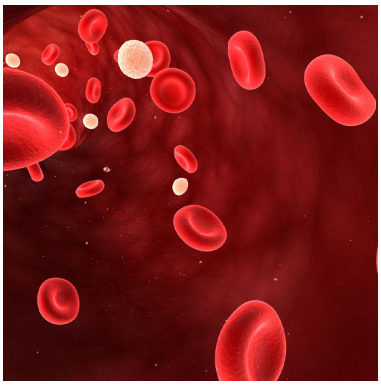
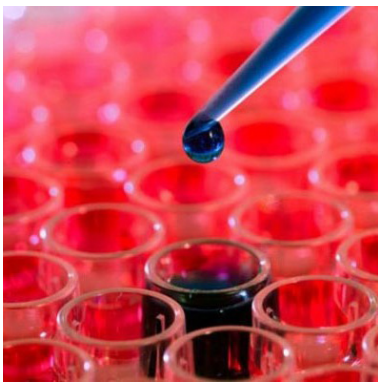
Scientific Tracks & Sessions
August 23, 2018

Hematology 2018




2nd International Conference on

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August 23-24 | London, UK

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Molecular and laboratory characteristics of recessive von Willebrand Disease 2N anno 2018

Jan Michiels
Good Heart Centre, The Netherlands

Introduction: The FVIII binding site on von Willebrand factor (VWF) is located in the D' (766-864) and D3 (1054-1060) regions of the VWF gene. The cysteine residues in the D' domain Cys767-Cys808;Cys776-Cys804;Cys810-Cys821 form disulfide bridges between two D' trypsin-inhibitor-like (TIL') and E' regions, which are of critically importance for the binding between Til'E' and FVIII.

Aims: To study the genotype phenotype relationship of VWF in von Willebrand disease (VWD) 2N

Methods: We critically analyzed the molecular and laboratory characteristics of VWD 2N reported in the literature and describe experiences from three VWF Research Centers in Europe.

Results: Homozygous non-cysteine R854Q/R854Q mutation and of R854Q double heterozygous with non-cysteine E787K, T791M and R816W mutations in the D' domain result in a mild FVIII binding defect (FVIII:BD) (about 30%) featured by mild to moderate hemophilia A with normal bleeding time and normal VWF functions and multimers. The FVIII:BD is markedly decreased (less than 10%) in E787K, T791M, R816W, 869 and C1060 either homozygous or double heterozygous with a null allele. FVIII:BD due to 2N non-cysteine mutations in the D' domain of VWF gene and FVIII mutations in the C1 and C2 domain in FVIII gene have no influence on synthesis, storage, secretion and multimerization of VWF. The VWD type 2N cysteine mutations C788R/Y; Y795C and C804F in TIL'; C858C/F in E' are associated with aberrant multimerization, poor secretion and reduced FVIII binding to VWF. Homozygous R760W/R760 (D2 domain) and R788/R788 (D' domain) induce a pronounced secretion and multimerization consistent with recessive VWD 2C in which a mild FVIII:BD of about 35% does not contribute to the severity of bleeding phenotype. The combination of R854Q and R760 in the D'D2 domains produce VWD type 2N with a smeary pattern of VWF multimers due to a mixture of normal VWF and of proVWF. Heterozygous R763/WT mutated VWD type 1 and VWD 2N double heterozygous for R854Q and R763 (Furin cleavage site) show a smeary VWF multimeric pattern due to a mixture of normal VWF and pro-VWF protein. The homozygous C1060R/C1060R and the double heterozygous D879N/null, C1060R/R854Q and C1060R/null mutations in the D3 domain are associated with a hybrid phenotype of 2N/2E VWD.

Conclusion: Classical VWD 2N due to the homozygous non-cysteine mutations in D' Domain of the VWF R854Q and R816W impair the binding of FVIII capacity of VWF (FVIII binding defect: FVIII-BD) but do not impair the multimeric structure of VWF. The cysteine mutations inside the D' domain C788R/Y, C788T and C804F in TiL', and C858S/F in E' and outside the D' domain C760C in D2, R763C Furin cleavage site only produce VWD 2N when combined with the R854Q mutation and are associated with aberrant multimerization of VWF. Homozygous C1060R/C1060R mutation in the D3 domain, and the double heterozygous D879N/null, C1060R/R854Q or C1060//null mutations are associated with a hybrid phenotype of 2N/2E VWD.

