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ABSTRACT BOOK

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Oral Communications

Thursday, April 27, 2017

New studies session

Study Proposals

DUCSDATA: a Dutch Consortium Study on Diagnostics And Treatment of Antiphospholipid syndrome

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Background: Diagnosing antiphospholipid syndrome (APS) is, despite defined laboratory and clinical criteria, still challenging. APS is a rare disease and diagnostics are laborious. Laboratory tests are non-robust, and diagnostics are not standardized. The position of non-criteria antiphospholipid antibodies (aPL; such as anti-phosphatidylethanolamin (aPE) IgG/M, anti-prothrombin/phosphatidylserin (anti-PS/PT) IgG/M, and anti-annexin V IgG) is undetermined. Besides the diagnostic dilemmas, clinical difficulties arise on how to view and treat the non-criteria APS manifestations such as renal involvement, chorea, livedo reticularis and Libman-Sacks endocarditis. A clinical useful and reliable risk stratification, leading to more personalized treatment, is still lacking. Optimization of treatment starts with identification of – subgroups of – APS-patients. Standardized aPL diagnostics, including the non-criteria aPL, is the first step towards better identification.

Objectives: To estimate the prevalence and incidence of primary and secondary APS in the Netherlands; To standardize aPL-diagnostics within the Netherlands; To correlate (non-criteria-)aPL with clinical signs and symptoms; To develop a risk stratification system for APS patients, including the non-criteria aPLs and symptoms.

Methods: All academic medical hospitals in the Netherlands will send in citrated blood samples (at least two samples 12 weeks apart) from all primary and secondary APS patients for centralized aPL-diagnostics – including non-criteria aPL – at the University Medical Center Utrecht. Central aPL-results will be compared with results from the referring centers for quality assessment. Per center, clinical data related to APS will be gathered and stored in a central database. An estimated 500 APS patients will be included in this database. Presence of aPL and other auto-antibodies, presence of other autoimmune diseases, clinical signs and symptoms, and treatment regimens will be correlated. Clinical outcomes are defined as any thrombotic event (venous or arterial), obstetric complications, renal insufficiency, Libman-Sacks endocarditis, livedo reticularis, chorea and catastrophic APS. By means of logistic regression, a risk stratification system will be developed.

INSPIRE: the first Italian inception cohort of subjects positive for anti-phospholipid antibodies

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Background: Epidemiological and methodological data about testing for antiphospholipid antibodies (aPL) in general laboratories in Italy are lacking.

Objectives: FIRMA (Forum Interdisciplinare per la Ricerca nelle Malattie Autoimmuni), the Italian branch of EASI founded in the 90s and devoted to research in autoantibody field, is promoting a national prospective study, named INSPIRE (Italian Survey on Antiphospholipid antibody positive individuals [aPL Register]), which will be the first Italian inception cohort of aPL-positive individuals.

Methods: Subjects will be recruited when testing positive for the first time ever for one or more criteria aPL tests (anti-cardiolipin and anti- β 2GPI IgG/IgM, lupus anticoagulant), at any titre. Patients with previously known aPL positivity will not be eligible for study inclusion. Blood will be drawn 12 weeks after the first sampling to confirm autoantibody positivity; aPL tests will be repeated in a single core laboratory

for confirmation. Demographic and clinical data (thrombosis, pregnancy complications, non-criteria clinical manifestations, systemic autoimmune disease, cardiovascular risk-factors, treatment) will be entered in a web-based REDCap registry. The study will last 3 years (one year of enrolment; two years of follow-up).

Results: At least 10 FIRMA centres will participate with a minimum number of 30 enrolled subjects per centre, yielding to a study cohort of 300-400 aPL positive patients. INSPIRE will allow to: i) quantify aPL positivity rate in Italian laboratories; ii) assess the frequency of positive aPL confirmed at 12 weeks; iii) evaluate the clinical reasons for aPL testing; iv) collect data on aPL testing (reagents, techniques, reference ranges), estimating the reliability of results between different Italian laboratories; v) acquire demographic and clinical follow-up data in the first year(s) after aPL-positivity.

Conclusions: INSPIRE, an Italian inception cohort of aPL-positive subjects, will allow to collect evidence on several, still unravelled, clinical and methodological aspects of "real life" aPL testing.

The obstetric risk and the effect of treatment in women with low titer anti-phospholipid antibodies

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Background: Persistent positivity for anti-phospholipid antibodies (aPL) at medium-high titres is required to diagnose anti-phospholipid syndrome (APS), but an increasing evidence suggests the clinical relevance of low titre aPL in obstetric APS.

Objectives: To raise further evidence, we propose to plan a multi-center, longitudinal prospective study aiming at i) investigating the association of low titre aPL with pregnancy complications and ii) assessing the efficacy of treatment in reducing the obstetric risk.

Methods: Longitudinal statistical models will be applied to quantify the obstetric risk conveyed by low titre and criteria aPL. Pregnant women with persistent positivity for aPL at any titre will be prospectively recruited. Demographic and clinical data (aPL profile, pregnancy complications, thrombosis, systemic

autoimmune disease, cardiovascular risk-factors, treatment) will be collected for each pregnancy.

Results: In a preliminary monocentric study, we have retrospectively collected data on 338 pregnancies in 111 women with persistent positivity for aPL at any titre. Among women with low titre aPL, the odds of pregnancy morbidity was 1.72 in case of single positivity and 3.78 for double positivity. Criteria aPL conveyed a 2.2-fold higher risk: a single test carried an odds of 3.82, raising to 8.41 for multiple aPL. Low-dose aspirin (LDASA) led to a significant reduction of the odds of obstetric complications in women with single but not multiple aPL, irrespectively of the titre. The association of LDASA with low-molecular weight heparin allowed a significant decrease of the odds of unfavourable outcomes among all subgroups except in women with multiple criteria aPL.

Conclusions: This large study would allow to i) confirm the association of low titer aPL with pregnancy complications, precisely quantifying the magnitude of obstetric risk and assessing the impact of different aPL profiles; ii) investigate the efficacy of additional treatments, as hydroxychloroquine and low dose steroids, among women with low titre aPL.

Abstracts

Increased prothrombin conversion causes elevated thrombin generation in APS patients with prior thrombosis

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Background: The antiphospholipid syndrome (APS) is characterized by the presence of antiphospholipid antibodies directed against β 2-glycoprotein I, and is associated with an increased risk of pregnancy morbidity and thrombosis. The global hemostatic state in a patient can be tested by measuring thrombin generation (TG). Recently, we developed a method to study the main pro- and anticoagulant processes at the basis of TG, called the thrombin dynamics method.

Objectives: To investigate the dynamics of thrombin generation in APS patients with and without a history of arterial or venous thrombosis.

Methods: APS patients (n=29) without prior thrombosis (n=11) and with prior venous (n=11) and/or arterial thrombosis (n=7) were enrolled in the study after obtaining informed consent. Patients on anticoagulant therapy were excluded from the study. TG was measured at 5 pM tissue factor (TF) and the dynamics of TG were determined by quantifying prothrombin conversion and thrombin inactivation.

Results: Thrombin generation was significantly enhanced in patients with prior thrombosis compared to patients without prior thrombosis (peak +18%, p=0.001 and ETP +40%, p=0.026), but the lag time did not differ. The pro- and anticoagulant processes underlying TG were studied to identify the cause of elevated TG in APS patients with thrombosis. The total amount of prothrombin conversion (+32%, p=0.028) and the maximum rate of prothrombin conversion (+23%, p=0.041) was elevated in APS patients with thrombosis, but the thrombin decay rate was comparable between the two patient groups.

Conclusions: Prothrombin conversion is elevated in APS patients that previously developed thrombosis, whereas thrombin inactivation is unchanged. This causes an imbalance between pro- and anticoagulant mechanisms, resulting in an increase of thrombin generation peak height and ETP.

Thrombin activatable fibrinolysis inhibitor (TAFI) – a possible link between coagulation and complement activation in the antiphospholipid syndrome (APS)

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Background: Thrombosis and complement activation are pathogenic features of antiphospholipid syndrome (APS). Their molecular link is plasma carboxypeptidase-B, also known as thrombin

activatable fibrinolysis inhibitor (TAFI), which plays a dual role: anti-fibrinolytic, by cleaving carboxyl-terminal lysine residues from partially degraded fibrin, and anti-inflammatory, by downregulating complement anaphylatoxins C3a and C5a.

Aim: To investigate the levels of TAFI (proenzyme) and TAFIa (active enzyme) in relation to complement activation, fibrin clot permeability and fibrinolytic function in clinical and immunological subsets of 52 APS patients and 15 controls.

Results: TAFI (p<0.001), TAFIa (p<0.05) and complement factor C5a (p<0.001) were increased, while fibrin permeability (p<0.01) was decreased and CLT was prolonged (p<0.05) in APS patients compared to controls. Furthermore, TAFIa was increased (p<0.01) in samples from APS patients affected by arterial thrombosis compared to other APS-phenotypes. Positive associations were found between TAFI and age, fibrinogen and C5a, and between TAFIa and age, fibrinogen and thrombomodulin.

Conclusion: TAFI and TAFIa levels were increased in patients with APS as a potential response to complement activation. Interestingly, TAFI activation was associated with arterial thrombotic APS manifestations. Thus, TAFIa may be considered a novel biomarker for arterial thrombosis in APS.

Lessons From The National Antiphospholipid Syndrome Cohort: Criteria And Non-Criteria Manifestations

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Background: the National Registry provides a good basis for evaluating APS diagnostic and management challenges in every country.

