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SLE, Sjögren's and APS - clinical aspects (other than treatment)

SAT0262 BCL2-ASSOCIATED ATHANOGENE 3 PROTEIN IS ASSOCIATED WITH B-CELL HYPERACTIVITY INCLUDING LYMPHOMA IN PRIMARY SJÖGREN'S SYNDROME

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Background: Bcl2-associated athanogene 3 (BAG-3) is a co-chaperone protein that interacts with the ATPase domain on heat-shock protein 70. BAG-3 is involved is several biologic processes including apoptosis, cytoskeleton organization and autophagy and, therefore, it has been extensively investigated in the field of tumorigenesis (1). In particular, BAG-3 expression is constitutive in human primary tumors including leukemias and lymphomas and it is induced in different normal cell types, including leukocytes, by a variety of stimuli. BAG-3 is able to induce and maintain cell proliferation, resistance to therapy and cell motility, namely metastatization. On this basis, a role of BAG-3 in chronic inflammatory diseases may be postulated, but data on this topic are not available.
Objectives: The purpose of our study was to investigate the expression of BAG-3 in primary Sjogren's syndrome (pSS) and the relationship with clinical and serological features.
Methods: BAG-3 concentration was assessed in the serum of 103 patients with pSS according to the 2002 American-European classification criteria and in 40 sex and age matched healthy donors (HD). Clinical and serological records were collected and statistical analysis was performed with SPSS 21.0.
Results: Twenty-six pSS patients were positive for BAG-3 (BAG-3+), with serum levels ranging from 32.1 to 950 pg/ml. When setting the cut-off value according to the highest value found in HD (300 pg/ml), we identified 13 pSS patients displaying a peculiar clinical serological phenotype. In detail, in this subgroup of pSS patients the prevalence of purpura, low C4, both anti-Ro and anti-La autontibodies, rheumatoid factor and lymphoma was higher, when compared to pSS patients with BAG-3 levels $<$300 pg/ml or BAG-3- (all $p<0.05$). Furthermore, they displayed less frequently sicca symptoms such as xerostomia and xerophtalmia (both $p<0.05$). Binary logistic regression analysis revealed that pSS patients with BAG-3 levels $>$300 pg/ml had on odds ratio (OR) of 12 (95% CI 1.9–86, p=0.009) for lymphoma and this association was independent of the presence of purpura, a well know marker of lymphoma in pSS. When including low complement, another feature associated with lymphoma, in the multivariable analysis, both low C4 and BAG-3 levels $>$300 pg/ml resulted independently associated to lymphoma (OR=24 and 12.4 respectively).
Conclusions: Our study assessed for the first time serum BAG-3 levels in a large cohort of pSS patients. The results showed that the highest levels of BAG-3 identify a peculiar clinical and serological pSS phenotype, as consequence of a B-cell hyperactivity. Since it is known that BAG-3 is an anti-apoptotic protein playing a pivotal role in cell survival, and that B-cell hyperactivity in pSS is the consequence of coordinated and integrated actions of several stimuli and appropriate cytokines, our results may suggest that BAG-3 overexpression is involved in B-cell proliferation and activity, as well as in oligoclonal and monoclonal expansion in pSS.
References:
[1] Rosati A et al. Cell Death Dis 2011;2:e141.
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SAT0263 NEOPLASIA IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS IN SPAIN: RELESSER REGISTRY DATA