Speaker Biography

Jan Michiels Professor of Nature Medicine & Health Blood Coagulation & Vascular Medicine Center in Netherlands. He also serves as an Editorial board member for many scientific journals.

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SLE as a hematological problem & the Kozhikode criterion for diagnosis of SLE

Sasidharan P K
Government Medical College, India

SLE can present with hematological manifestations alone or along with musculoskeletal, skin or other system involvement. In cases with hematological abnormalities as the predominant or only manifestation, the diagnosis is often delayed or missed at the time of presentation, this is especially so if the index of clinical suspicion is low or if there is improper and inadequate follow up. An observational study was conducted in our institution with the purpose of estimating the proportion of SLE with hematological manifestations as the initial presentation of the disease. It was observed that 76.8% of the patients had hematological manifestations at first presentation. Thus hematological manifestations were found to be the most common presenting manifestation of SLE in people of North Kerala which is not given due importance in the ACR criteria for diagnosing SLE. One of the common coexisting abnormalities in patients with initial hematological presentation was autoimmune hypothyroidism, which also is not included in the ACR criteria. The most common hematological abnormalities at presentation were ITP, autoimmune hemolysis and APLA. In addition there was an inverse association of arthritis with hematological manifestations. Thus it appears that SLE is more of a Hematological disorder rather than a Rheumatologic disorder. A significant number did not satisfy the ACR criteria at the time of diagnosis but did so on follow up. The ACR criteria are weak to diagnose such patients and therefore needs revision. We have developed an alternative to ACR criteria as "Kozhikode Criteria for SLE" which was validated in another study and was published, both these the issues will be presented.

Speaker Biography

Sasidharan P K is an Emeritus Professor, Department of Family Medicine, Govt.Medical College, Kozhikode. He was a Former Professor & Head, Department of Medicine & Haematology, Government Medical College, Kozhikode. He also served as the President Hypertension Society of India, Editorial Board Member Indian Journal of Hematology and PhD research Guide for University of Calicut.

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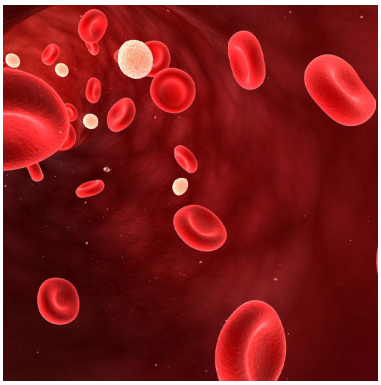


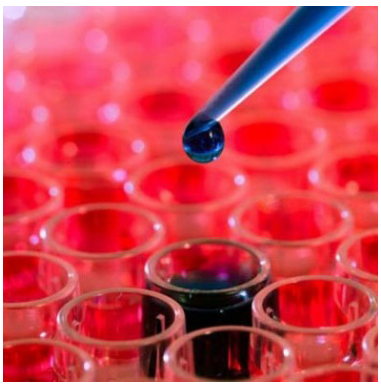


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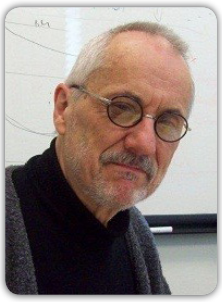

H Joachim Deeg

University of Washington, USA

When do we stop? Modern sequential therapies for hematologic malignancies and end of life questions

With modern medical developments various malignant disorders such as leukemia or solid organ cancers, have been transformed from acute life-threatening into chronic diseases. This transition continues with the growing number of novel agents that become available to treat diseases from chronic leukemias to breast cancer, or carcinoma of the lung. Patients are certainly aware of that, and a frequent question is: "Well, doctor, I know I have already received two treatments and have not responded. What are we going to do if this next treatment is not going to work?" In fact, it happens that you treat patients and basically have conveyed the message that we are at the end of the road, the patient considering transition to palliative or hospice care, when a new study is published with yet another agent, opening the door again, basically returning the patient from hospice to active therapy. These situations come with considerable psychological stress. In addition, however, the cost of this type of management to the health care system is phenomenal. Some groups have admonished physicians to exert some financial stewardship. Others have argued that we cannot withhold treatment if such treatment is available. Do we need a new set of ethical rules? No one likes to set priorities or ration care. Discussions within the medical community alone will not lead to substantial change. We must have a conversation within the society at large.