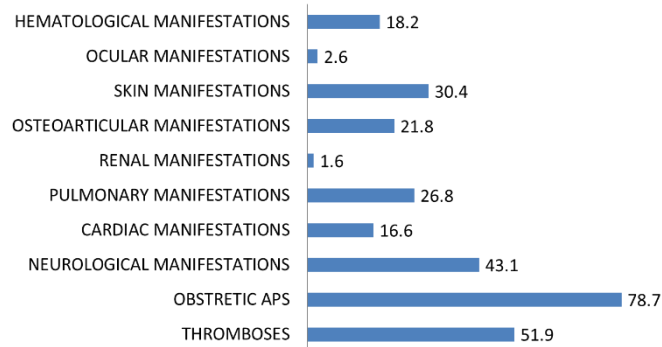
Material And Methods: We evaluated a total of 545 Caucasian APS patients; 385 had PAPS (79.0% female and 21.0%, male mean age 43.92±12.87 years), and 160 had SAPS (89.4% female and 10.6%, male mean age 47.42±14.66 years). Patients were included in Registry prospectively from the 2000 year. All patients were evaluated for the presence of aPL: LA, aCL IgG/IgM, β2GP-1 IgG/IgM. Prevalence of the diagnostic criteria (obstetric APS and arterial and/or venous thromboses) have been determined. On the grounds of, in our Center established, multidisciplinary approach regarding the diagnose and

treatment of APS patients, we were able to diagnose different system involvement, including NON-CRITERIA MANIFESTATIONS: neurological (stroke, chorea, epi, migraine, multiinfarct dementia, cerebral venous sinus thrombosis), cardiac (stable or nonstable coronary artery disease, myocardial infarction, valve dysfunction and thickening of the leaflets, vegetations/ pseudoinfective endocarditis), pulmonary (pulmonary infarction, pulmonary hypertension, major pulmonary embolism, pulmonary microthromboses, ARDS), renal (renal infarctions and vein thrombosis), osteoarticular (avascular necrosis, arthritis), skin (livedo reticularis, skin ulcerations, pseudovasculitic, digital gangrene), ocular (amaurosis fugax, retinal vein and artery thrombosis, optic neuropathy), and hematological manifestations (thrombocytopenia, autoimmune hemolytic anemia, leucopenia). Prevalence of the standard atherosclerotic risk factors has also been evaluated.

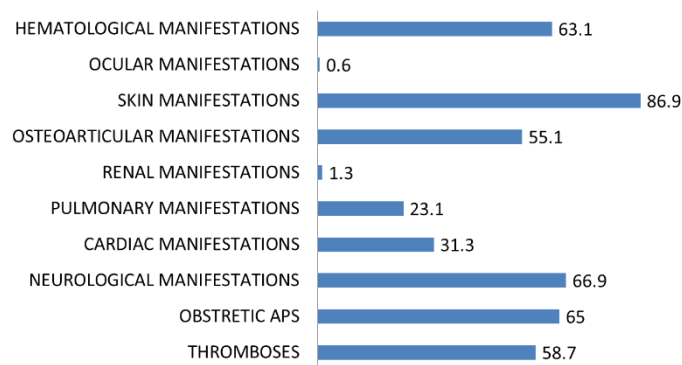
Results: Among PAPS group there was 1.6% of patients with catastrophic APS (CAPS) and among SAPS group prevalence was higher – 6.9%. Those patients were included in international CAPS registry. Mortality of PAPS patients was 1.6% and SAPS patients 15.0%. Prevalences of all manifestations are presented on Graph 1 and Graph 2. Chorea, epilepsy, livedo reticularis, pseudovasculitis, skin ulcerations and trombocytopenia were observed significantly more frequently in patients with SAPS. Prevalences of the aPL analyzed are presented on Graph 3 and Graph 4. Prevalence of the standard atherosclerotic risk factors was below 40% in both groups. In SAPS, high aCL IgG levels were more common in major pulmonary arterial thrombosis ($p=0.006$), medium aCL IgG levels in ARDS ($p=0.047$). LA correlated with pulmonary embolism ($p=0.03$) and microthrombosis ($p=0.03$) in SAPS, and with pulmonary microthrombosis ($p=0.03$) in PAPS.

Conclusion: Variety of the manifestations of the APS emphasizes the need of multidisciplinary approach regarding diagnose and treatment of this population of patients. National registries and proper follow up are essential.

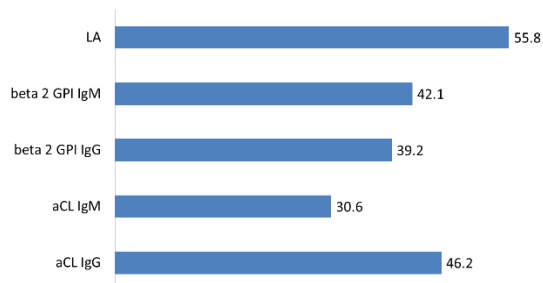
Graph 1: Prevalence of different manifestations in patients with PAPS



Graph 2: Prevalence of different manifestations in patients with SAPS



Graph 3: Prevalence of different aPL in PAPS group



Graph 4: Prevalence of different aPL in SAPS group



aPS/PT antibodies: a clue to predict intrauterine growth restriction and preeclampsia in APS patients

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Background: Antiphospholipid syndrome (APS) is associated with adverse perinatal outcomes. Antiphosphatidylserine / prothrombin antibodies (aPS/PT) recognize the phosphatidylserine / prothrombin complex and are associated with standard aPL. They might play a pathogenetic role in thrombosis in SLE patients, but relatively little is known about the association with pregnancy complications.

Objectives: To evaluate the possible association between aPS/PT and pregnancy complications in APS patients.

Methods: In order to address this issue, we enrolled 47 APS patients that experienced a pregnancy prospectively followed in the Clinic (27 from University Hospital of Padova and 20 from Ospedale San Raffaele, Milan) and characterized their aPL profile. In particular aPS/PT were assessed using QUANTA Lite ELISA tests (INOVA Diagnostic Inc).

Results: 33/47(70%) were aPS/PT+, 14/47(30%) aPS/PT-. Eighteen were Triple positivity, defined as patients with the simultaneous presence of anticardiolipin (aCL) antibodies, anti β 2 glycoprotein I (a β 2GPI) antibodies, lupus-like anticoagulant (LLAC), and 17 of them were also aPS/PT+. 41/47 patients delivered an alive baby. The mean gestational week and the mean newborn weight at delivery were significantly lower in aPS/PT+ than aPS/PT- (33.1 \pm 4.7 vs 36.2 \pm 3.4 weeks and 2058 \pm 964 vs 2784 \pm 746g). Late pregnancy complications, in particular intrauterine growth restriction and/or preeclampsia (IUGR&preecl), remained frequent in aPS/PT+ patients despite the therapy (low dose aspirin associated with low molecular weight heparin) during pregnancy. IUGR&preecl occurred in 18 patients: seventeen were aPS/PT+ (p<0005). Interestingly this event didn't depend on the presence of the Triple positivity (Figure1). We also noticed a significant correlation between high titer of aPS/PT IgG and low neonatal weight at delivery (p<0.005).

Conclusions: These data suggest that aPS/PT are promising markers of aPL-related pregnancy complications, in particular IUGR&preecl,

independently from the Triple positivity. These data encourage the extension of these investigations to larger cohorts of patients.

Thrombotic manifestations in antiphospholipid antibody-related to virus infections

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Background: Viral infections can become a risk factor for the development of thrombotic events. It has been hypothesized that virus could provoke an endothelial injury that temporally facilitated the apparition of autoantibodies, particularly antiphospholipid antibodies (aPL). However, many authors agree with the non-pathogenic-thrombotic role of these autoantibodies.

Objectives: To evaluate the role of viral infections in the development of thrombotic events associating aPL transitory (or permanent) positivity.

Methods: Currently, prospective, observational study that include cases with current virosis and thrombotic manifestation, looking for the association with aPL are conducting in two teaching hospitals in Barcelona area's (Spain). A panel of aPL according to Sydney recommendations were performed. A battery of virus serological tests were also yielded. Normal PT and APPT test were observed in all previous patient's blood tests.

Results: To date we have collected 15 cases with a demonstrated acute virosis and an aPL positive results with a thrombotic manifestation. 3 cases were positive for Influenza A H1N1,3 for Epstein-Barr virus, 3 for CMV, 3 for Parvovirus B19, 1 for RSV, 1 for HCV and 1 case for Rotavirus. Lupus anticoagulant (L A) positivity was showed in all cases, and 6 cases also tested positive for IgM anticardiolipin antibody. No patients tested positive for anti- β 2GPI antibodies. Unfortunately, anti-prothrombin antibodies could not be analysed. The clinical manifestations were: pulmonary embolism (5 cases), leg deep venous thrombosis (3 cases), livedoid vasculopathy (3cases), splenic infarction (1 case), ovarian venous thrombosis (1 case), digital ischemia (1case) and transverse

myelitis (1 case). In addition to this we have observed how the IgM virus related antibody became negative and the aPL became negative in parallel in 10/15 cases.

Conclusions: We hypothesized that thrombotic manifestations of aPL-related viral infections are underdiagnosed, and probably in predisposed host, some viral infections may induce the transient apparition of aPL-non related to anti- β 2GPI, mainly those with LA activity with potential pathogenic thrombotic properties.

Thursday, April 27, 2017

New tests/techniques session

A thrombin generation-based assay to distinguish anti- β 2glycoprotein I and anti-prothrombin antibodies: paving the way to a better thrombotic risk assessment in patients with antiphospholipid syndrome

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Background: The antiphospholipid syndrome (APS) is characterized by thrombosis and/or pregnancy morbidity with persistent presence of antiphospholipid antibodies. Although the lupus anticoagulant (LAC) assay correlates well with thrombosis, we showed a stronger association for anti- β 2GPI -dependent LAC than conventional or β 2GPI-independent LAC.

Objectives: We aim to design a new functional thrombin generation-based assay, allowing better thrombotic risk stratification by measuring the whole scheme of coagulation of APS patients.

Methods: Thrombin generation (TG) was measured using calibrated automated thrombinography. Briefly, TG was triggered with tissue factor, kaolin, silica, ecarin or Russel's viper venom with 4 μ M phospholipids or with commercially available ellagic acid and silica based reagent in the presence or absence of 50 μ M cardiolipin vesicles. 7 LAC positive

patient samples were tested for anti- β 2GPI and anti-prothrombin positivity.