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Background: There is limited evidence on the risk of neoplasia in autoimmune diseases such as systemic lupus erythematosus.
Objectives: The objective of this study is to analyze the incidence of cancer in the Spanish population with SLE and the factors associated in its development: RelesSER Registry Data.
Methods: We calculated the incidence density of malignant neoplasms, the standardized incidence ratio and the average time to develop the first neoplasm after diagnosis of SLE in patients of the SLE registry of the Spanish Rheumatology Society (RelesSER) fulfilling ACR97 criteria. We carried out a bivariate analysis of the associated factors to neoplasms and multivariate by logistic regression.
Results: A total of 3607 patients (90.4% female) were included. We registered 140 neoplasms in women (4.3%) and 14 in men (4%) ($p<0.821$). Incidence density 7.3/1000 patient-years (95% CI:4.85–10.98) (7.39 in patient-years women and 6.93 in men) without significant differences. After stratification by gender and age, cancer appeared in 3.2% of the women aged under 45 versus 3.8% of the men; 4.1% of women aged 45–65 years versus 5.9% of men and a 5.3% of women 65 and older versus 2.5% of men the same age. The standardized incidence ratio (SIR) was 2.16; 1.51 in men and 2.38 in women, highest for women under 65 years old. The SIR for $>$65 years was 0.98; 0.59 in men and 1.55 in women.
The average time until de development of the first malignant neoplasm was 10 years (RI:5.75–17.00), being lower in women [9.5 (RI: 5.00–17.0) years] than in men [12.5 (8.75–17.5)] and in patients under 45 years versus over 45 years [8.0 (RI: 5.00–16.00)].
Malignant neoplasms were the cause of death in 10% of the patients (15/154), predominantly hematological and breast cancers, both at 19% followed by lung cancer in 14.3%.
Factors associated to malignant neoplasms in the bivariate analysis are shown in (table 1). No immunosuppressive therapy was associated with the development of neoplasms. In the multivariate model, adjusted for age and time of disease duration, age was the only significant variable (OR:1.030; 95% CI: 1.003–1.059; p=0.029) with a trend for ACE inhibitors use (OR:1.866; 95% CI: 0.808–4.306; p=0.144), SLEDAI (last visit) (OR: 0.904; 95% CI: 0.806–1.015; p=0.089, SLICC/ACR DI) (without neoplasias) (OR: 1.160; 95% CI: 0.961- 1.401; p=0.123), and duration of the disease in months (OR: 1.003; 95% CI: 1.000–1.006; p=0.068).

Table 1

	Cáncer	Control	*p*
Gender, men %	4	96	0.821
Gender, women %	4.3	95.7	0.821
Mean age at first criterion, years (DS)	38.35 (16.01)	32.72(14.29)	<0.001
Diagnostic age SLE, years (DS)	40.37 (15.68)	34.75 (14.46)	<0.001
Age at last evaluation, years, mean (DS)	57.74 (14.38)	46.17 (14.58)	<0.001
Disease duration (months), mean (DS)	208.71 (102.95)	140.1 (99.69)	<0.001
Follow-up in Rheumatology (months), mean (DS)	170. 1 (90.75)	118.12 (86.90)	<0.001
Sjogren´s syndrome, %	20.5	14.1	0.029
SLEDAI, median [p25-p75]	1.00 [0.00-3.25]	2.0 [0.00-4.00]	0.026
KATZ, median [p25-p75]	3 [2-4]	2 [1-3]	0.001
SLICC*, median [p25-p75]	1.00 [0.00-3.00]	0.00 [0.00-1.00]	<0.001
CHARLSON*, median [p25-p75]	3 [2.00-4.00]	1 [1.00-3.00]	<0.001
Time on antimalarals (months) median [p25-p75]	78.00 (27.75-136.50)	60.00 (24.00-119.00)	0.099

Conclusions: The incidence of neoplasia in Spanish women with SLE is higher than expected for age and gender. Malignant neoplasms were the cause of death in 10% of the patients, predominating hematological and breast cancers followed by lung cancer.
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SAT0264 VALVULOPATHY AND PULMONARY HYPERTENSION IN A SERIES OF PATIENTS WITH ANTIPHOSPHOLIPID SYNDROME

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Objectives: To evaluate the prevalence of cardiac valvular involvement and

pulmonary arterial hypertension (PAH) and predictive risk factors in a cohort of patients with antiphospholipid antibodies.
Methods: We included 232 patients from our cohort who underwent an echocardiogram. A total of 84 (36%) patients with primary antiphospholipid syndrome (PFS), 47 (20%) with APS secondary to systemic lupus erythematosus (SLE), 47 (20%) patients with antiphospholipid antibodies 23%) with SLE without AAF.
The determinations of AAF and lupus anticoagulant were performed according to the indications of the international thrombosis society.
Statistical analysis was performed with SPSS 18; using the Chi square test and the Fisher exact test.
Results: In patients with AAF, the echocardiogram was pathological in 88 patients (52%) (p=0.023). Valvular affectation was evidenced in 64 (38%) (p=0.005) and PAH in 16 (p = ns). Seventeen patients (35%), SAF (48%), SAFS (26%), AIF silent (14%) and 9 patients in the non-AAF group (12%) presented with valvular affectation (p=0.002). PAH presented 19 patients, 9 with SAFP (47%), 6 in the SAFS group (32%), 1 in the silent AAF group (5%) and 3 in the non-AAF group (16%) (p=). Both PAH and valvular involvement were asymptomatic in most cases, although two patients required valvular replacement. The most frequently affected valve in all groups was mitral valve (84%), except in patients with PAH where the most prevalent valvular pathology was tricuspid insufficiency. Patients with valvulopathy and APS had a higher prevalence of total thrombosis than SAF without valvulopathy (p=0.05). Patients with valvulopathy also significantly increased stroke and thrombocytopenia (p=0.04). Patients with valvulopathy had lupus anticoagulant more frequently (p=0.04), with no difference for the rest of AAF.
Conclusions: Subclinical valvular involvement is very common in patients with AAF. Every patient with AAA should be given an echocardiogram in the initial protocol of their study in order to rule out both significant valvulopathy and PAH that can modify the management of the condition.
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SAT0265 CLINICAL CHARACTERISTICS OF SYSTEMIC LUPUS ERYTHREMATOSUS IN AN EGYPTIAN POPULATION: A RETROSPECTIVE COHORT

