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Heparin-induced thrombocytopenia (HIT) is the most important non-hemorrhagic complication of heparin treatment. We report a case of a major thromboembolic event accompanied by thrombocytopenia following heparin exposure during coronary artery bypass graft surgery. Thrombocytopenia was documented one month after the surgery, and a major thromboembolic event which led to the patient's death diagnosed 6 weeks after heparin exposure.
We discuss the pathophysiology and clinical aspects of heparin-induced thrombocytopenia, focusing on the unique features of this patient, including late persistent thrombocytopenia. ●

TREATMENT OF IMMUNE THROMBOCYTOPENIC PURPURA IN ADULTS: UPDATE

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Primary immune thrombocytopenic purpura (ITP) is an acquired immune-mediated disorder characterized by isolated thrombocytopenia (platelet count less than $100X10^9/L$), caused by IgG autoantibodies which bind to platelets and megakaryocyte, T cell-mediated platelet destruction and impaired megakaryocytic function. Symptoms can manifest as petechiae, purpura, mucosal bleeding and rarely fatal intracranial hemorrhage, as well as reduced quality of life. A wide range of bleeding manifestations exists and it is impossible to tell who will bleed, when and where. The goal of treatment is to prevent severe/life-threatening bleeding. Treatment modalities target various aspects of ITP pathophysiology such as the inhibition of autoantibody production (decreased autoimmune process), modulation of T cell activity (with prolongation of platelets survival), and stimulation of platelet production.
The American Society of Hematology and the International Society of Thrombosis and Hemostasis published guidelines on the treatment of ITP patients, where first line treatment focuses on inhibition of autoantibody production and platelet degradation, second-line treatments include immunosuppressive drugs and splenectomy, and third-line treatments aim to stimulate platelet production by megakaryocytes. New available strategies might change the order of treatment lines. As in other situations, treatment should be tailored according to the patient's age, life style, comorbidities and compliance. ●

PRACTICAL ADVICE FOR THE APPROPRIATE USE OF DIRECT ORAL ANTICOAGULANTS

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The direct oral anticoagulants (DOACs) are a class of drugs used for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and for prevention and treatment of venous thrombo-embolism. They are as effective and are safer than the vitamin K antagonists that were the oral drugs previously used for this purpose. The DOACs are convenient to use because of their fixed dose-response relationship which makes routine monitoring of drug levels unnecessary. Further, they have no food interactions and relatively few drug interactions.
A number of practical considerations related to the routine clinical use of the DOACs have become apparent. These include choosing the appropriate drug and importantly dose-based on patient characteristics, managing the use of DOACs peri-operatively and the appropriate management of the acutely bleeding DOAC-treated patient. Recent controlled and observational studies provide guidance for dealing with these clinical situations thus enhancing the efficacy and safety of DOAC treatment in routine clinical practice. ●

כרוניקה

פירוק חלבון טאו במחלת אלצהיימר

חילוף החומרים של כולסטרול קשור לפתוגנזה של מחלת אלצהיימר, אך המסלולים המעורבים בכך אינם ברורים.
ואן דר קאנט וחב' (Cell Stem Cell 2018;10.1016/j.stem.2018.12.013) מצאו כי כולסטרול קשור עם זירחון של חלבון טאו בתאי עצב, חלבון הידוע כסמן למחלת אלצהיימר. המחקר סרק חומרים כדי למצוא כאלה המסוגלים לחסום הצטברות חלבון טאו מזורחן בתאי עצב שהתקבלו מחולי אלצהיימר. הממצאים הצביעו כי חומרים שהפחיתו יצירת כולסטריל־אסטר (CE) גם הפחיתו הצטברות חלבון טאו מזורחן. החומרים הפעילים כללו סטטינים, החוסמים יצירת כולסטרול, וחומרים נוספים המשנים את מסלולי חילוף החומרים של כולסטרול לכיוון של CE או 24 הידרוקסי־כולסטרול. הפחתת ריכוז CE בתאי העצב היה קשור עם הגברת פירוק חלבון טאו מזורחן בעזרת הפרוטאוזום.