Results: In our thrombin generation based assay, a confirmation step was included by adding cardiolipin vesicles. In both normal pooled plasma (NPP) supplemented with monoclonal anti- β 2GPI (27G7) or anti-prothrombin (28F4) antibodies as well as LAC positive patient samples, activators were compared for their LAC sensitivity and ability to discriminate between β 2GPI- and prothrombin-dependent LAC. In agreement with the previously published β 2GPI-dependent LAC test, in the thrombin generation assay triggered with aPTT-LA a different pattern for the lagtime in the presence/absence of cardiolipin was observed for anti- β 2GPI compared to anti-prothrombin positive samples. Interestingly, also other triggers allowed discrimination of anti- β 2GPI from anti-prothrombin positive samples using one or a combination of different thrombin generation parameters.

Conclusions: We have developed a functional β 2GPI-dependent thrombin generation-based assay which is able to detect LAC and discriminate between β 2GPI- or prothrombin-dependent LAC. The added clinical value of this assay, e.g. in the prediction of thrombosis and/or pregnancy complications, will be further investigated in a large multicentre study consisting of well-characterized APS patients, diseased and healthy controls.

Antiphospholipid antibody titer stability after repeated freeze-thaw cycle: Solid as a Rock

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Background: Solid phase assays (SPA) for antiphospholipid antibodies (aPL) are mostly analyzed in batch. Pre-analytical factors, like repeated freeze-thaw cycles (FTC) can potentially affect results and clinical interpretation. In contrast to the effect of freeze-thawing in phospholipid-dependent clotting assays used for lupus anticoagulants, there is almost no scientific literature on SPA. Nevertheless, repeated FTC can occur in daily practice. Consequently, a validation on the effect of FTC could provide useful information regarding APL stability.

Objectives: Evaluating the effect of repeated FTC on anticardiolipin (aCL) IgM/IgG and anti-beta-2 glycoprotein 1 (a β 2GPI) IgM/IgG.

Methods: Sample selection (n=42) was based on routine results to cover a wide range for all four aPL. After double centrifugation all samples were immediately frozen in aliquots. Samples were analyzed for five consecutive days with an additional, standardized FTC every day. At 10 a.m. all samples were thawed in a 37°C waterbath for five minutes. All analyses were performed by an automated chemiluminescent assay (HemosIL® AcuStar, Instrumentation Laboratory, Bedford, MA, USA) starting at 10:30 a.m. in a predetermined order. All samples were refrozen at 4 p.m. A Mann-Whitney U test for statistical differences (p< 0.05) between the first and following FTC was performed. In case of no significant statistical difference, a concordance correlation coefficient (CCC) was calculated. The coefficient of variation (CV) was calculated for every sample as an additional test for stability and precision.

Results: aPL titers showed no significant difference between earlier routine analysis and re-analysis at the time of this study. After five FTC none of the samples, including those with values around the cut-off, degraded from positive to negative. The Mann-Whitney U test for all analyses showed no statistical difference between the first and following FTC. The CCC between all FTC were between 0.98 and 1 for all four aPL (figure 1). CV's of all positive samples (between 1 and 10.4%) were comparable with the between-run CV of the quality controls (between 1.3-13.9).

Conclusions: ACL and aβ2GPI, over a broad titer range, are stable over time and after repeated FTC. With this study we excluded this preanalytical factor as source of variability in aPL titers measured by SPA.

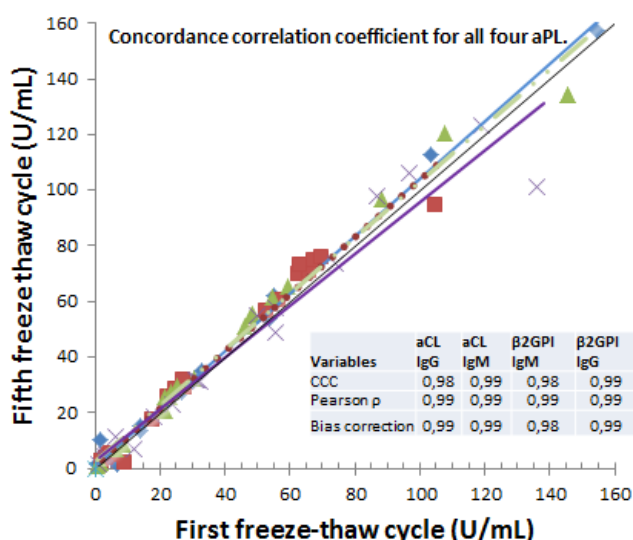


Figure 1. The CCC calculated between first and fifth FTC are graphically shown. Values above 200 U/mL are disregarded in the graph for visual purposes.

APSdb: a database for efficient computing of antiphospholipid positivity profiles from laboratory records

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Background: Antiphospholipid antibody (APL) positivity is monitored by standard laboratory tests. However in real life, patients can present very heterogeneous sequences of APL positivity (called here positivity profiles). For example, positive patients confirmed after 12 weeks or more can sometimes revert later to negative status. Thus, extracting various APL positivity profiles in a large population of consecutive patients is not an easy task. Moreover, interpretation of test positivity may require to adjust some thresholds.

Objectives: The goal is to propose a system for dynamic retrieval of patient sub-groups. For each set of thresholds, the system would recalculate test interpretation and categorize each sample into ISTH classes. For given time intervals and profile definitions, it would classify the patients into the desired subgroups.

Methods: We design a conceptual data model to represent the input data and their relations. The model includes inferred data with respect to test interpretation and patient classification (Fig. 1).

Implementation of APSdb involves SQL / PSM* stored procedures for the dynamic computation steps. Other procedures allow yearly updating the database from GLIMS.

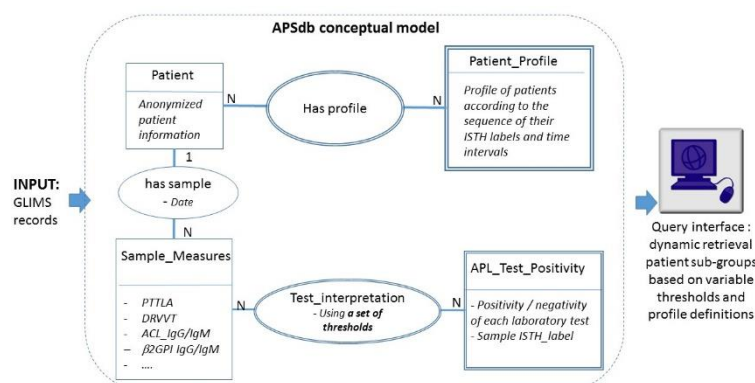


Figure 1 : Conceptual model of APSdb. Double boxes are for inferred data and double ellipses are for associations between data and inferred data.

Results: Data related to over 15,000 samples from around 12,000 consecutive patients visiting the University Hospital of Nancy between 2005 and 2014 have been stored in APSdb. Samples are described by 32 measures including those related to the APL standard tests (PTTLA, DRVVT, ACL IgG/IgM and β 2GPI IgG/IgM).

To illustrate our purpose, APSdb yielded a subset of 367 positive patients confirmed after a 12-week time interval (PP12). Among them, only 208 patients were further controlled after confirmation. About 90% of these controlled patients remained positive until the last recorded sample (186 PPP12).

Conclusions: The APSdb database and associated procedures allow clinicians to further analyse specific patient profiles. Moreover other use-cases can be envisaged such as best thresholds determination or retrospective evaluation of the 12-week confirmation delay.

*SQL/PSM : Standard Query Language / Persistent Stored Modules

Usefulness of the non-conventional antiphospholipid antibodies in the diagnostics of anti-phospholipid syndrome (APS)

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Background: The biological diagnostics of APS takes into account the persistent positivity for anticardiolipin and/or anti- β 2GPI antibodies and/or lupus anticoagulant (LA). However, the latter test is not suitable for patients treated by direct oral anticoagulants. Some new non-conventional antiphospholipid antibodies have emerged.

Objectives: We study the potential usefulness of non-conventional antiphospholipid antibodies in clinics, notably in the context of direct oral anticoagulants treatment.

Methods: 78 patients aged from 15 to 92 years were investigated for non-conventional antiphospholipid antibodies in a prospective study. Patients were classified in following groups: clinico-biological APS (i.e. positivity for the conventional antibodies with clinical criterion of APS), clinical APS (i.e. persistent negativity for the conventional antibodies with a strong clinical suspicion of APS), biological APS (i.e. persistent positivity for the conventional antibodies

without clinical evidence of APS), patients with thrombosis, and patients with obstetrical morbidity. IgG and IgM were detected to the following antigens: phosphatidylserine/prothrombin (PS/PT) by ELISA, and phosphatidic acid, phosphatidyl-ethanolamine, phosphatidyl-glycerol, phosphatidyl-inositol, phosphatidylserine, annexin V, prothrombin, cardiolipin and β 2GPI by immunodot.

Results: We found a strong correlation between the positivity for PS/PT antibodies and the presence of LA ($X^2 = 35.95$, $p = 10^{-5}$, Positive predictive value : 89%, Negative predictive value : 86%, sensibility : 83%, specificity 91%). Interestingly, among the 8 patients positive for LA without any APS clinical manifestation, 7/8 were positive for IgM anti-PS/PT whereas none was positive for IgG. Patients with catastrophic APS were found positive for 4 to 11 non-conventional antibodies. Five among 18 seronegative patients were positive for at least one of non-conventional antibodies.

Conclusions: Our findings suggest that these markers could be useful for patients classified as seronegative APS. Furthermore, anti-PS/PT antibodies could be a surrogate biological marker of LA for patients treated by direct oral anticoagulants in which LA detection cannot be achieved.

Anti-domain I- β 2Glycoprotein I antibodies in antiphospholipid antibody carriers

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Background: There is increasing evidence that antibodies against domain I (aDI) of β 2Glycoprotein I (β 2GPI) are mainly associated with clinical manifestations of antiphospholipid syndrome (APS).

Objectives: In this study we evaluated the prevalence and clinical significance of aDI antibodies in subjects fulfilling the laboratory but not clinical criteria for APS classification (antiphospholipid antibody "carriers").

