THE APPROACH TO A PATIENT WITH A BLEEDING DISORDER: FOR THE PRIMARY CARE PHYSICIAN

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Normal Hemostasis requires the interaction of platelets and the clotting cascade with normal blood vessels and supporting tissues. Bleeding problems and easy bruising are commonly encountered clinical problems. Assessment of these patients is a multistep evaluation process that involves a complete detailed history, thorough physical examination and relevant laboratory evaluation. Many disorders are usually relatively straightforward to diagnose, but in other disorders, patients may have "hidden" signs and symptoms making diagnosis more difficult. A meticulous approach must be used to plan the first steps of management.

Key Words: Bleeding disorder, clinical history, laboratory tests.

INTRODUCTION
Hemostasis is the process by which bleeding is arrested after injury to blood vessels. It is a delicate multiphase process that involves interactions between the blood vessels, platelets and coagulation factors. A defect in any of these phases of coagulation can result in a bleeding problem which may be inherited or acquired.1-4 This process of coagulation is a combination of cellular and biochemical events that function together to keep blood in the fluid state within the vessels and prevent blood loss following injury by the formation of a stable blood clot. Blood clots are eventually dissolved by the fibrinolytic system, a complex but well regulated system dependent also on several other additional systems. Interaction of these systems include vessel wall constriction, platelet adhesion and aggregation, blood coagulation, fibrinolytic system, kinin system, natural coagulation factor inhibitors i.e. mainly antithrombin III, Protein C, Protein S, and the complement system. Evidently, there is a delicate controlled balance between formation and dissolution of a blood clot during the haemostatic process (Figure 1). A disruption of this unique balance may cause bleeding or thrombosis.1-4

The objectives of this review is to provide primary care physicians with a systematic diagnostic approach in dealing with patients suffering from bleeding disorders, and demonstrate the importance of routine laboratory screening procedures.
CLINICAL ASSESSMENT

Careful history taking is always important, as is known in clinical medicine, but never more important and critical than when a bleeding disorder is suspected. A good detailed comprehensive history is the best predictor of a bleeding problem. Questions should be asked to assess the type and sites of bleeding, whether it involves the skin (cutaneous) and mucous membranes i.e. petechiae, purpura (Figures 2a, 2b and 2c), bruises, epistaxis, gingival bleeding, menorrhagia and/or hematuria which would suggest a platelet and/or vascular abnormality. Bleeding into deep tissue, joints and muscles (Figure 3) suggest a coagulation factor defect. Questions on whether the bleeding is spontaneous or follows trauma must also be asked. Usually a history of easy bruising or bleeding excessively after injury suggests an inherited bleeding problem. Information on the duration must also be sought. This would indicate whether symptoms have been lifelong (since childhood) or of recent onset. There should be questions on any childhood history of epistaxis, umbilical stump bleeding, bleeding after circumcision, the answers to any of which would suggest inherited bleeding disorders. Any history of blood transfusion or other blood components, as well as a comprehensive review of past medical and surgical history is very important. Information on all operations including tooth extractions are to be listed together with any abnormal bleeding during or after surgery or poor wound healing. Drug history is of extreme importance since a wide variety of drugs affect hemostasis. The discovery of isolated thrombocytopenia in a patient who is taking several medications is a challenging clinical problem. It is very important to distinguish between drug induced thrombocytopenia and idiopathic thrombocytopenic purpura (ITP) In ITP, all other causes of thrombocytopenia must be excluded. A very careful family history is critical; any family history of abnormal bleeding in both parents, maternal grandparents, aunts, uncles, and siblings as well as any history of consanguineous marriage (or among relatives) should be taken. A proper history is vital because the information gathered will ultimately guide the direction and extent of the laboratory evaluation and also help in determining how complications can be managed and prevented. A study has shown that a patient’s perception of his or her own bleeding may be understated or exaggerated. This study showed that 65% of women and 35%
of men without a laboratory confirmed bleeding disorder responded to the questions as if they did have a bleeding disorder, while 38% of women and 54% of men who had documented Von Willebrand disease or a functional platelet disorder, answered as if they were completely unaware of their bleeding disorder. Inherited bleeding disorders are found in a substantial number of women with menorrhagia during routine gynecological examination. This shows the importance of taking a detailed history. Questions with the four "W”s", who, when, where and what are crucial.

Who: who is the patient, sex, age, race and family history?
When: when did the bleeding occur, i.e. onset of bleeding? Is it related to drug ingestion or any underlying disorder? Did it develop after surgery or trauma?
Where: sites of bleeding, skin, muscle etc.
What: description of the type of bleeding.

