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SHORT COMMUNICATION

Summary and Review of the Abstracts on Hemostasis/Thrombosis Presented at Haematocon 2018, Kochi

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Abstract The hemostatic pathways involve a complex interplay of a vast array of inherited and acquired factors. Derangements of these pathways lead to several disorders that are complex and challenging not just for laboratory and clinical hematologists but also of concern to public health officials and policy makers. The past decade has seen an increased focus on research in this area with several recent meetings focusing on the diagnosis and management of persons afflicted with these disorders. Haematocon 2018 is the national conference of the Indian Society of Haematology and Blood Transfusion, and papers presented at this year's event offered a glimpse of the contemporary research efforts in India. This mini-review summarizes and places in perspective, salient results from this meeting. The papers are divided into broad subsections of hemophilia, rare clotting factor deficiencies, platelet function defects, macrothrombocytopenia syndromes, thromboelastography, inherited and acquired prothrombotic states, and finally a miscellaneous section. Relevant recent Indian publications on the theme are also discussed.

Keywords Bleeding · Coagulation · Hemostasis · Research · Thrombosis

Introduction

The hemostatic pathways involve several inherited and acquired factors, derangements in which lead to several disorders of clinical and public health importance. Recent years have witnessed an increase in research in this area. The papers presented at Haematocon 2018 in Kochi, Kerala offered a glimpse of contemporary research in this field in India. This article summarizes the salient papers from the Kochi meeting. They are divided into subsections of hemophilia (clinical and laboratory-based studies), rare factor deficiencies, platelet function defects, macrothrombocytopenia syndromes, thromboelastography (TEG), inherited and acquired thrombophilias including those associated with autoimmune diseases and miscellaneous disorders of coagulation and bleeding. Relevant recent Indian publications are also discussed.

Methodology

Published abstracts for oral and poster presentations at Haematocon 2018 (Kochi) were reviewed. Recent Indian papers (published within the last 2 years), were also evaluated.

Hemophilia A and B

Studies in this area addressed the epidemiology, diagnostic work-up and treatment strategies of these diseases in India. Yadav and colleagues [1] from CMC-Ludhiana described 211 hemophilia A and B patients collated over 9 years in an institutional hemophilia registry. Median age was 22 years, suggesting either early mortality or loss of follow-up. Although 62.5% had severe disease (factor level $< 1\%$), only 7.9% had been diagnosed with inhibitors. Joint deformities were present in 83.5% and transfusion-transmitted infections in 18.3%. Punjab has been a late-entrant in providing free factor support to

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hemophiliacs, and more heartening results were presented from Kolkata by Chakraborty et al. [2] when they reported a significant drop in annual bleed rates (from 8 to 1.13/year) and in new target joints in young patients on prophylactic factor VIII replacement as compared to those getting episodic treatment. Similar results from AFMC Pune were presented by Yadav et al. [3]. An industry-led paper on turoctocog-alfa, a recombinant antihemophilic factor VIII, also encouragingly reported that the product was stable even when stored at 40 °C and 75% humidity for up to 3 months [4]. This has implications for patient family/locally-administered prophylaxis in our tropical country.

The challenges of conducting surgeries in hemophiliacs were addressed in a study by Joshi et al. [5], who retrospectively evaluated 32 inhibitor-negative patients undergoing operations ranging from knee replacements and pseudotumor excisions to synovectomies and ophthalmological procedures. 16/32 patients received factor infusions 12-h post-op. They could prevent all intra- and post-operative bleeds, and the factor increments correlated well with the doses administered.

On the laboratory aspects, Patil and Shetty [6] described a unique aPTT-based screening strategy to differentiate hemophilia A and B. They used the ability of factor-adsorbed polystyrene beads to correct a prolonged aPTT. At ~ INR 95/patient, this cost-effective strategy holds out a promise to simplify the diagnostic work-up of suspected hemophilia. On the other (high-) end of the laboratory spectrum, Maddali et al. described their novel long-amplicon PCR-NGS based method to detect small mutations (substitutions, indels etc.) in hemophilia A and B. They could target the entire coding regions of FVIII and FIX genes along with the adjacent intronic sequences using a long amplification DNA polymerase [7]. Another paper from CMC-Vellore unraveled the cause of an intriguing finding where four severe hemophilia A afflicted males from Andhra Pradesh showed a *carrier* pattern for the intron 22 inversion on PCR [8]. MLPA analysis showed this to be due to exon 2–22 and 7–22 duplications, a heritable finding with a founder effect on haplotyping.

