| Factor XIII deficiency | 15 | 5.5% |
| Factor VII deficiency | 12 | 4.4% |
| Factor X deficiency | 9 | 3.3% |
| Factor I deficiency | 8 | 2.9% |
| Factor II deficiency | 3 | 1.1% |
| Multiple factor deficiency | 55 | 20.2% |