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Editorial

BLEEDING DISORDERS! A scare or properly reassured!

Dr. Namballa Naveen, M.B.B.S.
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Abstract

In an attempt to distinguish between ALL, CML, CLL, AML, ITP, DIC, hemophilia A, hemophilia B, von Willebrand disease, Microangiopathic Hemolytic Anemia, Bernard-Soulier syndrome, Glanzmann thrombasthenia, Vitamin K deficiency, Heparin-induced thrombocytopenia, Coagulation Factor Inhibitor, and Factor 5 Leiden, might influence the decision to work as a consultant clinical pathologist. Since most patients with bleeding disorders are at risk for post-surgical bleeding, CNS bleeding, post-trauma bleeding, nosebleeds (epistaxis), death from liver illness (hemorrhage), etc., it might become challenging for med school students or junior doctors to diagnose. When performing any type of invasive or non-invasive procedure, including emergency or elective surgery, hospitals, clinics, and the relevant junior doctors and medical students must treat these illnesses as the primary focus of care and conduct routine blood tests, platelet count, PT, PTT, hemoglobin, bleeding time, and, if necessary, a bone marrow biopsy. An abnormal ristocetin test (for Von Willebrand disease) and a D-dimer test (for DIC) can be considered. It needs proper interpretation with a strong command of concepts, evaluation, and then diagnosis.

Keywords: Haemorrhage, Bleeding disorders, differentiation, diagnosis, prognosis.

Acronyms Used:

ALL (Acute lymphoblastic leukaemia)`, CML (Chronic myeloid leukaemia), CLL (Chronic lymphocytic leukaemia), AML (Acute myeloid leukaemia), ITP (Idiopathic thrombocytopenic purpura), DIC (Disseminated Intravascular Coagulation), ICU (Intensive care unit), HDU (High density unit), ITU (Intensive therapy unit), CNS (Central nervous system), HA (Haemophilia A), HB (Haemophilia B), VWF (Von Willebrand factor), PTT (Partial thromboplastin time), ADP (Adenosine diphosphate), TXA2 (Thromboxane A2), COX (Cyclooxygenase), TTP Thrombotic Thrombocytopenic purpura), HUS (Haemolytic uremic syndrome), PT (Prothrombin time)

Patients with ITP and Microangiopathic hemolytic anemia have a normal PTT because coagulation factors are not affected; instead, primary hemostasis is disrupted. After platelet adhesion, platelets degranulate and change shape. ADP is then released, promoting the exposure of GP2b/3a receptors on platelets. TXA2 is synthesized by platelet COX. Platelets aggregate using the GP2b/3a receptor, and TXA2 promotes this aggregation, resulting in the formation of the platelet plug. In ITP, IgG antibodies are produced against Gp2b/3a (platelet antigens), leading to thrombocytopenia. On the other hand, in Microangiopathic hemolytic anemia, microthrombi formation occurs, causing shearing of RBCs when they pass through the microthrombi. This results in the formation of schistocytes, leading to anemia, thrombocytopenia, and bleeding from the skin and mucosal surfaces. Shearing also occurs in conditions like TTP and HUS, which have the same pathology. Patients with persistently low platelet counts in ITP have a poor prognosis [6].

The liver contains epoxide reductase, which activates Vitamin K. Once activated, Vitamin K gamma carboxylates (which is necessary for their functioning) factors 2, 7, 9, 10, protein C, and protein S. Therefore, Vitamin K deficiency leads to bleeding as it disrupts multiple coagulation factors. During heparin therapy, particularly with unfractionated heparin, direct platelet destruction occurs. But how are the platelets being destroyed? The answer lies in heparin's formation of a complex with Platelet factor 4. The presence of IgG autoantibodies leads to platelet consumption by the spleen, resulting in heparin-induced thrombocytopenia. Once this condition develops, the anticoagulant needs to be changed. Low molecular weight heparin is preferred due to its lower risk of inducing thrombocytopenia. Unfractionated heparin carries a higher bleeding risk compared to low molecular-weight heparin. For this reason, it is used in the management of venous thromboembolism and acute coronary syndrome.

Let's try to differentiate between ALL, CML, CLL, and AML! Don't know exactly? Be a hematologist to understand the contrast. Okay, let's now try to differentiate from the perspective of a second-year medical student to understand the differences between ITP, DIC, Hemophilia A, Hemophilia B, and Von Willebrand disease. Yeah, I knew then that these were bleeding disorders. I got convinced by professors that these disorders need to be memorized. The next day, I attended a lecture about Microangiopathic Hemolytic Anemia, Bernard-Soulier syndrome, Glanzmann thrombasthenia, Vitamin K deficiency, Heparin-induced thrombocytopenia, Coagulation factor inhibitor, and Factor 5 Leiden, and I decided to never become a consultant clinical pathologist ever. That's when the university hospital becomes overcrowded in the Emergency department (mainly in developing countries). The students go for conducting IV cannulation when the patients are critically ill and need to be shifted to ICU, HDU, or ITU. Theoretically, it's taught within the first two years of medical school for doctors. However, the majority of the students (except the front bench geniuses) find it difficult to differentiate, as most of the patients with bleeding disorders are at risk due to post-surgical bleeding, CNS bleeding, post-trauma bleeding, nosebleeds (epistaxis), mortality due to liver disease (hemorrhage), etc. Intracranial hemorrhage was the most frequent underlying or contributing factor in mortality among people under the age of 20 [1].