איתן ישראלי

Methods: FGL2 procoagulant activity levels were examined in peripheral blood cell samples of 93 patients with clinical diagnosis of various bacterial or viral infections or autoimmune diseases, and 39 healthy controls. Activity was determined according to clotting time measurements. Clinical and demographic data was collected.

Results: FGL2 activity in peripheral blood samples of healthy individuals and patients was rather similar. Moreover, no significant correlation was detected between measured FGL2 activity and clinical or demographic data of the patients. The range of activities was rather broad, indicating high variance (up to 2.5-fold from average) in the basal activity levels in the population.

Conclusion: The presence of infectious/autoimmune diseases does not significantly alter FGL2 activity in the peripheral blood.

Discussion and summary: While FGL2 activity in the blood is affected by malignancies such as lymphomas, the presence of inflammatory/infectious diseases does not significantly influence basal FGL2 activity. The broad range of FGL2 activities in tested samples indicates that FGL2 is a better marker for follow up implications than diagnostic screening.

PREGNANCY RELATED ACQUIRED HEMOPHILIA A

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Acquired hemophilia A is a rare disease. The incidence has been estimated to be 1.3-1.5 cases per 1 million persons per year. The etiology of acquired hemophilia A varies. It may develop in patients with autoimmune disorders, hematologic and solid cancers or in women during pregnancy or following childbirth. In about half of the cases no underlying disease can be found. The clinical picture is dominated by severe soft tissue hematomas especially in the cases of pregnancy-related acquired hemophilia A. Unlike congenital hemophilia A, bleeding into joints is rare.

Pregnancy-related acquired hemophilia A may develop following any pregnancy but is observed more often in primigravidas. In most cases it arises in the postpartum period, most commonly 1-4 months after delivery. If factor VIII inhibitors develop during pregnancy or labor, they are frequently associated with severe uterine bleeding. The prognosis of pregnancy-related acquired hemophilia A is good with a high percentage of spontaneous remissions especially if the inhibitor was detected postpartum. Patients with acquired inhibitors do not usually have personal or family history of bleeding tendency, thus it is the presence of bleeding at multiple sites with prolonged activated partial thromboplastin time not corrected by incubation with normal plasma (mixing study) that raises the suspicion of inhibitor. Prompt diagnosis and treatment achieved by close collaboration among gynecologists and hematologists may improve the prognosis and prevent severe bleeding.

PEDIATRIC VENOUS THROMBOEMBOLISM – A COHORT STUDY IN A TERTIARY CENTER

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Introduction: Deep Venous Thrombosis (DVT) is rare among children, yet may yield high morbidity and mortality. Due to the limited data regarding pediatric DVT, its management has been adopted from adults' protocols. Recent research reported associations of DVT and strokes with genetic thrombophilia, especially in the presence of transient risk factors (e.g.: hospitalization, malignancy, central venous lines...).

Aim: To evaluate the influence of risk factors within our pediatric DVT cohort of a tertiary center upon treatment and prognosis.

Methods: Retrospective analysis of prospectively collected data at the Sheba Medical Center.

Results: During the period 2014-2017, 76 out of 150 cases of acute DVT diagnosed at our center were fully followed. Upper extremity DVT was most commonly observed. Malignancy and a central venous line (CVL) were the most abundant risk factors. Genetic thrombophilia was diagnosed in one third of the cases. The majority of patients were treated with low molecular weight heparin for at least 3 months and 13% continued prolonged anti-coagulation treatment. Neither thrombophilia nor cancer affected the outcome.

Discussion and summation: Our results confirm previously published data indicating that malignancy and CVL are the most common risk factors associated with DVT in children, making the upper extremity the most common location of thrombosis. Neither the type of cancer nor genetic thrombophilia was found to be associated with treatment outcome, but they did influence the treatment duration. Risk factors influence the pathogenesis of DVT and influence the duration of treatment.