The history is followed by a careful thorough physical examination to assess the sites and severity of the bleeding and evaluate whether the bleeding is part of a systemic illness, a local anatomical defect or a haemostatic disorder. From the clinical assessment, one is able to assess whether: (1) the bleeding is the result of a local anatomic defect or part of a systemic defect in hemostasis, (2) the bleeding is due to a vascular defect, platelet abnormality or coagulation disorder, or (3) the haemostatic defect is inherited or acquired.

Often a careful history and physical examination will make the documentation of the presence or absence of a haemostatic disorder possible with at least 90% accuracy. It should also enable the categorization of the type of defect, i.e. coagulation versus platelet defect, and the possibility or absence of a systemic illness. This should also enable the physician to determine...
whether this bleeding problem is hereditary or acquired.

LABORATORY ASSESSMENT
Careful and thorough clinical assessment allows the adoption of a sensible plan for laboratory investigation. The use of these tests are never a substitute for clinical assessment, for there is evidence that screening tests are unhelpful in the prediction of a bleeding disorder especially when applied indiscriminately. For each phase of hemostasis, screening tests which help in distinguishing a platelet disorder from a coagulation defect are available. The tests include a complete blood count (CBC) to assess platelet count, the often ignored peripheral blood smear examination, prothrombin time (PT), activated partial thromboplastin time (APTT), a thrombin time and a bleeding time or platelet function analysis (PFA) (Table 1). PFA-100 is an instrument recently developed to assess the global platelet response. The PFA-100 is extremely sensitive to the presence of aspirin and may be used to monitor antiplatelet drug therapy. It is also used to screen patients for Von Willebrand disease as well as platelet function disorders.

Table 1: Screening tests of hemostasis

| Test                                    |
|-----------------------------------------|
| Complete blood count (CBC)              |
| Platelet count                          |
| Peripheral blood smear examination      |
| Prothrombin time (PT)                   |
| Activated partial thromboplastin time (APTT) |
| Bleeding time or PFA-100                |
| Thrombin time                           |

These baseline screening tests should be ordered before appropriate specialized tests are suggested. This is to avoid the unstructured ordering of unnecessary laboratory procedures. The CBC will reveal abnormalities in platelet numbers and the blood film will show platelet morphology, exclude the possibility of a systemic illness and other hematological disorders. The intrinsic pathway of coagulation is assessed by APTT (normal value 25-38 seconds) so that any abnormalities are detected. Prothrombin time (normal value 10-14 seconds), assesses the extrinsic coagulation pathway and the generation of fibrin, detected by the thrombin time (normal value 15-19 seconds). Normal control ranges vary somewhat from laboratory to laboratory. Bleeding time (normal value 3-9 minutes) or PFA-100 detect a platelet function abnormality; however, it is very important to ensure that the patient is not taking any drugs, aspirin, for instance, which are known to affect platelet function resulting in prolonged bleeding time and impact on PFA-100 result. Although the bleeding time has been clinically utilized for almost a century and modified several times in attempts to improve reliability, it is the least reliable of the screening tests. There are disadvantages. It is difficult to standardize and the results can be both poorly reproducible and insensitive to milder forms of platelet dysfunction. A definite advantage is that it is a simple test of natural haemostasis including the contribution of the vessel wall. It also avoids potential anticoagulation artifacts. However, the consensus is that the test does not necessarily correlate well with the bleeding risk, so an accurate clinical history is more valuable. A number of different in vitro methods have, therefore, been devised to measure such platelet function as PFA-100. In PFA-100, platelet function is measured within whole blood exposed to conditions that attempt to simulate in vivo haemostasis.

The aim of the screening tests is thus, to reveal broadly the source of problem, and accordingly request further investigations. It should be borne in mind that tests of hemostasis are not only numerous but also expensive. Specialized laboratory testing should only be directed by the initial clinical impression and results of baseline screening tests or else a lot of time, effort and money will be wasted. One should also be aware of conditions that may be associated with prolonged APTT but without a bleeding diathesis. Examples include deficiency of Factor XII, high molecular weight Kininogen, and Prekallekrein. Lupus anticoagulant can be a cause of a prolonged APTT without a bleeding disorder.

Specialized investigations may include, for example, mixing studies in the case of abnormal PT or aPTT for further information on the nature of the defect; coagulation factor assays to confirm and assess the severity of the coagulation factor deficiency such as in Hemophilia A or B; platelet aggregation studies to confirm platelet qualitative defects and investigations for Von Willebrand disease. If all baseline-screening tests are normal then investigations for factor XIII deficiency and alpha 2-antiplasmin deficiency which are not detectable by the routine screening tests are warranted. Factor XIII deficiency may be diagnosed by a clot solubility test, and the alpha 2-antiplasmin activity can be measured by a
chromogenic assay. It is also worth mentioning that some patients with a definite history of bleeding, have normal results for baseline screening tests. Further diagnostic evaluation for such patients are needed to consider mild hemophilia and Von Willebrand disease (VWD), for mild hemophiliacs may have a normal APTT. Therefore, repeated testing may often be needed to diagnose VWD, especially in mild cases because of the fluctuation of Von Willebrand factor in the plasma. This again demonstrates the importance of a complete history. If all investigations are found normal, the patient should be investigated for blood vessel wall abnormalities. A vessel wall defect can result in abnormal bleeding despite an otherwise normal coagulation system. Since there are no reliable clinical tests of vascular integrity, diagnosis depends on a high level of suspicion, when all laboratory tests are normal. Blood vessel disorders can be hereditary like hereditary hemorrhagic telangiectasia and Ehlers-Danlos Syndrome, or acquired like Henoch-Schonlein purpura, scurvy and Cushing’s syndrome. Table 2 summarizes the interpretation of various screening tests.