Speaker Biography

H Joachim Deeg completed his MD in Wilhelms Universitaet, Germany. Presently he is working as a Professor of medicine in the University of Washington. He is also a member of the Fred Hutchinson Cancer Research Center. He is also a visiting professor at Carl Carus University, Dresden, Germany. His research interests are Pathophysiology, genetics and epigenetics of MDS (role of transcription factors in regulation) Inflammatory responses and GVHD (effects of alpha1 anti-trypsin [AAT]), Separation of GVHD and GVL effects by AAT, Iron and allogeneic responses.

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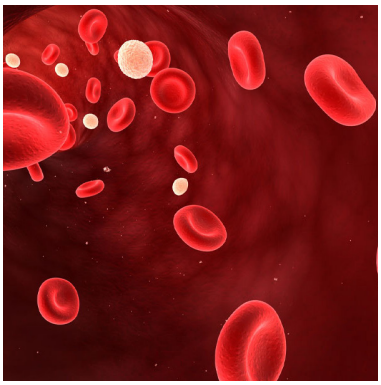


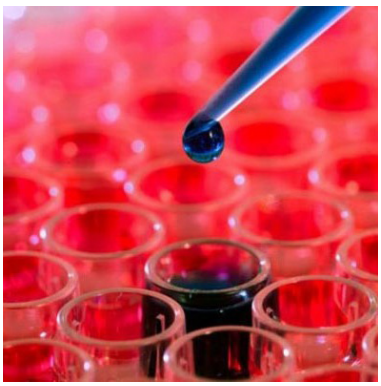


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A Report of Cytogenetic abnormalities Found In 246 Mexican patients clinically diagnosed with Myelodysplastic Syndrome (MDS), given the importance of Cytogenetic results in calculating the Risk Assessment proposed by the IPSS-R

Marcelo F Rosales
Mendel Laboratory, Mexico

Myelodysplastic syndromes (MDS) is a group of clonal disorders characterized by progressive cytopenia's and dishematopoiesis. Anemia is frequently observed along with a defect of protoporphyrin synthesis like ring sideroblastic which are seen in patients with deletion 5 q. The dysplastic changes like macrocytosis is the most commonly observed. In neutrophils and eosinophils is also commonly found hip granulation. The etiology of primary MDS is unknown, its general biological characteristics include impaired hematopoiesis, which may be accompanied by molecular, immunological and/or cytogenetic abnormalities. These group of chromosomal abnormalities considered as a prognostic factor within the MDS (very good, good, intermediate, poor and very poor), being the most recent the Revised International Prognostic Scoring System (IPSS-R). This article gives a description of several cytogenetic abnormalities found as evidence within 246 Mexican-mestizo patients with a diagnosis of MDS. In each of the 246 cases, two unstimulated cell cultures of bone marrow or peripheral blood were set up, and the GTG banding technique was performed. An analysis of twenty (20) metaphases were done on average in each case, and chromosomes with a resolution of 300 to 500 bands. The nomenclature report was written sing an up to date International System of Human Cytogenetics Nomenclature (ISCN). Most of the findings of cytogenetic abnormalities in this population with MDS are directly related to patient age, given the 76.5% of the reports generated with abnormal karyotypes belong to patients older than 50 years old. The chromosomal abnormalities found in our study coincides with that reported in the literature, which is del (5q), this abnormality was observed in 28% (18 cases). Also, the abnormalities of chromosome 7 and 8 were observed by the same percentage as the literature reports, being 12.5 % (8 cases). From the abnormalities found, 17% of them involved chromosome 11, including t(9;11). Other abnormalities observed include additions, inversions, translocations involving different chromosomes. Finally, there is a correlation between the abnormalities found in our study and the stratification of risk classification proposed by the IPSS-R.