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Background: Systemic lupus erythrematosus (SLE) is an autoimmune disease with a myriad of manifestations, that could vary among different ethnic and racial groups.
Objectives: To study the prevalence of various manifestations of SLE in an Egyptian population.
Methods: Information in this study was derived from the medical records of SLE patients who followed up in a private clinic in Cairo from January 1980 to June 2016.
Results: This descriptive retrospective case series included 1109 juvenile (19.4%) and adult (80.6%) patients, of which 114 (10.3%) were males and 995 were females (89.7%). Age of onset showed a mean of 26±11.19 years, and the mean of disease duration was 48.78±58.46 months (median: 26 years). The most common manifestations were synovitis (76.7%), malar rash (48.5%), leukopenia (45.7%), and photosensitivity (45.6%). At least one of the antiphospholipid antibodies was present in 41.8% of the patients tested for APL (636 patients). However thromboembolic manifestations and/or recurrent fetal loss occured in 11.5% of the patients. Neuropsychiatric manifestations were evident only in 6.4% of the patients, with seizures being the most common neuropsychiatric manifestation, present in 4% of the patients. 33.1% of the patients had nephritis, which followed the onset of the disease by a mean duration of 20±21.3 months (median=12 months). There were gender differences in the disease characteristics. Cutaneous vasculitis, nephritis, and hypocomplementemia were statistically higher in males (p=0.012, p=0.01, and p=0.041 respectively). Whereas, synovitis, and alopecia were statistically higher in females (p=0.012 and p=0.006 respectively). Patients with juvenile onset had a statisticaly higher frequency of nephritis (0=0.01), seizures (p=0.012) haemolytic anemia (p=0.001), and hypocomplementinemia (p=0.02).
Conclusions: Synovitis and malar rash were the most common manifestations in our study. Secondary antiphospholipid was present in 11.5% of the patients. Male patients and juvenile patients showed a tendency towards a more severe disease.
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SAT0266 EFFECT OF THE METABOLIC SYNDROME ON ORGAN DAMAGE AND MORTALITY IN CHINESE PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS: A LONGITUDINAL ANALYSIS