Methods: IgG aDI antibodies were detected by QUANTA Flash[®] Beta2GPI-Domain I chemiluminescence immunoassay (INOVA Diagnostics USA), according to manufacturer instructions, in 71 carriers (mean age: 44.3 years, range 21-66) and in 84 patients affected with primary APS (mean age: 44.1 years, range: 20-70). Lupus anticoagulant (LAC) using a series of coagulation tests, IgG/IgM

anticardiolipin (aCL) and IgG/IgM a β 2GPI antibodies using ELISA method were also measured.

Results: IgG aDI antibodies were tested positive in 17 carriers (23.9%) and in 42 primary APS patients (50.0%). There was a significant prevalence IgG aDI antibodies in APS patients with respect the carriers ($p=0.001$). Laboratory and clinical characteristics of IgG aDI antibody positive carriers are shown and compared with those of IgG aDI antibody negative carriers in the Table. As expected, IgG aDI antibodies were significantly associated with IgG a β 2GPI and aCL antibodies. Interestingly, a significant association was found between IgG aDI antibodies and LAC or triple antiphospholipid antibody (aPL) positivity (LAC plus a β 2GPI plus aCL antibodies). In particular, the predictive positive and predictive negative values of aDI antibodies for triple aPL profile were 0.60 (CI: 0.36 - 0.80) and 0.90 (CI: 0.78 - 0.96), respectively with a likelihood ratio of 4.8.

Conclusions: As triple aPL positivity is considered to be closely associated with thrombosis, the presence in aPL carriers of its significant association with aDI antibodies suggests that aPL carriers tested positive for aDI antibodies could be at risk of developing thrombosis, thus requiring closer monitoring.

Thursday, April 27, 2017

Obstetrical APS session

A survey of the European Registry on Obstetric Antiphospholipid Syndrome (EUROAPS).

Authors: Enrique Esteve-Valverde¹⁻¹³, Raquel Ferrer-Oliveras², Arsene Mekinian³, Elmina Lefkou⁴, Sáez-Comet L⁵, Amelia Ruffatti⁶, M^a Tiziana Bertero⁷, Sara de Carolis⁸, Gerard Espinosa⁹, Ricard Cervera⁹, Patrizia Rovere-Querini¹⁰, Valentina Canti¹⁰, Angel Robles¹¹, Elisa Picardo¹², Angela Tincani¹⁴, Micaela Fredi¹⁴, Hoxha Ariela¹⁴, Anna Martí-Cañamares¹⁵, Jaume Trapé¹⁶, Anna Arnau¹⁷, Mayer-Pickel K¹⁸, Elisa LLurba¹⁹ and Jaume Alijotas-Reig^{1a} for the EUROAPS Study Group.

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Background: The differences between women with aPL-related obstetric complications (OMAPS) not fulfilling Sydney criteria, and those with complete obstetric antiphospholipid syndrome (OAPS) are still disputed.

Objectives: To present a summarize of current data obtained after analysing the EUROAPS registry and to compare clinical, laboratory, morbidity, treatment and follow-up data between women with aPL-related obstetric complications but not fulfilling the Sydney Obstetric Antiphospholipid Syndrome classification criteria (OMAPS) with those women strictly fulfilling them (OAPS).

Methods: Retrospective and prospective multicenter study performed in sixteen European tertiary hospitals. Data were entered into The European Registry on Antiphospholipid Syndrome included within the framework of the European Forum on Antiphospholipid Antibody projects and placed on a web-site from June 2010 since February 2017. (<https://euroaps.wordpress.com>)

Results: 1000 women were analyzed: 575 fulfilled the Sydney criteria (OAPS group) and 425 did not (OMAPS group). In the OMAPS group, 88/425(20,70%) fulfilled laboratory Sydney criteria but not clinical (subgroup A), and 337/425(79,29%) had a low-medium aPL titer and/or non-persistent aPL-positivity (subgroup B). Overall, aPL laboratory categories in OAPS vs. OMAPS showed differences: 171/575(29,73%) vs. 95/425 (22,35%) ($p<0.0001$) for category I (≥ 2 aPL positive),

404/575 (70,26%) vs. 330/425(77,64%) ($p < 0.0001$) for category II (1 aPL positive). No differences were observed when current obstetric complications were compared ($p < 0.005$). 447/575 (77,73%) of OAPS women were treated vs. 292/425(68'71%) of OMAPS ($p < 0.002$), particularly regarding the LDA+LMWH schedule ($p < 0.004$). No differences between groups were observed in live births.

Conclusions: Considering that treatment rates were higher in OAPS, both groups shared similar clinical characteristics. Significant differences were found among aPL categories between groups. Both OAPS and OMAPS groups had similarly good foetal-maternal outcomes when treated. The proposal to enlarge the OAPS classification criteria, mostly laboratory requirements, is reinforced by these results.

Prevalence of antiphospholipid antibodies in pregnant women at the time of preeclampsia detection.

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Background: Preeclampsia (PE) is a systemic complication of pregnancy associated with increased maternal and perinatal morbidity and mortality. Antiphospholipid Syndrome (APS) is an autoimmune disorder. Though PE is one of the obstetric criteria of the Antiphospholipid syndrome (APS), the association between antiphospholipid antibodies (aPL) and PE still remains unclear and controversial.

Objectives: To determine the prevalence AF at the time of PE detection.

Methods: Observational, prospective, and analytic. The study was approved by the ethics committee of our Hospital. Normal pregnant women (NPW) ($n=40$) : >20 weeks of gestation, without infection, hypertension, autoimmune disease, antithrombotic drugs, thromboembolic and/or pregnancy complications, who delivered a newborn at term with adequate weight for gestational age. Patients: PE ($n=100$); 73 with primary PE (PP) and 27 with superimposed (SPE). Laboratory tests: Lupus anticoagulant (LA) according to the ISTH recommendations; ELISA tests aPL Ig G and IgM (Louisville) anti $\beta 2$ Glycoprotein I antibodies IgG and IgM (a $\beta 2$ GPI). Blood samples were taken from the patients at the time of PE onset and in NPW after 20 weeks of gestation.

Results: The prevalence of LA in all PE was 24% (24/100) in comparison with NPW 5% (2/40) ($p < 0.01$); when considering PP 27, 4 % (20/73) and SPE 14,8% (4/27). LA was statistically significant only in primary preeclampsia ($p < 0.01$). Only a $\beta 2$ GPI IgM levels were higher in PE (5, 57 ± 3 , 21 UI/ml vs 7, 77 ± 4 , 57UI/ml $p < 0.01$). Most of them in grey area according to Louisville ELISA test.

Conclusions: In our study the prevalence of LA was statistically significant in pregnant women at the time of primary preeclampsia detection in relation to normal pregnant women and women with superimposed preeclampsia.

Additional treatments combined with conventional therapies for high risk obstetric primary antiphospholipid syndrome: An international multicentre retrospective study

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Background: Patients with primary antiphospholipid syndrome (PAPS) and a high-risk antiphospholipid antibody (aPL) profile and/or a history of thrombosis and/or previous severe maternal-fetal complications while receiving conventional treatment have a worse pregnancy outcome with respect to those with a low-risk aPL profile and a history of uncomplicated pregnancy loss.

Objectives: The current study was undertaken to examine the effect of different additional treatments on pregnancy outcomes in high-risk PAPS patients in order to identify the most effective treatment for this subset of patients.

Methods: The study's inclusion criteria were: 1) positivity to lupus anticoagulant alone or associated to anticardiolipin and/or to anti- β 2 Glycoprotein I antibodies; 2) a history of maternal thrombosis and/or one severe obstetrical complications including eclampsia, severe pre-eclampsia, HELLP syndrome, intrauterine growth restriction (complicated pregnancies) and/or refractory unexplained fetal death occurring without severe obstetrical complications (uncomplicated pregnancies). The following additional treatments administered alone or combined were considered: low-dose steroids equivalent to 10-20 mg prednisone daily, a 200- 400 mg hydroxychloroquine (HCQ) daily dose, intravenous immunoglobulins at 2 g/kg per month, plasmapheresis administered following a well-defined timetable. The live birth rate was the study's primary outcome and pregnancy complications were secondary outcomes.

Results: A total of 194 patients attending 20 centres were enrolled. Data concerning the pregnancy outcomes linked to oral or parenteral additional treatments and to the single additional treatments are outlined in the Table. HCQ 400 mg versus 200 mg ($p=0.036$) and its administration before versus during pregnancy ($p=0.021$) were associated to a significant increase in live birth rate. Failed pregnancies during HCQ treatment were significantly associated with thrombosis ($p=0.025$). In fact, previous thrombosis was present in 10 of the 12 women failing pregnancies (83.3%).

Conclusions: These results will hopefully help to point the direction of future clinical trials involving high risk pregnant PAPS patients.

Effect of adjusted doses of heparin and switch therapy on pregnancy outcome in primary antiphospholipid syndrome. A prospective cohort management study

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Background: Most investigators currently advocate treating otherwise healthy pregnant patients affected with obstetric APS with prophylactic heparin plus low dose aspirin (LDA). Whereas, women with a history of thrombosis are usually treated with therapeutic heparin doses and LDA. Providing that appropriate treatment is prescribed, 70-80% of APS women now concludes in birth births.

Objectives: We design this prospective cohort study to evaluate the efficacy and safety of different treatment strategy in pregnant APS patients

Methods: One hundred twenty-seven consecutive pregnancies occurring between 1999-2016 in 96 APS patients, median age 36 years (range 25-47) were followed-up. Eighty-seven (68.5%) were treated with prophylactic low molecular weight heparin (LMWH)+LDA [group I], 40 (31.5%) with therapeutic LMWH+LDA (group II). Adjusted LMWH doses, increasing through pregnancies following the fetal/maternal body weight gain, were used. Primary outcome was considered live birth; secondary outcomes were maternal, fetal and/or neonatal complications.