Speaker Biography

Marcelo F Rosales completed his degree of specialist in diagnostic hematology by laboratory in 2012 at the Institute of Hematopathology in Mexico City. He is director of the Rosales laboratory founded in 1958 in Rio Bravo Tamaulipas Mexico He is currently a main professor of Hematology courses in the northern area of Tamaulipas and is a collaborator of the Leading Cytogenetic Laboratory in Mexico, Mendel Laboratory

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Cell-mediated immunotherapy of cancer by intentionally mismatched donor lymphocytes

Shimon Slavin

Biotherapy International, Israel

Chemotherapy-resistant hematopoietic malignancies and metastatic solid tumors remain incurable due to residual multi-drug resistant cancer cells after conventional anti-cancer modalities and cancer stem cells that are a priori resistant to available anti-cancer modalities. We have previously documented that patients with hematological malignancies fully resistant to myeloablative chemoradiotherapy may be cured by donor lymphocyte infusion [DLI] following failure of myeloablative stem cell transplantation (SCT), indicating that alloreactive lymphocytes can eliminate "the last cancer cell" regardless of resistance to all available anti-cancer modalities. When immunotherapy by donor lymphocytes is applied following allogeneic SCT, elimination of resistant cancer cells may be accomplished at the cost of hazardous, not infrequently fatal, acute and chronic graft-vs-host disease [GVHD]. We have developed a new approach for elimination of resistant malignant cells using safe outpatient procedure based on the use of intentionally mismatched, related haploidentical or even unrelated donor lymphocytes, activated in vitro and in vivo with low dose interleukin 2 [IL-2] including activated T & NK cells. No GVHD develops because intentionally mismatched killer cells are always rejected after less than 7-10 days, before there is any chance for GVHD to develop. IL-2 activated intentionally mismatched donor lymphocytes, including T cells and NK cells, can induce very potent anti-cancer effects without causing GVHD. Anti-cancer effects of intentionally mismatched donor lymphocytes can be further amplified by targeting killer cells against residual malignant cells using monoclonal and bispecific antibodies against antigens over-expressed on targeted malignant cells. In conclusion, accordingly, based on our successful cumulative pre-clinical experimental data and ongoing clinical experience, clinical application of intentionally mismatched killer cells at the stage of minimal residual disease may represent a simple, safe and cost-effective procedure that my result in cure in patients with otherwise incurable cancer.

Speaker Biography

Shimon Slavin is the professor of medicine and he is also the medical and scientific director at the Biotherapy International.

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Diagnostic difficulties in myelodysplasia: Role of morphology and molecular techniques in age related clonality, cytopenia and life-style choices

Manzoor Mangi
University of East Anglia, UK

Back ground: MDS are heterogenous clonal disorders ranging from single to multi-lineage cytopenia and dysplasia. The link between haematopoietic aging, clonality and bone marrow failure syndromes remains unclear. There are diagnostic difficulties. To this end we present a case of myeloneuropathy and myelodysplasia.

Methods: 47-year old care worker referred for worsening myalgia and weakness in lower limbs. She was anemic with low BMI and short stature. Neurological examination revealed loss of pin-prick/vibration up to both knees and mild tandem gait. Her Complete blood count (CBC) showed HB:82g/L,WCC:1.5x109/L,Plt:219x109/L,ANC:0.6x109/L, no blasts. All other blood and radiology investigations normal. Neutropenia got worse (WCC:0.8x109/L). A bone marrow test and molecular myeloid makers were performed. Bone marrow Fish for trisomy 8. Monosomy7,5qwerenormal.Furtherbiochemicaltestsincluding trace elements for lead, mercury, copper, zinc was performed. Lumber puncture and CSF examination was unremarkable.

Results: Trace element results show normal levels of Selenium, lead and mercury. Serum iron and Vit D was low. Serum Copper low <1.0 (NR=11-22umol/L). 24-hour urinary copper was low at 0.06umol/L (NR: 0.1-1), high ceruloplasmin, raised serum zinc 27.1umol/L (NR:11-22) . Patients diet and Upper GI endoscopy normal. Patient was commenced on Iv copper and Iron, no growth factors or blood products were used. Further investigations revealed that patient has been using dentures for 16-years and some of the denture cream/glue contain zinc which may have caused zinc overload and neurological symptoms.

Conclusions: In patients with unexplained neutropenia and anemia, trace elements and copper level should be checked and denture questions should be asked in patients with MDS/cytopenia.

Speaker Biography

Manzoor Mangi is a Consultant Haematologist and Hon. Senior Lecturer Norwich Medical School.

