Thrombosis — The Newer Dimensions

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Clinicians and haematologists are confronted more and more with diagnosis and management of patients with venous and arterial thrombo-embolic phenomenon. In the recent past there have been major advancements in the field and understanding of the aetiopathogenesis of haemostasis. Traditionally the coagulation pathway consists of three separate systems - the intrinsic pathway, the extrinsic pathway and the common pathway.

A state of heightened activation of the coagulation system is called as 'hyper-coagulability'. This manifests predominantly as venous thrombo-embolism and is a major cause for pulmonary embolism in United States [1]. This has also been seen though less commonly, in arterial thrombotic disorders in young adults.

The modern view depicts haemostasis, through its three pathways, leading to formation of fibrin under normal circumstances. However, the coagulation system is kept under check by anti-thrombin mechanisms which inhibit thrombin (IIa), factor Xa and IXa. The activated protein C (APC) with its co-factor protein S, are also part of anticoagulation mechanism and lead to inactivation of factors Va and VIIIa. Factor Xa is also inhibited by protein Z protease inhibitor (ZPI). The tissue factor pathway inhibitor (TFPI) down regulates the tissue factor IIa complex. However, a small amount of fibrin is generated through intra-vascular injuries in spite of various anticoagulation mechanism which in turn gets degraded by plasmin [2]. Therefore, it is obvious that failure of any of the above mechanisms shall lead to generation of pathological quantity of fibrin and impending thrombo-embolism.

Apart from coagulation factors, the platelet plasma membrane provides a highly reactive surface on which haemostatic activity is initiated through a large number of receptors. Other components which take part in the process include various proteins of subendothelial matrix, plasma proteins, platelet proteins and platelet granules, namely alpha granules, dense granules and lysosomes. Therefore, it is observed that platelet aggregation and adhesion are important in coagulation reactions resulting

in fibrin formation which stabilizes the platelet aggregates which are adhered to subendothelial matrix through receptors. The subendothelial matrix has glycoproteins - GP Ia and IIa, GP VI and VWF. In the process, the platelet fibrinogen receptors GP IIb-IIIa get activated leading to subsequent aggregation [3].

The inhibitors of haemostasis act through (a) TFPI (b) protein C / protein S system and (c) heparin-anti-thrombin pathway. The importance of these mechanisms, is well known as the deficiency of either of these inhibitors, leads to hypercoagulability and to risk of thrombosis in the affected individuals. Important amongst these is protein C and S pathway. APC inactivates Va and VIIIa as they bind to phospholipid membrane with protein S. Both protein C and protein S are vit K dependent proteins. Protein C gets activated by thrombin (IIa) which binds to thrombomodulin (TM), a membrane receptor on endothelial cell. This IIa-TM complex rapidly converts protein C to APC and enzymatically degrades factor Va and VIIIa.

Antithrombin is a glycoprotein synthesized by the liver which inhibits activity of thrombin and Xa and thus prevents fibrin formation. It also helps to inactivate factors XIIa, Xa and IXa. Heparin catalyses the actions of thrombin against Xa. The antithrombin activity is potentiated by heparin sulphate, an analog of heparin, present on the luminal surface of endothelial cells. Another inhibitor, present in vivo, is plasminogen activator enzyme which binds to fibrin and converts bound plasminogen to plasmin [4].

In the above settings, venous thrombosis is one of the commonest occurrence seen clinically in pregnancy, malignancy, after use of intravenous catheter and other interventional devices and in patients with hypercoagulable states. This manifests clinically as superficial thrombophlebitis, deep vein thrombosis, pulmonary embolism and strokes of various kind in young adults. The whole blood D-dimer assay is an important test to diagnose DVT with a negative predictive value of 98%. Therefore a negative test rules out DVT. Radio

imaging techniques such as colour flow Doppler ultrasound, CT scan and MR angiography are other important diagnostic tools.

Hypercoagulable state encompasses congenital or acquired deficiencies of antithrombin, protein C or protein S, APC resistance, or anti phospholipid antibodies singly or in combination. Therefore, primary hypercoagulable states are due to (a) qualitative defect or quantitative deficiency of anti-thrombotic proteins such as antithrombin, protein C and protein S or (b) increased level of prothrombotic clotting factors such as factor V Leiden (APC-R), (c) prothrombin gene mutation G 20210A and (d) increased levels of factors VII, XI, IX, VIII and von-Willebrand factor. In one study, it has been reported that overall incidence varied from 1.07% for antithrombin deficiency, 0.54% for protein C deficiency, 0.50% for protein S deficiency and 0.30% for APC - R [5]. It is also reported that risk of thrombosis varied in acquired conditions irrespective of risk of congenital thrombophilias; for example risk, is much higher after hip and knee surgery than during pregnancy or cancer. Prolonged air travel has the least risk. Frederic et al in their study found that incidence of pulmonary embolism is 1.5 cases per million in passengers who travel 5000 km by air and it rises to 4.8 cases per million for those who travel more than 10,000 km by air [6]. All such studies have led to the conclusion by various authors

that many of these abnormalities are not only due to single gene factor or mutations in structural genes for proteins but can be attributed to polymorphisms that increase their rate of transcription and translation. Therefore, individuals with inherited thrombophilias have a higher risk of venous thromboembolism in the setting of acquired thrombogenic events.

References

1. Hirsh J, Hoak J. Management of deep vein thrombosis and pulmonary embolism. A statement for health care professionals from the council on Thrombosis. American Heart Association Circulation 1996; 03 : 2212-45.
2. Arkel YS, Paidas MJ, Ku DH. The case of Coagulation activation marker in the assessment of hypercoagulability in patient with inherited and acquired prothrombotic disorders. Blood Coag Fibrinol 2002; 13 : 199-205.
3. George JN, Shattil SJ. The clinical importance of acquired abnormalities of platelets function. N Engl J Med 1991; 324 : 27-39.
4. Julie H, James G. Hemostasis and thrombosis. American Society of Haematology Self Assessment Program. 1st ed, 2003, chapter 13, 249-54.
5. Andrew IS, Mark NL, Barbara AK, Clire K. Thrombotic disorders : Diagnosis and Treatment in Haematology 2003, American Society of Haematology Education Program Book 2003; 520-22.
6. Frederic L, Vanessa S, Stephen WB et al. Severe Pulmonary Embolism Associated with Air Travel. N Engl J Med 2001; 345 : 779-83.

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