Results: There was no significant difference in live birth rate between group I (95.4%) and group II (87.5%). There was a significant higher prevalence of maternal complications in group II than in group I ($p=0.0005$), while no difference was found regarding fetal complications. The infants in group II had a significantly lower gestational age and birth weight ($p=0.0001$ and $p=0.0005$, respectively), compared to group I. Moreover, they presented a significant higher rate of neonatal complications ($p=0.01$) due to prematurity. As illustrated in Table 1, five patients in group II switched to higher risk protocol therapy (therapeutic LMWH+LDA+plasma exchange+intravenous immunoglobulins) and two

patients in group I to group II; all concluded with live birth. No side effect was observed in any groups.

Conclusions: Overall, using adjusted LMWH doses and switch from one grade of therapy to the upper one, when a pregnancy complication came out, lead to a high rate of live birth in APS patients.

Friday, April 28, 2017

New anticoagulants session

Direct thrombin inhibitors in patients with antiphospholipid syndrome.

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Background: Antiphospholipid syndrome (APS) is an acquired thrombophilia characterized by recurrent venous and arterial thrombosis, obstetric pathology (fetal loss), and synthesis of antiphospholipid antibodies. Warfarin is a "golden" standard of APS therapy. However it has number of disadvantages. Dabigatran etexilate is a direct thrombin inhibitor and its main differences from warfarin are fixed dose, no need of regular INR monitoring, less elimination half-life.

Objectives: To evaluate efficacy and safety of dabigatran etexilate in patients with antiphospholipid syndrome

Methods: 38 patients (pts) (F:26, M:12) with primary and secondary antiphospholipid syndrome, 37,2±9,9 years old. 24 pts with primary APS, 14 pts with secondary APS: 13 had systemic lupus erythematosus (SLE) + APS, 1 rheumatoid arthritis (RA) + APS. The diagnosis of APS was established due to international APS criteria (Sydney), SLE – SLICC 2012, RA - ACR/EULAR 2010. The majority number of pts (n=28) received warfarin and the remaining patients were treated with other anticoagulants such as: sulodexide (n=1), low molecular heparin (n=1), 5 pts received dabigatran etexilate before inclusion to trial. Three 38 patients did not have anticoagulant therapy before.

The control of coagulogram was done 3 times: before inclusion to trial, in 24 weeks and in 48 weeks after inclusion. APPT and thrombin time tests were done with the automated coagulometer Coaglysys Plus C (Behnk Electronic, Germany); thrombin time test was done with STA-thrombin reagent (Diagnostica Stago, France), APPT with STA-Cephascreen reagent (Diagnostica Stago, France). Lupus anticoagulant was assessed by the dilute Russell's viper venom time, using Siemens Healthcare (Germany) LA1 (screening) and LA2 (confirmation). IgG or IgM antibodies against cardiolipin and β 2 glycoprotein I (β 2GPI) were measured with automated enzyme-immunoassay analyzer Alegria with Anti-Cardiolipin IgG/IgM and Anti-beta-2-Glycoprotein I IgG/IgM reagents (Orgentec Diagnostika GmbH, Germany). Triple positivity was defined as positive antibodies against cardiolipin and β 2GPI and a positive test for lupus anticoagulant.

Results: 32 pts had high or medium level of aPL (anticardiolipin antibodies IgG,IgM, anti- β 2glycoprotein antibodies IgG,IgM), 6 had low or normal level of aPL. 12 patients were triple positive. APPT and thrombin time before inclusion to trial were 44,2 [36,5;53,5] and 16,1 [14,9;17,0], on 24 week after dabigatran etexilate start 51,0 [40,5;65,7] and 163,5 [108,7;240,0] and on 48 week 58,7 [45,6;63,2] and 194,1 [152,6;255,2] respectively. 1 patient was excluded due to non-compliance. During follow-up period from 1,5 to 12 (10,6±3,2) months 7 pts (22,6%, 20,7 per 100 patient-years) experienced recurrent thrombosis including superficial vein thrombosis (n=2; 6,5%, 5,9 per 100 patient-years), thrombosis of paranephric veins (n=1; 3,2%, 2,9 per 100 patient-years), acute cerebrovascular disorders (n=4; 12,9%, 11,8 per 100 patient-years). All pts with recurrent thrombosis had high or medium level of aPL; 2/7 were triple positive, both had acute cerebrovascular disorders. 5 patients (16,1%, 14,8 per 100 patient-years) experienced bleeding: 2 hemorrhoidal bleedings, 1 uterine bleeding, 2 nasal bleedings. There was no case of severe bleeding.

Conclusions: Dabigatran etexilate could be used in patients with APS in the case of warfarin non-effectiveness. or there are difficulties in achieving a therapeutic INR level.

Friday, April 28, 2017

Neuropsychiatric/Cardiac APS

Relationship Between Cerebrovascular And Valvular Manifestations In Patients With Primary And Secondary Antiphospholipid Syndrome

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Introduction: Antiphospholipid syndrome (APS) may manifest itself as a primary (PAPS) or secondary disease, most commonly in the context of Systemic Lupus Erythematosus (SLE) with various neurological and cardiac manifestations in its occurrence.

Aim: The aim of this study was to investigate relationship between cerebrovascular (stroke and transient ischemic attack (TIA)) and valvular manifestations in APS patients as well as their connection with type of antiphospholipid antibodies.

Patients and methods: Our study comprises a total of 508 patients: 360 PAPS patients and 148 SLE patients with secondary APS. Antiphospholipid antibody (aPL) analysis included detection of aCL (IgG/IgM), β 2GPI (IgG/IgM), and LA. Transthoracic echocardiography was performed in all patients, significant valvular dysfunction or presence of vegetation has been confirmed with transesophageal echocardiography.

Results: TIA and valvular manifestations mostly in the means of valvular vegetations, occurred more often in SAPS patients ($p=0.024$, $p=0.001$ respectively). In PAPS patients presence of β 2GPI IgG was highly significantly related to TIA occurrence ($p=0.05$) as well as overall β 2GPI positivity (IgG and IgM) ($p=0.030$). Presence of β 2GPI IgG was significantly related to stroke ($p=0.018$), β 2GPI IgM to valvular thickening and dysfunction ($p=0.045$) and overall β 2GPI (IgG and IgM) positivity was significantly related to TIA ($p=0.023$) and valvular thickening and dysfunction ($p=0.045$) in SAPS patients. Valvular manifestations overall and valvular vegetations were significantly related to TIA (not to stroke) in both groups of patients (PAPS $p=0.0001$, $p=0.0001$ respectively, SAPS $p=0.045$, $p=0.025$ respectively). After adjustment for age,

gender, β 2GPI IgG positivity, hypertension, presence of vegetations or valvular manifestations overall was not independent risk factors for TIA neither in SAPS nor PAPS patients studied.

Conclusions: Our large cohort of APS patients' data analysis demonstrated significant relationship between some cerebrovascular and valvular manifestations, especially in β 2GPI (IgM or IgG) positive SAPS or PAPS patients. For that reason, multidisciplinary approach and assessment of patients of higher risk is mandatory.

Antiphospholipid Antibodies as a Risk Marker of Embolic Events in Infective Endocarditis

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Background: A link between antiphospholipid (aPL) antibodies and the occurrence of embolic events (EE) has been suggested among patients with infective endocarditis (IE).

Objectives: We aimed to evaluate the value of aPL as predictors of EE in IE in the light of the improved knowledge on those antibodies.

Methods: Consecutive patients ($n=186$) with a definite IE had storage of blood specimens and systematic imaging to detect both symptomatic and asymptomatic EE. Anti-cardiolipin (aCL) and anti- β 2-glycoprotein I (β 2GPI) antibodies (G and M isotypes) were a posteriori assessed by means of ELISA (home made for CL including a no coating blank according to the former forum guidelines, and commercial kit for β 2GPI ORGENTEC).

Results: At least one EE was detected in 118 (63%) patients, after IE diagnosis in 80. At least one type of aPL antibody was found in 31 patients (17%). EE were

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more frequent among patients with anti-β2GPI IgM antibodies (Kaplan Meier, log-rank $p=0.0036$). Cerebral embolism ($n=37$) was more frequent among patients with aCL ($p=0.002$) and anti-β2GPI IgM antibodies ($p<0.0001$). By multivariate analysis (Hazard Ratio, 95% CI), factors predictive of EE were anti-β2GPI IgM antibodies (3.45, [1.47-8.08], $p=0.0045$), plasma creatinine ($> 180 \mu\text{moles/L}$) (2.74, [1.55-4.84], $p=0.0005$) and vegetation size ($> 15 \text{ mm}$) (2.41, [1.41-4.12], $p=0.0014$). Factors predictive of cerebral embolism were aCL IgM antibodies (2.84, [1.22-6.62], $p=0.016$) and anti-β2GPI IgM antibodies (4.77, [1.79-12.74], $p=0.0018$).

Conclusion: Our results show a strong association between the presence of aCL and anti-β2GPI antibodies of IgM isotype and EE, particularly cerebral ones. These biomarkers could help in the assessment of embolic risk of IE patients. Interestingly the data in this setting fit neither with the dogma of the peculiar nature of infection-associated 'aPL' antibodies contrasting with genuine auto-antibodies of the APS, nor with the restriction of the prothrombotic effect to the IgG isotope.

Posters

Thursday, April 27, 2017

Late Breaking Posters Session

Refractory obstetrical antiphospholipid syndrome: features, treatment and outcome in a European multicentre retrospective study.

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Aim: To describe the consecutive pregnancy outcome and treatment in refractory obstetrical antiphospholipid syndrome (APS).

Methods: Retrospective multicentre open-labelled study from December 2015 to June 2016. We analyzed the outcome of pregnancies in patients with obstetrical APS (Sydney criteria) and previous adverse obstetrical event despite low-dose aspirin and low-molecular weight heparin LMWH (LMWH) conventional treatment who experienced at least one subsequent pregnancy.

