AB0159 SILENT CEREBRAL MRI FINDINGS IN LUPUS NEPHRITIS AND NON NEPHRITIS PATIENTS

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Background: Lupus nephritis carries high morbidity and mortality and whenever added to neuropsychiatric manifestations lead to more unfavorable prognosis. The current work focused on LN patients comparing them to those without kidney affection, studying their cerebral MRI and its correlation with the histopathological classes of LN and disease activity.

Objectives: To study the effect of renal affection on the brain in SLE and their clinical significance with early detection and management of such lethal comorbidity

Methods: Cerebral MRI and MRA were studied in 40 SLE patients without neuropsychiatric manifestation; 20 LN patients with different histopathological classes and 20 patients without kidney affection. Disease activity was assessed for all patients using SLE disease activity index

Results: Abnormal MRI brain findings were more common in LN patients "though non significant" ($P=0.9$). The most common lesions were white matter hyperintense lesions. Number and size of such lesions were significantly higher in LN patients (1.8 fold that of non nephritis, $P=0.003$ and 0.03 , respectively) and positively correlated with urea, creatinine, urinary albumin/creatinine ratio, SLEDAI, ESR, CRP, and grades of renal biopsy and negatively correlated with c3 and c4. cortical atrophy and prefrontal space dilatation were also significantly higher in LN patients ($P=0.01$).

Conclusion: Asymptomatic MRI brain lesions in LN patients, they are usually clinically significant and correlate to laboratory parameters of LN, grades of renal biopsy, and disease activity independent to age, sex and hypertension.

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Disclosure of Interests: None declared

DOI: 10.1136/annrheumdis-2019-eular.224

AB0160 LUPUS PODOCYTOPATHY-CASE REPORT

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Background: Lupus podocytopathy is a recently recognized new entity of lupus nephritis characterized by diffuse foot process effacement with or without mesangial expansion. Capillary wall immune deposits and glomerular proliferation are lacking in the histopathological analysis. (1) Clinically, it is manifesting as nephrotic proteinuria in the majority of reported cases.(1) Nevertheless, there is insufficient knowledge about the epidemiology, precipitant etiology and choices of management. Here, we describe a case presented with significant proteinuria secondary to foot process effacement with the absence of immunocomplement deposition or glomerular inflammation.

Objectives: To describe unusual presentation of proteinuria in lupus patient secondary to podocyte effacement which is unusual underlying pathology.

Methods: 45 years old female diagnosed to have SLE 14 years back in the setting of malar rash, alopecia, arthritis and positive serology (ANA, Ds DNA). She was doing fine on HCQ till a years ago when she presented to the clinic with gradual onset lower limbs swelling.

Laboratory results showed a significant proteinuria 2781 mg/dl/day, urine analysis showed RBC 1-2 cells/microliter, WBC 2-3 cells/microliter, normal renal profile and normal C3-C4 counts. Kidney

Kidney biopsy was taken and described a picture of minimal change glomerulonephritis with mild mesangial expansion. In addition, the study was negative for the presence of Immunocomplement deposition with the absence of capillary basement membrane and tubulointerstitial inflammation. Patient was treated with Mycophenolate Mofetil 2 grams twice per day and 1mg/kg/day oral steroid.

3 months later, protein was noticeably reduced in urine to 731 mg/dl/day but the patients had a side effect of MFM inform of significant weight loss, gastritis, and diarrhea. Azathioprine had been instituted alternatively with low dose prednisolone 10 mg. Proteinuria level had peaked again after 4 months of starting azathioprine to reach 5660 mg/dl. Kidney biopsy performed again which showed minimal light microscopic changes, the ultrastructural study showed extensive podocyte injury and foot process effacement up to 70% by the electron microscope. Mild mesangial proliferation and focal tubulointerstitial chronic changes. There was no evidence of endocapillary proliferation, subendothelial deposits or glomerular scarring. Immunofluorescence was negative for immunocompetent deposition. Mycophenolate Mofetil has been instituted again but unfortunately, proteinuria inadequately responded and remained between 3-4 grams. Laterally, Cyclosporin 1.25 mg/kg/day has been commence few days ago. All laboratory results like renal profile and complements are with in normal values.

Results: Proteinuria was found to be attributed to diseased podocyte namely lupus podocytopathy. Unfortunately, she has inadequate response to azathioprine and mycophenolate mofetil.