Table 2: Interpretation of abnormalities of coagulation screening tests

| Test                     | Possible conditions                                      |
|--------------------------|---------------------------------------------------------|
| Prolonged PT             | Factor VII deficiency, early oral anticoagulation therapy |
| APTT                     | Deficiency of Factors VIII, IX, XI, XII, and Prekallikrien, Von Willebrand disease, Lupus anticoagulant |
| Prolonged PT and APTT    | Deficiency of Factors V, X, II, oral anticoagulants, vitamin K deficiency, liver disease. |
| Prolonged bleeding time or abnormal PFA result | Platelet function defect, Von Willebrand disease |

BRIEF SUMMARY OF BLEEDING DISORDERS

Platelet Disorders
1. Thrombocytopenia
A normal platelet count is 150 – 400 x 10^9/liter. Thrombocytopenia can result from a number of causes; a) congenital thrombocytopenia which is uncommon and typically presents with other features i.e. Wiscott-Aldrich syndrome accompanied by eczema and impaired immunity. b) Impaired bone marrow production i.e. aplastic anemia, megaloblastic anemia and bone marrow infiltration. c) Increased platelet destruction/consumption. Examples include, immune-related conditions like autoimmune thrombocytopenia (ITP), systemic lupus erythematosus, drugs and non-immune conditions such as disseminated intravascular coagulation (DIC), thrombotic thrombocytopenic purpura (TTP) and hypersplenism (splenic sequestration).

2. Disorders of Platelet Function: (Where numbers are adequate but bleeding is due to abnormal platelet function) a) Inherited: eg. Glanzmanns thrombasthenia, Bernard Soulier syndrome and Von Willebrands disease. Inherited disorders of platelet function may sometimes be difficult to diagnose, so family studies are needed. b) Acquired: eg. aspirin ingestion, uraemia and in myeloproliferative disorders.

Disorders of the Coagulation Cascade
1. Inherited Bleeding Disorders
Examples: Hemophilia A (Factor VIII deficiency), Hemophilia B (Factor IX deficiency), Von Willebrand disease and congenital fibrinogen deficiency. Studies from the Kingdom have shown that the distribution of hereditary bleeding disorders (HBD) resemble what has been established in western countries, with the exception of an increase of platelet disorders mostly due to the increased rate of consanguinity in the Kingdom. The most common HBD in the Kingdom is hemophilia A, followed by VWD, then hemophilia B followed by qualitative platelet disorders most commonly Glanzmanns thrombasthenia.

2. Acquired Bleeding Disorders
These include liver disease, vitamin K deficiency, DIC and anticoagulant therapy.

Disorders of vessels and supporting tissues
The weakening of the supportive tissues and blood vessel abnormalities as occurs in the aging process or corticosteroid usage should not be overlooked.

SUMMARY
The approach to a patient with a bleeding disorder needs a comprehensive detailed history and thorough physical examination. There must be a
logical systematic approach and a discriminate use of laboratory investigations to reach the diagnosis and assess severity. Particular emphasis should be placed on family and drug history. A simple approach to detect the cause is to look at the hemostatic system as three compartments, blood vessels, platelets and coagulation proteins.