Results: Forty nine patients with median age 27 years (23-32) were included from 8 European centers. Obstetrical APS was present in 71%, while 26% had obstetrical and thrombotic APS. Lupus anticoagulant was present in 76% and triple antiphospholipid antibody (APL) positivity in 45% of patients. Pregnancy loss was noted in 71% with a median age of gestation of 11 (8-21) weeks. The presence of APS non-criteria features (35% vs 17% in pregnancies without adverse obstetrical event; $p=0.09$), previous intrauterine death (65% vs 38%; $p=0.06$), of LA (90% vs 65%; $p=0.05$) were more frequent in pregnancies with adverse pregnancy outcome, whereas isolated recurrent miscarriage profile was more frequent in pregnancies without any adverse pregnancy outcome (15% vs 41%; $p=0.04$). In univariate analysis considering all pregnancies (index and subsequent ones), an history of previous intrauterine death was associated with pregnancy loss (odds-ratio 2.51 (95% CI 1.27-4.96); $p=0.008$), whereas previous history of prematurity related to APS (odds-ratio 0.13 95%CI 0.04 0.41, $P=0.006$), steroids use during the pregnancy (odds-

ratio 0.30 95% CI 0.11-0.82, $p=0.019$) and anticardiolipids isolated profile (odds-ratio 0.51 95% CI 0.26-1.03, $p=0.0588$) were associated with favorable outcome. In multivariate analysis, only previous history of prematurity, steroids use and anticardiolipids isolated profiles were associated with live-birth pregnancy.

Conclusion: The main features of refractory obstetrical APS were the high rates of LA and triple APL positivity. Steroids could be effective in this APS profile, but prospective studies are necessary.

Non-conventional antiphospholipid antibodies in patients with clinical obstetrical APS: prevalence and pregnancies treatment efficacy

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Objectives: To describe the prevalence of non-conventional APL in patients with obstetrical APS without conventional APL and the impact of treatment on pregnancy outcome.

Methods: Patients with clinical obstetrical criteria were tested for anti-phosphatidylethanolamine (aPE) IgG/M, anti-prothrombin/phosphatidylserine (anti-PS/PT) IgG/M and anti-annexin V IgG. Pregnancies losses rates were compared between APS, non-conventional APS and non-APL and in untreated pregnancies to treated ones for each group.

Results: Using the cut-offs (ROC), 65/96 (68%) patients have been considered as non-conventional APS and compared to 83 APS and 31 patients without APL. The obstetrical history in non-conventional APS did not differ in comparison to confirmed APS. The frequencies of anti-annexin V IgG antibodies tended to be more frequent in non-conventional APS (88% versus 73%; $p=0.06$), and those of anti-PE IgG and M were similar. The anti-PS/PT IgG and M antibodies were more frequent in confirmed APS than in non-conventional APS (63% and 37% versus 4% and 5%, $p<0.0001$).

Overall 261 pregnancies in patients with non-conventional APS were compared to 81 pregnancies of confirmed APS and 132 pregnancies from non-APL group. 136/474 (29%) patients have been treated during pregnancies and treatment significantly increased the rate of live birth (26% in untreated versus 72% in treated pregnancies, $p<0.0001$). In univariate analyses, treatment effect on pregnancies losses was similar in patients with APS and non-conventional APS, with odds ratio at 3.3 [95% CI; 1.8 to 6.1] and 6.9 [95% CI; 3.9 to 12.3] ($p=0.49$) and significantly more important for the 2 APS groups pooled versus non-APL group (OR at 1.9 [95% CI; 1.1 to 3.5] for non-APL group versus 5.3 [95% CI; 3.5 to 8.1] for APS groups, $p=0.0025$).

Conclusion: In this study 68% of patients with clinical criteria for obstetrical APS seronegative for conventional APL have non-conventional APL. These patients have a significant decrement of pregnancy losses if they receive treatment for APS during their pregnancy.

Antibodies against S100A10 protein in antiphospholipid syndrome

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Introduction: Annexin A2 (ANXA2), an endothelial cell receptor for plasminogen and tissue plasminogen activator, has been identified as a new autoantigen in antiphospholipid syndrome (APS). ANXA2 can exist as a monomer or a heterotetrameric complex with S100A10 protein (a member of the S100 family of proteins, sometimes referred to as p11). This S100A10 subunit plays also a pivotal role in the regulation of fibrinolysis. The aim of this study was to evaluate the prevalence of autoantibodies directed against S100A10 protein in patients with APS.

Methods: Patients with primary antiphospholipid syndrome (PAPS) and patients with systemic lupus erythematosus (SLE) were included retrospectively in this study. Patients were followed at the department of Internal Medicine of Amiens University Hospital, Amiens, France. Anti-S100A10 IgG and IgM antibodies were detected, using an enzyme-linked immunosorbent assay, in the serum of patients. The

cut-off value for positivity was defined as 3 standard deviations above the mean optical density (OD) obtained in the sera from 80 healthy blood donors.

Results: The study group consisted of 80 healthy individuals and 44 patients : 30 APS patients (18 patients with PAPS and 12 patients with secondary APS related to SLE) and 14 SLE patients without APS. The median age of APS patients, SLE patients without APS and healthy individuals was 43, 33 and 42 years, respectively. Anti-S100A10 antibodies were detected in 13.3% of APS patients and this prevalence was higher than that observed in SLE patients without APS (6.2%) and healthy individuals (2.5%) but without difference statistically significant. High levels of anti-S100A10 were observed in sera from one PAPS patient with venous thrombosis and one SLE patient with APS presenting ischemic colitis and superior vena cava thrombosis.

Conclusion: We identified S100A10 protein, the binding partner of ANXA2, as a target of autoantibodies in sera from patients with APS. Further studies are required to determine whether these antibodies could play a role in thrombogenic mechanisms of APS and to determine their diagnostic value in discriminating clinical subgroups of patients with APS, particularly those with seronegative APS.

Posters

Friday, April 28, 2017

Posters Session

Endothelial Dysfunction In Antiphospholipid Syndrome: Myth Or Truth

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Objective: Antiphospholipid syndrome (APS) can be defined as an autoimmune syndrome that depends on endothelial cell responses and function. Asymmetric Dimethylarginine (ADMA) as endogenous nitric oxide synthase inhibitor leads to vascular dysfunction.

Aim: In the present study, we assessed the availability of ADMA as a marker of endothelial dysfunction in APS patients.

Methods: The study involved 140 APS patients [59 primary APS (PAPS), 46 patients diagnosed with APS and systemic lupus erythematosus (SAPS) patients] and 40 age and sex matched controls. High-resolution ultrasound was used to assess vascular function in the brachial artery by measuring flow mediated dilatation (FMD, endothelium-dependent function) and sublingual glyceryltrinitrate dilatation (NMD, endothelium-independent function). ADMA (micromol/L) was studied by enzyme-linked immunosorbent assay (ELISA, Cusabio kit). Chi-square, Fisher's exact test, Mann-Whitney U test, and Spearman's correlation tests were used for analytical analysis, and $p < 0.05$ was considered as the level of statistical significance.

Results: It was found that FMD in patients with APS was significantly lower than those of the controls ($p = 0.048$) without difference between APS groups. Risk factors for endothelial impairment were age ($p < 0.05$), obesity ($p = 0.048$) and hypertension ($p = 0.020$) but there was no correlation to antiphospholipid antibodies (aPL) and hsCRP. There were not differences in NMD between groups. In our study, ADMA plasma concentrations were significantly higher ($p < 0.001$) in the patient cohort (1.31 ± 1.32) than in the control group (0.56 ± 0.16) and significantly higher ($p = 0.009$) in SAPS (2.1 ± 1.69) comparing to PAPS patients (0.71 ± 0.21). ADMA levels were higher in hypertensive patients ($p = 0.026$) and correlated to B2gplgG ($p = 0.207$; $p = 0.034$) and aClIgM ($p = 0.2$; $p = 0.041$). Since age cannot be excluded as a determinant of high ADMA levels we performed a correlation analysis of ADMA levels and age, which showed no association. The ADMA level was inversely correlated with FMD ($p = 0.472$; $p < 0.001$). However, there were no statistically significant correlations of FMD and ADMA to hsCRP, hyperlipoproteinemia or previous history of clinical APS manifestation (thrombosis or fetal loss).

Conclusion: Endothelial dysfunction is present in APS patients, and more frequently in SAPS patients. Our results support the hypothesis that ADMA may be used as a simple and cheaper method for the determination of endothelial dysfunction in these patients.

SLE: Quality Of Life And Fatigue In Secondary Antiphospholipid Syndrome

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Introduction: Quality of life (QOL) measures have become a vital and often required part of health outcome appraisal in lupus patients with secondary APS. Because lupus causes pain, inflammation and fatigue the very thought of exercising can be a challenge for patients.

Aim: To determine if supervised aerobic training or exercise improves fatigue and QOL in lupus patients with secondary APS.

Methods: 60 women with SLE and secondary APS (39.74±10.58 year) in steady state (measured by SLEDAI score) were evaluated using Fatigue Severity Scale (FSS) and Short Form 36 (SF36) on baseline and after 6 weeks. One randomly chosen group of 30 women had aerobic training on bicycle ergometer for 15 minutes, 3 times a week and other had exercise (same time of training).

Results: Considering all 60 women, FSS values show significant improvement in fatigue 53,78±5,75 vs 29,08±7,84 ($p<0,001$) during 6 weeks. But, there is no statistical difference in FSS values comparing two training groups (29,23±7,86 vs 28.37±7,66; $p<0,005$). Statistical analysis of SF36 parameters shows significant improvement of QOL in all parameters as in 2 general parameters: physical health (46.30±7,01 vs 60.0±7,05; $p<0.001$) and mental health (33,65±3,93 vs 64.6±5,32; $p<0.001$). But, there is no statistical difference in SF36 parameters between two training groups at the end of 6 weeks. Training did not exacerbate disease measured by SLEDAI score.

Conclusion: This study showed significant improvement in fatigue and consequently quality of life after training in lupus patients with secondary APS.

Effects of Hydroxychloroquine for the prevention of miscarriages in obstetrical antiphospholipid syndrome

Authors: C Belizna, C Bertrand, C Bertrand, L Sentilhes
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Introduction: Data from the literature report a percentage of 20 to 30% of patients with obstetrical APS refractory to maximal treatment. Therefore, in these patients different treatments were suggested including Hydroxychloroquine. This treatment could be an additional therapy in these refractory cases, based on preclinical data and few case reports and small series.