The journal has recently published a comprehensive editorial on "Evolution of Hemophilia Care in India" [9]. Besides being a goldmine of information on how the concepts evolved over decades, this "must-read" article for hematologists also laid down a roadmap and offered valuable suggestions on the road ahead.

Rare Clotting Factor Deficiencies

Ramakrishnan and colleagues [10] described combined factor V and VIII deficiencies (including TEG findings) and Suman et al. [11] reported factor VII deficiency. The latter case was of a remarkable 54-year-old lady with abnormal vaginal bleeding who had previously uneventfully undergone two natural deliveries and a tooth extraction.

Platelet Function Defects

Three papers evaluated Glanzmann thrombasthenia (GT) in different settings. Chandra et al. [12] from Lucknow reported the clinicopathological spectrum in 11 GT cases aged 2–42 years. They found a male preponderance (7:4) and reduced ristocetin-induced agglutination in 23%. The latter highlighted the important role of flow cytometry in confirming this disorder. Ahammad et al. [13] studied 9 GT patients by TEG and reported that a reduced maximal amplitude coupled with a normal platelet count could serve as a screening test before platelet aggregometry and flow cytometry. Shanbhag et al. [14] presented two interesting patients. The first had variant/type III GT with normal flow cytometric results on GPIIb/IIIa receptor testing and was compound heterozygous for two novel *ITGA2B* variants. The second had coexisting mild FVII deficiency (caused by 3 co-inherited polymorphisms) along with GT.

Macrothrombocytopenia Syndromes

Asymptomatic persons with large platelets and low platelet counts are known to be common from the northern and eastern parts of India. Sultan et al. [15] reported 25.3% of their 510 healthy Assamese subjects had thrombocytopenia on automated counters, and that a low platelet count was significantly associated with higher mean platelet volumes. On the other hand, Patel et al. [16] from Surat, Gujrat found the prevalence of platelet count $< 150 \times 10^9$/l and MPV > 11 fl to be 1.9% in 10,047 healthy college students. An expansive review on inherited macrothrombocytopenia by Ghosh and colleagues [17] concluded that an extensive region-based study of the molecular genetic factors underlying this condition is required in india, as nearly 40–50% of the cases can be explained by currently known genetic defects, and novel mechanisms may underlie the remainder.

Thromboelastography

The growing acceptability of this long-standing but often derided technique by hematopathologists was reflected by at least 6 papers on its applications. In 223 patients suspected to have a hemostatic disorder, Kafley and colleagues [18] found sensitivity and specificity of TEG alone to be 86 and 85.7% respectively. Sensitivity rose to 97.5% when TEG was combined with the ISTH bleeding assessment tool (BAT). A study from AIIMS, New Delhi found TEG to outperform the platelet count in identifying coagulopathy and bleeding risk in traumatic brain injury patients [19]. Mohan et al. [20] described their experience with TEG wherein 84% massively transfused patients had hemostatic abnormalities and the positive predictive value of TEG to predict bleeding was 100%. In a neoplastic setting, David et al. [21] studied rotational thromboelastometry (ROTEM) in 50 acute promyelocytic leukemia cases. A maximum clot firmness (MCF) $\leq$ 30 mm was found to be significantly associated with death ($p = 0.012$) and 4/6 major bleeds, 4/5 thromboses and all coagulopathy-related deaths occurred in patients with MCF $\leq$ 30 mm.