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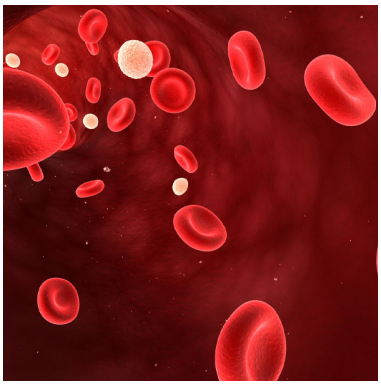


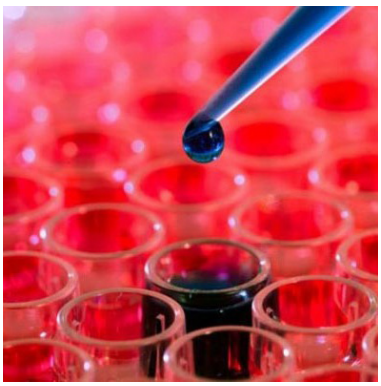


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Jan Michiels

Good Heart Centre, The Netherlands

Novel insights in the diagnosis and classification of autosomal recessive and dominant von Willebrand diseases anno 2018

The European Clinica Laboratory and Molecular (ECLM) criteria define 10 distinct von Willebrand diseases (VWD) due to mutations in the D1, D2, D', D3, A1, A2, A3, D4, C1-6 and CK domains of the von Willebrand factor (VWF) gene: recessive VWD type 3, severe type 1, 2C and 2N; dominant VWD type 1 clearance (C), secretion (SD) or clearance/secretion defect (CSD); dominant VWD 2A, 2B, 2E, 2M and 2D; and mild type 1 (Low VWF) frequentl carriers of recessive VWD. Recessive VWD type 3 is caused by homozygous or heterozygous double null mutations as the cause of recessive pseudo-hemophilia first described by Erik von Willebrand. Recessive VWDs type 1 are mainly caused by homozygous or double heterozygous missense secretion defective mutations in the D1, D2, D4 or C1-6 domains of the VWF gene. Recessive VWD due to mutations in the D1 domain is featured by persistence of pro-VWF and characterized by severe secretion and FVIII binding defect and therefore mimicking VWD type 3. Recessive VWD 2C due to mutations in the D2 domain are featured by secretion and multimerization defect and no clearance defect. Recessive VWD 2N is a mild hemophilia due to mutations in the D'-FVIII binding domain. The VWF function and multimers are normal in noncysteine 2N mutations and defective in cystein 2N mutations in the D'domain, whereas the 1060 2N mutation in the D3 show a hybrid 2N/2E VWD phenotype. Dominant VWD 1E or 2E are caused by heterozygous missense mutations in the D3 domain and are featured by variable degrees of secretion (SD) multimerization and clearance (C) defects. VWD 1C as the most pronounced clearance defect is caused by the Vincenza mutation R1205H in the D3 domain. Dominant VWD 2B is caused by a gain of function mutation in the A1 domain showing spontaneous interaction between VWD 2B mutant and platelet glycoprotein Ib (GPIb) with the consequence of increased ristocetine-induced platelet aggregation (RIPA) followed by increased proteolysis at the VWF cleavage site leading to the loss of large VWF multimers mimicking VWD type 2A. Dominant VWD 2M is due to loss of RIPA function mutations in the A1 domain and characterized by decreased (RIPA), decreased VWF:RCo as compared to VWF:CB (I-III), with normal or smeary VWF multimers or some loss of large mutimers, a poor response of VWF:RCo and normal response of VWF:CB to DDAVP. Dominant VWD type 2A are hypersensitive to ADAMTS13 (VWF cleavage protein) caused by mutations in the A2 domain of the VWF gene, which results in proteolysis of large VWF multimers by ADAMTS13 into VWF degradation products resulting in the loss of large VWF multimers, triplet structure of VWF bands and decreased ratios of both VWF:RCo/Ag and VWF:CB/Ag. A new category of secretion and/or clearance defects are due to mutations in the D4 and C1-6 domains. The D4 and C1-6 mutations in the VWF gene mainly consist of two groups of VWD type 1 secretion defects (SD) those with normal VWF multimers and those with a smeary VWF multimeric pattern. Homozygosity or double heterozygosity null or missense mutation in the C1-6 domain produce recessive severe type 1 VWD with smeary VWF multimers (eg mutation 2362). VWD mutations in the CK dimerization domain of the VWF gene produce dominant or recessive VWD type 2D (or even recessive type 1) featured by the loss of large VWF multimers and intervening VWF subbands.

Speaker Biography

Jan Michiels Professor of Nature Medicine & Health Blood Coagulation & Vascular Medicine Center in Netherlands. He also serves as an Editorial board member for many scientific journals

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