Objective: We report our preliminary experience as regards Hydroxychloroquine effects on preventing miscarriages in obstetrical primary APS refractory to standard therapy (curative doses low molecular weight heparins plus aspirin).

Methods: We have performed a prospective two years study (2014-2016) in APS patients refractory to high doses low molecular weight heparins and aspirin and who refused intravenous immunoglobulins and/or other alternative therapies. APS was defined according to Sidney criteria. In these patients, Hydroxychloroquine was added to their standard therapy in an open label preliminary study. An ophthalmological check up was performed in the first 10 days after the initiation of the treatment. A regular blood test during routine check up of their liver blood test and an ECG at the entrance in the study were performed. Hydroxychloroquine blood dosage was performed every 3 months. Regular phone calls were performed monthly additionally to their standard follow-up.

Results: 14 patients were included in our study. All of them had HCQ added to their standard therapy at a dose of 400 mg/day. The tolerance of HCQ was excellent, no side effects were observed. HCQ blood dosage was in the normal range, inferior to toxic doses in all patients. 12 of 14 patients had a normal pregnancy and gave birth to at least a living child (3/12 gemelar pregnancies). 2 miscarriages occurred in the first three months of pregnancy.

Conclusion: Our data suggest the effects of HCQ in preventing miscarriages in refractory primary APS patients.

Arterial rigidity in antiphospholipid syndrome and effects of treatments

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Introduction: Arterial rigidity is an independent cardiovascular risk factor, that increases with several parameters such as inflammation, high blood pressure, age. Some data in the literature suggested

an increased arterial rigidity in secondary antiphospholipid syndrome, but also in primary antiphospholipid syndrome. The outcome of this increased rigidity and its dependence on various treatments was evaluated in few studies.

Objective: As the arterial rigidity could be easily estimated by a quick and non-invasive new technique, popmetre (Axelife SAS, France), the main purpose of this study was to evaluate the rigidity in APS patients measured by popmetre as compared to the gold standard techniques (echo doppler M) in both primary and secondary APS patients before and after various treatments.

Methods: We have performed a prospective two years study (2014-2016) in APS patients. 25 patients with APS secondary to SLE and 25 patients with primary APS syndrome were included in the study. They were compared with normal controls age and sex matched. The patients were followed during two years. Popmetre measures and echo doppler M were performed at inclusion in the study, at one year and at two years of treatment. Data as concerns their treatment, cardiovascular associated risk factors were recorded.

Results: A statistical significant difference as regards rigidity values was observed in APS patients as compared to controls ($p < 0.05$). These data were similar both with popmeter and echo doppler M techniques. There were no statistical significant differences between primary and secondary APS and between obstetrical and vascular pattern APS. At two years of treatment there was a statistical significant difference between patients at inclusion in the study and at two years of follow-up in secondary APS patients treated with Hydroxychloroquine, aspirin, immunopressors (Azathioprin, Méthotrexate), low dose corticoids (positive correlation). No differences in rigidity values were found as concerns two years oral anticoagulants administration.

Conclusion: Our data confirm an increased rigidity in APS patients both with primary and secondary APS and both obstetrical and vascular pattern. We suggest that some treatments are beneficial in improving arterial rigidity, but these data need a larger prospective study. The popmeter measure of rigidity could be a useful quick and non invasive technique allowing then assessment of cardiovascular risk in APS patients.

Anti-factor-Xa-activity of selective and nonselective factor Xa inhibitors in patients with antiphospholipid syndrome and systemic lupus erythematosus.

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Introduction: Lupus anticoagulant (LA) is one of the diagnostic criteria of both antiphospholipid syndrome (APS) and systemic lupus erythematosus (SLE). Measurement of anti-factor-Xa-activity (aXa) is used to monitor anticoagulant therapy (selective and nonselective factor Xa inhibitors) in the presence of LA.

Aim: to evaluate aXa in patients with APS and SLE depending on the clinical and laboratory symptoms.

Material and methods: The total of 70 patients (54 females and 16 males) in the age of 39 [31; 43] years was included: 10/70 (14%) «Primary» APS patients, 15/70 (21%) SLE patients and 45/70 (65%) SLE+APS patients. Informed consent was obtained from all patients. Clinical and laboratory parameters were retrospectively analyzed in APS and SLE patients who protractedly received low weight molecular heparins (LWMH) and selective factor Xa inhibitor fondaparinux and rivaroxaban. Complex examination included ECG, echocardiography, chest CT, head MRI, peripheral vessel Doppler Ultrasound and CT angiography, clinical blood and urinary tests, biochemistry. Anticardiolipin antibodies (aCL) were detected by enzyme-linked immunosorbent assay (ELISA), using commercially available kits «Orgentec». The cutoff values were 11 IgG phospholipid (GPL)/IgM phospholipid (MPL) units/ml for negative aCL, 11–23 GPL/MPL units/ml for indeterminate aCL, and 24 GPL/MPL units/ml for positive aCL. LA was detected using activated partial thromboplastin time (ATTP, Diagnostica Stago) and diluted Russell's viper venom time (Trinity Biotech) according to international guidelines. Serum IgG and IgM anti-beta2-glycoprotein 1 (aB2GP1) were detected by ELISA technique (ORG 521 aB2GP1 IgG/IgM) with cutoff values of 10 units/ml for IgM and 10 units/ml for IgG. The IgG intraassay variation was 2.1–5.0% and interassay variation was 2.6–7.95%. The IgM intraassay variation was 2.1–3.8% and IgG interassay variation was 4.1–6.3%. SLE activity was measured by SLEDAI 2K. 33/70 (47%) patients had prolonged ATTP, and 24 out of them due to LA. 53/70 (75%) patients had positive antiphospholipid antibodies (aPL): aCL, aB2GP1 and/or LA. Triple aPL positivity was diagnosed in 23/70 (32%) patients. All the patients received

anticoagulants: 29 – fondaparinux with mean dose 5 [5.0; 7.5] mg/day, 29 – nadroparin -98.3 [67.8; 129.5] U/kg/day, 3 - enoxaparin - 1.2 [0.8; 1.5] mg/day and 9 - rivaroxaban - 20 mg/day. Median extent of exposure amounted to 21 [14; 28] days for fondaparinux, 23 [14; 30] days for nadroparin, 41 [14; 212] day for enoxaparin and 194 [28; 372] days for rivaroxaban.

Results: 43/70 (61%) patients had therapeutic interval of aXa 0.1-1.5 U/ml. Low aXa 0.34 [0.14; 0.4] U/ml was detected in 14/60 (20%) cases. Increased Xa 1.7 [1.6; 1.99] U/ml was measured in 13/70 (19%) cases. Patients with low aXa underwent dose correction. There was not any case of recurrent thrombosis or hemorrhage during the treatment. High and mild SLE activity was more frequent than moderate: 25/60 (41%) patients with SLEDAI 2K 14 [13; 16] and 21/60 (35%) patients with SLEDAI K 2 [1; 4] vs 14/60 (23%) patients with SLEDAI 2K 7 [6; 8], accordingly ($p=0.04$). Thromboses in the history were documented in 54/70 (77%) pts: arterial – in 29/70 (41%) patients, venous – in 16/70 (23%) patients and combined - in 9/70 (13%) patients. Acute thromboses were diagnosed in 15/70 (21%) patients. 23/54 (43%) women had fetal losses in the history. High aXa of fondaparinux appeared more often (in 9/29 (31%) patients), then high aXa of nadroparin (in 2/29 (7%) patients) or rivaroxaban (in 2/9 (23%) patients), ($p=0,02$). There was aXa of enoxaparin in therapeutic interval in all 3 patients. IgG-aCL was higher in patients with increased aXa, than with normal or low: 70.5 [10.7; 120] vs 41.8 [1.5; 120] and 13.8 [0.6; 32.9] GPL, accordingly ($p=0.037$). Increased aXa associated with the following manifestations without bleeding events:

- 1) positive LA at the beginning of treatment: LA was measured in 10/13 (76%) patients with high aXa and in 25/57 (43%) patients with normal (OR 3.3 (95%CI [0.8; 13.4], $p=0.03$);
- 2) skin necroses/gangrene of foot fingers: necroses were more frequent in patients with increased aXa, then with normal: 8/13 (62%) vs 9/57 (16%), accordingly (OR 4.9 (95% CI [1.3; 18.8], $p=0.001$);
- 3) peripheral artery disease (endothelial proliferation, vessel wall thickening and obliteration of the lumen): the disease was detected in 4/13 (31%) patients with increased aXa and in 4/57 (7%) patients with normal (OR 3.4 (95% CI [0.7; 16.3], $p=0.03$);
- 4) poststroke ischemic brain damage (PSBD): PSBD was diagnosed in 10/13 (77%) and in 22/57 (39%) patients with high and normal aXa, accordingly (OR 3.9 (95% CI [0.9; 15.9], $p=0.01$);

5) nonbacterial Libman - Sacks endocarditis with the third degree mitral insufficiency: endocarditis developed in 9/13 (69%) patients with increased aXa and in 11/57 (19%) patients with normal aXa (OR 5.6 (95% CI [1.5; 21.7], $p=0.01$).

Positive dynamics of all these manifestations were noted on the treatment.

Conclusion: positive LA and aCL, poststroke ischemic brain damage, skin necroses, peripheral artery disease and nonbacterial endocarditis with mitral insufficiency in patients with APS and SLE were found to increase anti-factor-Xa activity of anticoagulants without bleeding complications. Therapeutic range of anti-factor-Xa activity in such patients have to be extended. Further investigations are needed.

Knowledge Management in Immunology with Content Curation

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Background: In Science and Medicine, knowledge increases at very fast pace, leading to “infobesity” and raising challenges for learning, teaching and research. Finding methods and tools to overcome this situation would be helpful for teachers, students and researchers.

Objectives: Content Curation tools help collecting, elevating and sharing information available on the web. We have herein evaluated the interest of one of them, **Scoop.it**, well designed for the knowledge management of “serious” information.