REFERENCES
1. Handin RI, Lux SE., Stossel TP. In: Blood Principles and Practice of Hematology. J.B. Lippincott Company Philadelphia 1995. 949-72.
2. Ogedegbe HO. An Overview of Hemostasis. Lab Med 2002;12(33):948-53.
3. Bick RL Clinical assessment of patients with Hemorrhage. In: Disorders of Thrombosis and Hemostasis Clinical and Laboratory Practice. Lippincott William’s and Wilkins Philadelphia PA, USA, 2002, 3rd edition:1-37.
4. Schiffman F.J. Hemostasis and Thrombosis In: Hematologic Pathophysiology. Lippincott’s Pathophysiology series. Lippincott-Raven Publishers, Philadelphia and New York, 1998:161-223.
5. Liu MC, Kessler CM. A systematic Approach to the bleeding patient. In: Consultative Hemostasis and thrombosis. 2002 W.B. Saunders Company USA:27-39.
6. Goodnight SH, Hathway WE. Evaluation of Bleeding Tendency in the Outpatient Child and Adult In: Disorders of Hemostasis and Thrombosis A Clinical Guide. Second edition 2001. The Mc Grow-Hill Companies;52-60.
7. Beatty C. The Patient with Easy Bruising and Bleeding. Medicine 1995;23(12):514-71.
8. Colman RW, Marder VJ, Clowes AW, George JN, Goldhaber SZ. Clinical approach to the bleeding patient: In Hemostasis and Thrombosis: Basic Principles and Clinical Practice. Fifth edition 2006, Lippincott Williams and Wilkins ,USA:1147-58.
9. Kujovich J. Approach to a Bleeding Patient. Lab. Med 2001; 32(5): 250-6.
10. Hillman RS, Ault KA. Clinical Approach to Bleeding Disorders. In: Hematology in Clinical Practice. McGraw Hill Medical Publishing. Division 3rd edition 2007:308-15.
11. George JN, Raskob GE, Shah SR, Rizvi MA, Hamilton SA, Osborne S., Vondracek BA, Vondracek T. Drug-Induced Thrombocytopenia: A Systemic Review of Published Case Reports. Ann Intern Med. 1998;129:886-90.
12. Pedersen-Bjergaard U, Andersen M, Hansen PB. Drug-Induced Thrombocytopenia: Clinical data on 309 cases and the effect of corticosteroid therapy, Eur J Clin Pharmacol 1997; 52:183-9.
13. Wahlberg T, Blomback M, Hall P, Axellsson G. Applications of indicators, Predictors and Diagnostic Indices in Coagulation Disorders. Evaluation of a self-administered questionnaire with binary questions. Methods Inf Med 1980; 19:194-200.
14. Kadir RA, Economidou DL, Sabin CA, Owens D, Lee CA. Frequency of Inherited Bleeding Disorders in Women with Menorrhagia. The Lancet 1998;351:485-9.
15. Mammen EF, Comp PC, Gosselin R, et al. PFA-100 system: a new method for assessment of platelet dysfunction. Semin Thromb Hemost. 1998;24:195-202.
16. Carcao MD, Blanchette VS, Dean JA, He L, Kern MA, Stain AM, et al. The platelet function analyzer (PFA- 100): A novel in Vitro system for evaluation of primary hemostasis in children. Br J Haematol 1998; 101:70-3.
17. Kotke-Marchant K, Powers JB, Brooke L, Kundu S, Christie DJ. The effect of antiplatelet drugs, heparin and preanalytical variables on platelet function detected by the platelet function analyzer (PFA- 100). Clin Appl Thromb Hemost 1999;5:1-10.
18. Kundu SK, Heilmann EJ, Sio R, Garcia C, Davidson RM, Ostgaard RA. Description of an in Vitro platelet function analyzer – PFA- 100. Semin Thromb Hemost 1995;21:106-12.
19. Kitchen S, Makris M. Laboratory tests of hemostasis. In: Practical Hemostasis and Thrombosis, Blackwell Publishing Ltd 1st edition 2005;8-17.
20. Lind SE. The bleeding time does not predict surgical bleeding. Blood 1991;77(12):2547-52.
21. Kouides PA. Females with Von Willebrand disease: 72 years as the silent majority. Hemophilia 1998; 4: 665-76.
22. Nicholls WC, Ginsburg D. Von Willebrand disease. Medicine 1997;76 1-20.
23. Tritlet DA. Coagulation and Bleeding Disorders: Review and Update. Clin Chem 2000; 46 (8B):1260-9.
24. George JN. Platelets. Lancet 2000; 355: 1531-9.
25. Colman RW, Koneti RaO A, Rubin RN. Platelet Bleeding Disorder in a 30 Year Old Female. Mechanisms of Congenital Platelet Function Defects. Am J Hematol 1993;44: 139-44.
26. George JN, Shattil SJ. The clinical importance of acquired abnormalities of platelet function. N Engl J Med 1991;324:27-39.
27. Al Fawaz IM, Gader AMA., Bahakim HM, Al Mohareb F, AlMomen AK, Harakati MS. Hereditary Bleeding Disorders in Riyadh, Saudi Arabia. Ann Saudi Med 1996;16(3): 257-61.
28. Ahmed MAM, Al-Sohaibani MO, AlMohaya SA, Sumer T, AlSheikh EH, Knox-Macaulay H. Inherited bleeding disorders in the Eastern province of Saudi Arabia. Acta Haemat 1988; 79:202-6.
29. Bashawri L, Qatary A, Fawaz N, Al-Attas R, Ahmed M. Glanzmann’s Thrombasthenia. Bahrain Med Bull 2005; 27(3):123-8.