Inherited Thrombophilia

Kumar et al. [22] studied 337 pediatric cases with splanchnic vein thrombosis over 10 years and found inherited cause(s) in 30. Protein S deficiency and factor V Leiden were nearly equally frequent, followed by protein C deficiency. 5 children had an acquired cause in the form of APLA syndrome. Kishor et al. [23] and Sharma et al. [24] from AIIMS, New Delhi examined the tissue factor promoter polymorphism 603A > G and factor V-related parameters (HR2 haplotype and Arg485Lys polymorphism) respectively in 100 deep vein thrombosis (DVT) patients each. The TF 603 A > G and Arg485Lys polymorphisms significantly affected risk, indicating a need to evaluate them further in Indian DVT patients.

Two studies examined inherited prothrombotic risk factors for coronary artery disease (CAD). Maru et al. [25] reported a paraoxonase 2 gene polymorphism to likely not be associated with CAD while Ranjan et al. [26] reported that the FXIII Val34Leu may contribute to a protective effect in case of persons who inherit the Leu allele. They verified the low frequency of this allele in north Indians [27]. A study from New Delhi on 50 women with recurrent 1st or 2nd trimester fetal losses did not find the factor V Leiden mutation in any patient but acquired protein C resistance was seen in 10 women [28].

Acquired Thrombophilia

Sharma et al. [29] examined thrombophilic risk factors in 40 patients with systemic lupus erythematosus (SLE) and found antiphospholipid antibodies (APLA) in 45% (LA and/or IgG ACA). Thromboses occurred in 6 (15%) patients, and were significantly associated with the presence of LA (lupus anticoagulant). A laboratory-based study from JIPMER, Puducherry found that out of 199 LA-positive or indeterminate cases, 39.1% had SLE, 12.3% had another autoimmune condition, 30.1% had pregnancy-related morbidities and 13.5% had thrombosis [30]. dRVVT was significantly more sensitive than LA-sensitive aPTT. Murari et al. [31] from SGPGI Lucknow studied 84 SLE patients and found fetal loss or macrovascular thrombosis in 21 of them. The LA-positive cases among them showed an association with lymphopenia and low complement levels.

Among other causes, Vimal et al. [32] studied 33 pediatric ischemic stroke cases and found low vitamin B12 and folate levels in 33% and 18% respectively. Bhattacharya et al. [33] evaluated 40 non-CML myeloproliferative neoplasm patients to report that bleeding and thrombosis were exclusively seen in the JAK2 positive cases (85%). Tiwari and colleagues [34] described a girl with paroxysmal nocturnal hemoglobinuria (leukocyte clone size 80%) who developed hepatic vein thrombosis and was managed with eculizumab. Among the newer anticoagulants, a published study had compared the safety and efficacy of rivaroxaban with dalteparin in cancer-associated venous thromboembolism (VTE). VTE or pulmonary embolism recurrence rates and rates of major bleeding were similar in both arms [35].

Miscellaneous

Ganguli et al. [36] reported that platelet and monocyte-origin microparticles increased with ascent in 15 healthy volunteers, with the initial induction being more robust than that after moderate exercise. No significant changes were noted in the blood count, biochemical, arterial blood gas (other than alkalosis) and Sonoclot parameters, suggesting that altitude per se rapidly causes an increase in microparticles. The armed forces have recently published valuable reference ranges for hematological parameters in native pediatric populations from Ladakh [37].

An important poster from Novo Nordisk updated the 20-year safety record of recombinant activated factor VII (rFVIIa). Of the over 5 million standard doses of rFVIIa administered, 249 thrombotic adverse events were reported in 217 individuals. No thrombotic microangiopathies or

instances of development of antibodies against rFVIIa were reported in hemophilia with inhibitors or GT [38].

A case of large granular lymphocytic leukemia with acquired hemophilia A (AHA) was reported [39]. A recent study from India on this rare condition found only 8 AHA cases over a 15-year period out of over 2000 patients worked up for bleeding. Only one AHA patient was known to have leiomyosarcoma. No cause was identified in the others [40].

Conclusion

Papers at the last national conference of the ISHBT and recent publications in the IJHBT reflect the challenges and patterns encountered in Indian clinical and laboratory hematology practice as well as the fast pace of scientific discoveries today.

Compliance with Ethical Standards

Conflict of interest The author declares that he has no conflicts of interest.

Ethical Approval Not sought as this article does not contain any studies with human participants performed by the author.

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