THROMBOCYTOPENIA, LEG EDEMA AND SHORTNESS OF BREATH FOLLOWING CORONARY ARTERY BYPASS SURGERY

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showed good response to Clopidogrel in 72 hours but not in 24 hours after its loading. Preterm cord blood platelets showed decreased ADP-induced activation in both activation markers: PAC1 and p-selectin, but only p-selectin reached statistical significance. We identified possible platelet activation markers in response to commonly used agonists' stimulation for FC analysis.

Conclusion: FC analysis of platelet function has added value in the diagnosis of impaired platelet function and anti-platelet drug response. Using FC enables us to test platelet function in minimal blood volume and regardless of platelet count. Identification of the unique activation marker for each agonist is prerequisite for FC analysis of platelet function.

HEMOPHILIA – A ROYAL DISEASE IN THE HOLY LAND

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Introduction: Hemophilia is a hereditary congenital hemorrhagic diathesis caused by mutations in blood coagulation factor VIII (FVIII) or IX (FIX) genes, causing hemophilia A and B, respectively. Most cases are familial but a significant minority is sporadic.

Objective: To examine the presenting symptoms of patients with hemophilia in Israel and identify causes for delay in diagnosis.

Methods: Retrospective analysis of data from medical files of newly diagnosed patients with hemophilia during the period from 1st January 2010 to 31st December 2017.

Results: During the study period 104 children had been diagnosed with hemophilia. Fifteen percent were diagnosed with hemophilia B and 85% with hemophilia A. In most familial cases the diagnosis was established by examination of aPTT and the level of the relevant clotting factor shortly after birth. Diagnosis of sporadic cases (40 cases) was performed due to suggestive clinical symptoms. Perinatal complications were observed in 6 newborns. The most common presenting symptom was disproportionate bleeding following circumcision. In 6/21 patients who experienced excessive bleeding following circumcision there was a delay in diagnosis. Severe bleeding requiring intensive care admission was observed in twelve neonates.

Discussion: Diagnosis of hemophilia in Israel is made at an earlier age than in Europe. This is probably due to the performance of ritual circumcision during the neonatal period. In recent years a reduction in familial cases of severe hemophilia has been noted due to genetic counseling of hemophilia carriers. In cases of excessive bleeding following circumcision aPTT and PT should be examined promptly.

ELABORATION AND TREATMENT DECISION IN INCIDENTAL SPLANCHNIC VEIN THROMBOSIS

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In the present article, a patient with incidental findings in computerized tomography (CT) of cavernous transformation of the splanchnic veins, thrombosis of the splenic and portal veins, esophagus and gastric varicose veins and splenomegaly is presented. The CT was performed due to mild chronic normocytic anemia known for two years and the elevated level of LDH (Lactic dehydrogenase). Although usually such incidental findings without cirrhosis do not necessitate anticoagulation therapy according to the literature, in cases of myeloproliferative diseases, anticoagulation is required in order to prevent thrombus propagation. The Calreticulin (CALR) mutation is associated with more bleeding tendency and less thrombotic manifestations while the Janus kinase 2 V617F (JAK-2) mutation increases the risk of thrombosis. In the present article, we present the case report and review the relevant literature.

THE EFFECT OF INFECTIOUS AND AUTOIMMUNE DISEASES ON PROCOAGULANT ACTIVITY OF FIBRINOGEN-LIKE PROTEIN 2 IN THE PERIPHERAL BLOOD

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Background: Fibrinogen-like protein 2 (FGL2) is a novel prothrombinase capable of initiating thrombin generation independent of the classical coagulation pathway. FGL2 is involved in immune-coagulation response. Considering the tight relationship between coagulation and cancer, FGL2 had been suggested to be utilized as a potential biomarker for cancer. Recently, we have shown that FGL2 activity is increased in blood of B-cell lymphoma patients and decreased during remission. However, it is unclear whether FGL2 activity is simultaneously affected by the presence of conditions other than cancer.

Aim: In this article we address the effect of bacterial or viral infections as well as autoimmune diseases on FGL2 activity in the blood.