According to reports, there are 77 countries home to about 100,000 hemophiliacs, and these individuals' hemorrhagic symptoms might range from minor ecchymosis to deadly central nervous system (CNS) bleeding events that are almost consistent with the severity of Hemophilia A (HA) and Hemophilia B (HB) [2]. Hemophilia A is Factor 8 deficient, and Hemophilia B is Factor 9 deficient. The rest of the features of both types are similar, as both are X-linked recessive and can arise from a new mutation without any family history. Mostly, they present with deep tissue and post-surgical bleeding, indicated by prolonged PTT along with normal PT, platelet count, and bleeding time. If there's any acquired antibody against factor 8, it will impair its function, resulting in a 'Coagulation factor inhibitor.'

Now, let's talk about Von Willebrand disease. How does it work? It's an inherited deficiency, with the most common type being autosomal dominant, in which patients complain about bleeding in mucosa and skin. Everyone might have memorized this, but what's the story behind it?

It's important to note that if a patient is on warfarin, it should be discontinued five days before planned surgery, and heparin should be initiated.

The target INR should be less than 1.5 before proceeding with the surgery. Teenagers with bleeding problems are more susceptible to developing menorrhagia or severe menstrual bleeding, as well as experiencing other abnormal bleeding from the reproductive system [7]. Evidence suggests that women with bleeding disorders are more likely to develop endometriosis and hemorrhagic ovarian cysts [8].

Furthermore, let's differentiate these conditions for a better understanding of bleeding in conjunction with leukemia. ALL mostly occurs in children and adults under 40 years of age. Patients with ALL present with thrombocytopenia, anemia (hemoglobin <5g/L), and sometimes even pancytopenia. Consequently, these patients experience bleeding, petechiae, purpura, ecchymosis, and DIC. On the other hand, AML presents with bleeding and anemia, as well as gum hypertrophy and gum bleeding, which typically occur in adults. Supportive care is provided for both conditions, including blood and platelet transfusion, intravenous antibiotics, and chemotherapy. Now, let's consider CML and CLL. Both conditions may exhibit a decreased platelet count and leukocytosis. CLL is more likely to have a decreased platelet count, which may require transfusion and antibiotic treatment. In conclusion, hospitals, clinics, junior doctors, and medical students should prioritize these disorders in their treatment approach when performing invasive or non-invasive procedures and emergency/elective surgeries. Routine blood tests should include platelet count, PT, PTT, Hb, bleeding time, and if necessary, a bone marrow biopsy, abnormal Ristocetin test (for Von Willebrand Disease), and D-dimer (for DIC). Implementing these measures will help reduce the number of patients with increasing mortality due to bleeding disorders in the future.

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So, when there is damage to the vessel wall, there is vasoconstriction of the vessel wall at the damaged part, which is neurotic stimulation. Consequently, endothelin gets released by the endothelial cells, causing subendothelial collagen to adhere to Von Willebrand factor (VWF).

VWF then leads to platelet adhesion through the GP1B receptor. You might wonder, where does this VWF come from? It is derived from Weibel-Palade bodies of endothelial cells and alpha granules of platelets. This can cause post-surgical bleeding in deep tissues and joints, which is not seen in most cases. A substantial correlation between elevated VWF levels and poorer cardiovascular health has been demonstrated in the majority of studies conducted [3]. The majority of inherited bleeding disorders are caused by von Willebrand disease. Some patients might have GP1b deficiency genetically, which leads to impaired platelet adhesion, resulting in thrombocytopenia and enlarged immature platelets. This condition is known as Bernard-Soulier syndrome. In addition, if there is a genetic deficiency of GP2b/3a receptors, platelet aggregation is impaired, which leads to Glanzmann thrombasthenia. A distant history of arterial or deep vein thromboses may also indicate DIC, as patients may experience bleeding at various locations, including the gingiva, wounds after surgery or trauma, the vagina, the rectum, or through objects like urinary catheters [4]. Catheterization is performed by junior doctors and 3rd-year medical school students. I hope they have ample practical knowledge to deal with the possible complications. If it's a male with benign prostatic hyperplasia (BPH), there is a high risk of injury during catheterization, and it should be done under supervision, even in densely populated countries such as India, China, Pakistan, Sri Lanka, and many more. If DIC is not identified and treated promptly, it can quickly result in multi-organ failure and death. Therefore, a high index of suspicion for this high mortality condition is essential in critically ill patients [4].

When the coagulation cascade is pathologically activated, microthrombi are formed, leading to platelet and factor consumption, resulting in ischemia, infarction, and bleeding from IV sites, body orifices, and mucosal surfaces. During this process, PTT is prolonged, along with prothrombin time and D-dimer, while fibrinogen and platelet count decrease. However, a prolonged PTT is not a reliable indicator of hemorrhage, and a normal PTT does not offer protection from hemorrhagic risk, as there are numerous circumstances unrelated to hemorrhage that can cause PTT disturbances [5].

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Dr. Namballa Naveen, M.B.B.S.
Internal Medicine, California Institute of Behavioural Neuroscience and Psychology, Fairfield, California, USA
Emergency Medicine, Steel Authority Of India (SAIL) hospital, Chasnalla, Dhanbad, India
Email: namballanaveen.95@gmail.com