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Objectives: To study the effect of the metabolic syndrome (MetS) on organ damage and mortality in patients with SLE.
Methods: Consecutive patients who fulfilled ≥4 ACR criteria for SLE and were assessed for the presence of the MetS between 2010 and 2011 were included. Those patients who did not have MetS assessment or succumbed before 2010 were excluded. The MetS was defined by the updated joint consensus criteria, using the Asian criteria for central obesity, when ≥3 of the following components were present: (1) Increased waist circumference to ≥90cm in men or ≥80cm in women; (2) Elevated blood pressure to ≥130/85mmHg or requiring drug therapy; (3) Elevated serum triglyceride level to ≥1.7mmol/L; (4) Reduced serum high density lipoprotein (HDL)-cholesterol to ≤1.0mmol/L in men and ≤1.3mmol/L in women; and (5) Elevated fasting glucose level to ≥5.6mmol/L. Longitudinal data regarding new organ damage, vascular events and mortality on follow-up were retrieved from our cohort database. The association of the MetS with new organ damage and mortality was studied by logistic regression analyses.
Results: 577 SLE patients were studied (93% women; age at entry 41.2±13.4 years; SLE duration 9.3±7.2 years). The mean follow-up time of the patients since entry was 66.3±1.8 months. The mean body mass index (BMI) of the patients was 22.3±3.9kg/m^2 (11% >27kg/m^2). A total of 85 (14.7%) patients qualified the MetS (28% fulfilling waist; 20% fulfilling blood pressure; 25% fulfilling triglyceride; 33% fulfilling HDL and 9.2% fulfilling glucose criteria). New organ damage and vascular (coronary, cerebrovascular and peripheral vascular) events developed in 128 (22%) and 23 (4.0%) patients, respectively. The most common new arterial events were stroke (50%), acute coronary syndrome (33%) and peripheral vascular disease (17%). Thirty-nine (6.8%) patients died (infection 36%; vascular causes 18%; cancer 15%; lung fibrosis 8%; suicide 3%). Patients with the MetS (N=85), when compared to those without (N=492), had significantly higher SDI accrual at their last clinic visits (0.70±1.0 vs 0.26±0.6; p<0.001). Regarding individual systems, the increase in SDI scores in the ocular, renal, cardiovascular, musculoskeletal and endocrine (new diabetes mellitus) systems were significantly higher in the MetS group of patients. New vascular events (11% vs 2.8%; p=0.001), all-cause mortality (14% vs 5.5%; p=0.003), death due to vascular complications (7.1% vs 0.2%; p<0.001) were significantly more common in patients with MetS than those without. Logistic regression revealed that the MetS was significantly associated with new damage in the ocular (OR 2.77 [1.05–7.34]; p=0.04, renal (OR 4.72 [1.86–12.0]; p=0.001), cardiovascular (OR 3.66 [1.03–12.9]; p=0.04] and endocrine system (OR 41.9 [4.93–357]; p=0.001), adjusted for age, sex, SLE duration and the antiphospholipid antibodies (IgG-anticardiolipin or the lupus anticoagulant). The presence of the MetS increased the risk of new vascular events (OR 2.94 [1.18–7.31]; p=0.02), all-cause mortality (OR 1.60 [0.73–3.47]; p=0.24) and vascular mortality (OR 30.3 [3.42–268]; p=0.002) after adjustment for the same covariates.
Conclusions: In this 5-year longitudinal study, the MetS is significantly associated with new organ damage, vascular events and mortality in patients with SLE.
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SAT0267 SERUM 25-HYDROXYVITAMIN D3 LEVELS AND FLARES OF SYSTEMIC LUPUS ERYTHEMATOSUS: A LONGITUDINAL COHORT ANALYSIS

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Objectives: To study the relationship between serum 25-hydroxyvitamin D3 levels and flares of systemic lupus erythematosus (SLE) in a longitudinal cohort of Chinese patients.
Methods: Patients who fulfilled ≥4 of the ACR criteria for SLE were recruited from our rheumatology out-patient clinics in November 2011. Blood was taken at 10 AM and was assayed for the serum levels of 25-hydroxyvitamin D3 by liquid chromatography tandem mass spectrometry (LC-MS/MS). Patients were stratified according to the 25-hydroxyvitamin D3 levels; group 1 (<15ng/ml, deficiency); group 2 (15–30ng/ml, insufficiency); and group 3 (>30ng/ml, adequate); and were followed longitudinally every 2–4 months for serial assessment of disease activity (by SELENA-SLEDAI) and the occurrence of mild/moderate or severe SLE flares (by SELENA flare instrument). Comparison was made among these groups in the baseline and mean summated SLEDAI over time (area under the curve), and the annual incidence of mild/moderate and severe flares by the one-way ANOVA test.
Results: 276 SLE patients were studied (94% women; age 41.0±13.8 years; SLE duration 8.7±6.6 years). 25 (9.1%) patients had eGFR ≤60ml/min. The proportion of patients with 25-hydroxyvitamin D3 levels of <15, 15–30, >30ng/ml was 26%, 54% and 20%, respectively. Patients with vitamin D deficiency (group 1) were significantly younger, had lower body mass index (BMI) but higher baseline eGFR and SLEDAI scores when compared with the other groups. No significant differences in the clinical manifestations were observed among the three groups of patients except for lower prevalence of facial rash in group 3 (p=0.02). After a mean follow-up of 32.5±5.5 months, 153 mild flares and 91 severe flares developed in our patients. The mean summated SLEDAI score over time was: 3.2±2.0 (group 1); 2.4±1.9 (group 2); and 2.7±2.1 (group 3), respectively (p=0.02). The annual incidence of mild/moderate and severe flares was: 0.26±0.39 and 0.20±0.45 (group 1); 0.20±0.33 and 0.09±0.22 (group 2); and 0.20±0.32 and 0.14±0.46 (group 3), respectively (p=NS in all). In a subgroup of 73 patients who did not have clinical or serological SLE activity at baseline (SLEDAI=0), a similar