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Background: The diagnosis of heparin-induced thrombocytopenia (HIT) requires clinical data and laboratory detection of platelet activating factor 4/heparin (PF4/H) antibodies by immunological or functional assays. Although antigen screening assays are widely used, the functional assays are performed only by several expert labs.
Aims: To analyze the experience of a tertiary medical center in clinical and laboratory diagnosis of suspected HIT.
Methods: A retrospective review of the Hematology Laboratory database on patients evaluated between the years 2008-2016 at Rambam, identified 412 individuals with clinical suspicion of HIT. Till 2011, 135 cases were screened using particle gel PaGIA (Biorad) and between the years 2012-2016, a total of 277 cases were screened by lateral flow Milenia (Biotec GmbH). All patients diagnosed with HIT were treated with Fondaparinux (Arixtra). Functional assay with heparin/LMWH induced platelet aggregation was performed using light transmission aggregometry (Helena AggRAM) to validate borderline or positive results in indistinct cases.
Results: From the tested samples, 63% vs. 75% were negative in PaGIA and Milenia, respectively (P=0.03), and were considered negative for HIT. During 2008-2011, only 38% of cases with non-negative immunoassay results underwent functional aggregation, whereas, in 2012-2016, 83% of such cases were further evaluated. None of the borderline PaGIA samples was positive in the functional assay compared to 13.3% borderline Milenia results; 25% of positive PaGIA and 51.7% of positive Milenia were confirmed by a positive functional HIT assay (P=N.S.). The survival rate among 14 patients with a positive functional assay was 42.7 % (6 patients).
Conclusions: The Milenia assay introduced at our lab in 2012, has improved the screening process. The functional assay provides a more accurate HIT diagnosis. The combined approach of an optimal laboratory and clinical investigation is crucial to obtain a precise HIT diagnosis.

ACQUIRED HEMOPHILIA A AND THE TIMING OF IMMUNOMODULATORY THERAPY

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Acquired hemophilia A is an autoimmune disease affecting men and women equally and is idiopathic in 50% of the cases. As the mortality rate reaches 50%, prompt diagnosis and treatment are needed. Diagnosis is made in a patient with a bleeding manifestation and prolonged PTT (partial thromboplastin time) that is not corrected in a mixing study with normal plasma. The level of antibodies in the plasma is measured by Bethesda units and a level above 5 units is considered high. Patients with a high titer of antibodies are treated with factor VIII, prothrombin complex, recombinant factor VIIa and tranexamic acid, in combination with immunomodulatory therapy, including steroids, cyclophosphamide, rituximab and immunoglobulins. The timing of rituximab therapy remains debatable.
To date, it has not been established whether to use it as a first-line or second-line therapy. According to the currently available literature that relies on a database, the use of rituximab as a first-line modality increased survival without increasing the rate of infections, compared to steroids alone or steroids combined with cyclophosphamide.
The current article describes a 79-year old woman who presented with diffuse hematomas in the limbs. A rapid diagnosis and treatment, including factor VIII, tranexamic acid, steroids, cyclophosphamide and rituximab as a first-line therapy, facilitated her complete recovery at a one-year follow-up.

PLATELETS FUNCTION IN A DROP OF BLOOD: FLOW CYTOMETRY ANALYSIS COMPARED TO PLATELET AGGREGATION

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Introduction: Light transmission aggregometry (LTA) is the most commonly used test for the diagnosis of platelet function disorders, but requires large amounts of blood samples and normal platelet count.
Objectives: To compare flow cytometric (FC) platelet function testing to standard LTA in the general population, in patients treated with anti-platelets drugs and in term and preterm neonates.
Methods: Platelet function was assessed with LTA and FC using PAC1 binding and p-selectin expression, as platelet activation markers, in response to agonist activation. A comparison between LTA and FC was performed in a Clopidogrel treated patient, before and after (24 and 72 hours) loading the drug. The platelet activation markers PAC1 and p-selectin, were compared in umbilical cord blood samples of in-term and preterm neonates.
Results: ADP-induced platelet aggregation was comparable to p-selectin expression assayed by FC (r=0.79-0.86) as measured before and after Clopidogrel loading. Both tests

COAGULATION – A PHYSIOLOGICAL SYSTEM INTERFACING ALL OTHER BODY SYSTEMS

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The coagulation system is a rapidly advancing area of clinical and basic research. Among the critical clinical issues to be urgently addressed are those related to the application of new direct oral anticoagulants in real life. Extensive research in the challenging field of thrombosis and bleeding is ongoing and has already resulted in new pharmacological modalities such as siRNA. The well-established close association between coagulation and cancer provides a strong incentive for developing drugs capable of interfering with the coagulation system and attenuating tumor growth. The multifaceted research field in coagulation requires dedicating specialized personnel in the hospitals along with bridging staff mediating between the hospital and the outpatient clinics to ensure proper patient management.