Methods: **Scoop.it** has been used during the past 5 years by teachers, researchers and students individually or in networks to cover scientific information in various immunology domains, either fundamental or clinical.

Results: The topics gathered more than 20K highly selected scoops, compared to 200K or 400K results found with Pubmed or Google Scholar respectively. Scoops deal with published and grey literature, allowing rapid access to recent relevant information. Audience is steadily increasing (over 200K views, >100K visitors). The most successful topic entitled *Immunology* (<http://www.scoop.it/t/immunology>) covers basic immunology since summer 2011.

Immunological basic Science, Biotechnologies, Bio-Therapies are covered by: *From Flow Cytometry to Cytomics, Immunology and Biotherapies, Mucosal Immunity* and more recently *History of Immunology*. Immuno-Pathology is covered through the following topics: *Autoimmunity* (<http://www.scoop.it/t/autoimmunity>) >2500 scoops, 7K views; *Allergy* (and clinical immunology); *Rheumatology* (<http://www.scoop.it/t/rheumatology-rhumatologie>); *Neuro-immunology*. Resources on Anti-Phospholipid Syndrome represent #60 scoops including published papers, international meetings announcements, guidelines, videos, websites.

Conclusions: Content Curation allows end-users collecting relevant scientific information and retrieving it later in order to stay up to date in rapidly evolving fields such as immunology and clinical medicine. Usage of Scoop.It allows researchers and teachers building knowledge content hubs for teaching and research purposes, and nurturing curiosity and creativity through serendipity. It allows students accessing validated selected information, discovering and mastering scientific information, becoming media and information literate as well as autonomous for their professional life-long learning.

Use of TNF- α blockers in aPL-positive women with recurrent infertility (refractory cases)

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Background: No absolute data on the treatment of antiphospholipid antibodies (aPL) related to refractory obstetric complications exist to date. TNF- α seems to play a major role in the pathogenesis of this disorder.

Objectives: To assess the effectiveness of TNF- α blockers in 14 aPL-positive women with recurrent infertility after therapy with low-molecular-weight heparin (LMWH) plus aspirin (LDA) plus hydroxychloroquine – refractory cases–

Methods: Prospective case series of 10 women fulfilling Sydney criteria for obstetric antiphospholipid syndrome (OAPS) and 4 with incomplete forms. 10/14

were primarily OAPS and 4 secondary forms. All women tested positive for aPL at least twice. Atypical aPL were also tested in 11/14. Complement levels, TNF- α and IL-10 were also evaluated. Active or latent infections such as tuberculosis were ruled out before treatment. Women were closely monitored for foetal well-being and possible malformations throughout gestation and the postpartum period.

Results: Ten women complete gestation: 8 at term and 2 at 36 weeks. Twelve cases were put on adalimumab and 2 on certolizumab. First trimester miscarriage recurred in 4 cases. No foetal malformations were observed. No maternal-foetal complications related to TNF- α blockers appeared.

Conclusions: In this case series, good obstetric results were obtained in 71% of previous refractory cases. TNF- α blocker-based schedule was well tolerated and no related adverse effects were seen. Neither malformations nor infections were seen in the newborns. The combination of LMWH plus LDA plus TNF- α blockers seems to be a promising treatment for refractory obstetric complaints related to aPL.

Laboratory and clinical characteristics of isolated Lupus Anticoagulants.

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Background: Lupus Anticoagulants (LAC) are considered the strongest risk factor for thromboembolic events in antiphospholipid syndrome (APS) patients. Usually LAC are associated to other antiphospholipid antibodies (aPL) such as anticardiolipin and/or anti- β 2Glycoprotein I antibodies. LAC isolated is an uncommon finding characterized by a controversial clinical significance.

Objectives: To evaluate the laboratory and clinical characteristics of isolated LAC.

Methods: The study group included 44 cases of isolated LAC obtained by testing positive for LAC 180 patients. In all cases LAC was confirmed no earlier than 12 weeks later. Diluted Russell's viper venom (dRVVT), silica clotting (SCT) and diluted activated

partial thromboplastin (dAPTT) times were used as screening tests. Samples with a prolonged screening test that was not corrected by mixing with a normal plasma pool were tested for confirmation by using an excess of phospholipids.

Results: Overall, isolated LAC were found in 44 patients: with SCT in 41 (93.2%), with dRVVT in 30 (68.2%) and with dAPTT in 20 (45.5%), respectively. In order to evaluate sensitivity and specificity for APS of each clotting test, ROC curves were analysed. dAPTT had specificity 97%, sensitivity 25% and likelihood ratio (LR) 8.3%, dRVVT specificity 96.8%, sensitivity 20% and LR 6.3% and SCT specificity 87.5%, sensitivity 28.6% and LR 2.3%. Demographic and clinical characteristics of patients with isolated and of those with associated LAC are shown in the Table along with the results of statistical comparison.

Conclusions: The most sensitive test for detection of isolated LAC was SCT, while the most appropriate assay for APS diagnosis in patients with isolated LAC was dAPTT. Isolated LAC were significantly found in patients without APS.

Table. Demographic and clinical characteristics of patients with isolated or associated LAC

	LAC Isolated	LAC + other aPL	P value
N°	44	136	n.a.
Age (mean ± DS)	49.4 ± 15.7	46.0 ± 13.3	0.17
Gender (M/F)	10/34	26/110	0.67
APS	8 (18.2%)	94 (69.1%)	* 0.0001
Vascular	5 (11.4%)	68 (50.0%)	* 0.0001
Obstetrical	3 (6.8%)	5 (3.7%)	0.38
Vascular & obstetrical	0	21 (15.4%)	* 0.0055
no APS	36 (81.8%)	42 (30.9%)	* 0.0001
Autoimmune diseases	20 (45.5%)	30 (22.1%)	* 0.0026
Psoriatic arthritis/psoriasis	7 (15.9%)	2 (1.5%)	* 0.0001
Carriers	9 (20.5%)	10 (7.4%)	* 0.0140

LAC: lupus anticoagulants; aPL: antiphospholipid antibodies; APS: antiphospholipid syndrome; n.a: not applicable; * statistical significance.

Catastrophic antiphospholipid syndrome (CAPS) in pregnancy: maternal and perinatal outcome in next pregnancies.

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Background: CAPS is an accelerated form of the antiphospholipid syndrome (APS) resulting in multi-organ ischemia and failure. In pregnancy there is not clear consensus about the preconceptional counseling for a next pregnancy and which the risk of recurrence is.

Objectives: To describe a case of CAPS in pregnancy and discuss its management and maternal and obstetric outcome in next two pregnancies.

Methods: A fifteen years old women at 16 weeks of gestation, was admitted to the Intensive Care Unit (ICU) with nausea, vomiting and headaches and progressive sensory impairment with a Glasgow of 10/15. Obstetric echography showed foetal positive cardiac activity. Cerebral tomography was normal. Magnetic nuclear resonance informed a venous thrombosis of sagittal, rectus and lateral sinuses.

Laboratory: Mild thrombocytopenia and a positive lupus anticoagulant with negative anticardiolipin and anti-b2 GP antibodies. No evidence of microangiopathy. Respiratory insufficiency that required mechanical assistance and neurological deterioration with quadriplegia. An obstetric CAPS was considered, treatment with low molecular weight heparin(LMWH) was started and corticoids were added. She presented an spontaneous abortion and severe thrombocytopenia. LMWH was stopped and intravenous gammaglobulin (IVGG) was indicated. A neurological improvement was observed, elevation of platelets and anticoagulation was reinitiated. A deep vein thrombosis in inferior left leg and vena cava was confirmed so a filter was placed. She left the ICU.

Results: She continued with long term anticoagulation. She was counselled about anticonceptions methods. In spite of this she have two pregnancies after de CAPS without recurrences, aPL were negative. Table

Conclusions: The CAPS has a very high mortality rate. Treatment with anticoagulation, corticosteroids, and IVGG was effective in our patient. The optimal treatment in case of a new pregnancy and/or the risk of recurrence needs to be addressed in well-designed prospective studies. In our experience continuing with full dose anticoagulant therapy was enough to prevent recurrence.

Maternal and perinatal outcome in antiphospholipid syndrome (APS) with first line therapy (FLT) with low molecular weight heparin (LMWH) and low dose aspirin (LDA)

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Background: The APS is an autoimmune disorder characterized by an elevated risk for arterial and/or venous thrombosis and pregnancy-related morbidity. APS is defined by two major components: 1. Presence of at least one type of autoantibody known as antiphospholipid antibody (aPL) 2. The occurrence of at least one of the following clinical features: venous or arterial thromboses and/or pregnancy morbidity. The use of LDA and heparin has improved the pregnancy outcome in obstetric APS and approximately 70% of pregnant women with APS will deliver a viable live infant. However, current management does not prevent all maternal, fetal, and neonatal complications of APS. The current treatment fails in 20 to 30% of APS pregnancies.

Objectives: To describe the maternal and perinatal outcome in next pregnancy of women with APS after receiving FLT with LMWH+LDA.

Methods: Only patients that fulfilled the Sydney criteria were included n=14, Pregnancies (pg)=16. Classification: 1) Thrombotic: 1; 2) Pregnancy morbidity: 15; a) Fetal death (FD):10; b) (i) Severe preeclampsia (sPE): (ii); placental insufficiency (PI)1; c) Recurrent abortion (RPL):2; one with PI and one with FD had previous thrombosis too. According to the laboratory categories 8/13 were in category I (4 double and 4 triple positivity), 7 in IIa, 1 in IIb and none in IIc. Treatment: LMWH: Enoxaparin 40 mg initial dose and aspirin 100 mg/d; Intermediate or therapeutic doses in thrombotic APS. Period: 2011-16.

Results: Obstetric outcomes are detailed in the table. There were no thrombotic events.

Conclusions: It seems that the current adequate FLT for APS in pregnancy might rather prevent the development of RFL/FD, but not previous sPE PI and/or PI. The poorest obstetric outcome was observed in women with triple positivity. The division

into two groups of obstetric APS (RPL/FD and PI/sPE) and triple positivity might facilitate the choice of additional therapy in these women.