RISK FACTORS ASSOCIATED WITH THE DEVELOPMENT OF UPPER EXTREMITY DEEP VEIN THROMBOSIS FOLLOWING PERIPHERALLY INSERTED CENTRAL CATHETER INSERTION

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Background: The occurrence of upper extremity deep vein thrombosis (UEDVT) is not uncommon following peripherally inserted central catheter (PICC) insertion. However, the risk factors associated with this condition are unknown. Moreover, the role of prophylactic anticoagulation in the prevention of PICC-related UEDVT is not well established.
Methods: A review of the medical records of all patients who underwent PICC insertion during 2016 at the Hadassah Medical Center.
Results: Overall, 500 patients underwent PICC insertion during the study period. Of them, 199 (39.8%) received prophylactic anticoagulation following insertion. Patients with active cancer were less likely to receive prophylactic anticoagulation. Twenty-five (5.0%) patients experienced PICC-related UEDVT, which occurred after a median of 8 days following PICC placement. The only factors associated with the development of UEDVT were the presence of active cancer (P=0.04) and higher C-reactive protein level (P=0.02). The rate of UEDVT was comparable between those who received prophylactic anticoagulation and those who did not (P=0.98)
Conclusion: PICC-related UEDVT is a common complication. Active cancer and higher baseline C-reactive protein level were associated with the occurrence of this condition. Future studies are warranted to confirm our findings and further assess the role of prophylactic anticoagulation in this setting.

FETAL/NEONATAL ALLOIMMUNE THROMBOCYTOPENIA (F/NAIT) - THE PREVALENCE VERSUS AWARENESS OF A LIFE-THREATENING CLINICAL CONDITION

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Background: In fetal/neonatal alloimmune thrombocytopenia (F/NAIT) the fetus suffers from thrombocytopenia mediated by maternal IgG antibodies directed against fetal platelets leading to intracranial hemorrhage (ICH) in about 20% of cases. The antibodies are directed against Human Platelet Antigens (HPA). Diagnosis of F/NAIT is essential because thrombocytopenia may recur and worsen in subsequent pregnancies; hence awareness of F/NAIT is crucial.
Aims: To determine the prevalence and incidence of HPA antigens and antibodies in the Israeli population and to evaluate the degree of awareness to F/NAIT in Israel.
Methods: We conducted a retrospective analysis of cases referred to the platelet immunology laboratory between the years 2011-2015 and medical records of newborns born at Rambam Medical Center during 2010-2015.
Results: Of the 322 cases studied, 175 (54.35%) had anti-platelet antibodies. The most common antibody was anti-HPA1a (41.85%) followed by anti-HPA5b (28.75%). The prevalence of HPA antigens was similar to that of the Caucasian population. About 80% of the cases were referred due to neonatal thrombocytopenia, found in a random blood count or after bleeding, and 13% of cases were referred due to suspected ICH during pregnancy. In only 22.6% of cases, the diagnosis was made immediately after birth, and 18.7% of the suspected cases were referred only during the subsequent pregnancy. About 84% of infants with severe thrombocytopenia were not referred to F/NAIT diagnosis.
Conclusions: The prevalence of platelet antigens in the Israeli population is similar to that of the Caucasian population. The paucity of referrals points to the need to establish diagnostic guidelines and raise awareness among caregivers.

EXPERIENCE IN DIAGNOSTIC ASSAYS FOR HEPARIN-INDUCED THROMBOCYTOPENIA - EXPERIENCE OF A TERTIARY HOSPITAL IN ISRAEL

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