Conclusion: Lupus podocytopathy is a recently recognized new entity of lupus nephritis characterized by diffuse foot process effacement without capillary wall immune deposits and glomerular proliferation. This case presentation illustrate an attention toward this new lupus entity. However, the lack of efficient knowledge about the frequency, clinical features and treatment necessitate further investigation. (2)

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Acknowledgement: Abdulrahman K. Alabdulsalam, MBBS. Anatomic Pathology Assistant Consultant Department of Pathology and Laboratory Medicine King Saud bin Abdulaziz University for Health Sciences Ministry of National Guard

Disclosure of Interests: None declared

DOI: 10.1136/annrheumdis-2019-eular.3108

AB0161 CLINICAL ASSOCIATIONS AND DIAGNOSTIC POTENTIAL OF REGULATORY-LIKE B-CELLS IN SJOGREN'S SYNDROME

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Background: Some B-cell subsets contribute to the regulation of immune responses, mainly through the secretion of interleukin-10, which suppresses T-helper 1 (T_H1) and T_H17 cells and induces regulatory T-cells (Tregs). The role of Bregs and Tregs in Sjögren's syndrome (pSS) pathogenesis is an active field of research.

Objectives: To evaluate the distribution of regulatory and effector T and B-lymphocytes, in patients with pSS and healthy controls (HC), and the relation between regulatory-like B-cell subsets and the pSS phenotype.

Methods: Fifty-seven pSS patients (2002 AECG criteria) and 24 HC were included. Circulating T and B-lymphocytes were characterized by flow cytometry and groups were compared. Significance was considered for $p<0.05$.

Results: Compared to HC, pSS patients had lower percentages (16.9 vs 32.0%, $p<0.001$) and absolute numbers (28 vs 81 cells/ μ L, $p<0.001$) of Breg-enriched CD24^{hi}CD27⁺ B-cells, and a decrease in CD24^{hi}CD38^{hi} B-cells percentages (6.2 vs 7.7%, $p=0.09$).

Lower frequencies of CD24^{hi}CD27⁺ B-cells were found in anti-SSA-positive (n=38) compared to anti-SSA-negative (n=19) patients (15.0 vs 19.6%, $p=0.170$), as well as lower absolute counts (26 vs 31 cells/ μ L; $p=0.173$). Anti-SSA-positive patients presented higher CD24^{hi}CD38^{hi} B-cells percentages (6.2 vs 4.2%;

p=0.260) and absolute counts (10 vs 5 cells/ μ L; p=0.343) compared to anti-SSA-negative patients.

Although CD24^{hi}CD27⁺ B-cells frequencies and absolute counts did not differ between patients with active (n=27) or inactive disease (n=30), (16.9% vs 17.0%, p=0.946; 25 vs 31 cells/ μ L, p=0.179), patients with higher disease activity (ESSDAI $\geq$ 5) (n=9) presented lower absolute counts of CD24^{hi}CD27⁺ B-cells (18 vs 31 cells/ μ L, p=0.096) and lower CD24^{hi}CD38^{hi} B-cells (4 vs 10 cells/ μ L, p=0.075), and higher Th1/Breg CD24^{hi}CD27⁺ ratios, (16.2 vs 9.2, p=0.064).

Considering all patients, a negative correlation was found between the ESSDAI score and the absolute numbers of either CD24^{hi}CD27⁺ B-cells (r= -0.277; p=0.037) and Tregs (r= -0.311; p=0.019).

Correlations with ESSDAI was stronger when looking at patients with ESSDAI $\geq$ 5: for the percentages of CD24^{hi}CD27⁺ B-cells, r= -0.705, p=0.023; for CD24^{hi}CD27⁺ B-cells absolute counts, r= -0.644; p=0.045; and for the absolute counts of Tregs, r= -0.862; p=0.001.

Using ROC curves to discriminate pSS from HC, better AUCs were obtained for CD24^{hi}CD27⁺Breg cells (cut-off 34 cells/ μ L, AUC=0.81), Tregs/CD24^{hi}CD27⁺ Breg ratio (cut-off 1.98, AUC=0.74) and Th1/CD24^{hi}CD27⁺Breg ratio (cut-off 12.23, AUC=0.70), corresponding to a specificity for pSS of 0.83, 0.75 and 0.70, respectively, and sensitivity of 0.75, 0.72 and 0.67, respectively.

In pSS, lower CD24^{hi}CD27⁺ B-cell counts, as well as higher Tregs/CD24^{hi}CD27⁺ Breg and Th1/CD24^{hi}CD27⁺Breg ratios, were associated to a higher frequency of autoantibodies and higher gammaglobulin.

Conclusion: Our findings demonstrated a significant decrease in the Breg-enriched CD24^{hi}CD27⁺ B-cell subset in pSS, which presented a negative correlation with the disease activity. We have demonstrated significant differences in the CD24^{hi}CD27⁺ B-cell subset and respective ratios, presenting a good discriminatory capacity compared to HC. Therefore, this subset may have diagnostic utility in pSS, as it may support the presence of immune dysregulation in suspected cases that don't fulfil the pSS classification criteria. Further studies with increased number of samples and a prospective design are needed to explore this hypothesis.

Disclosure of Interests: Filipe Barcelos Consultant for: Pfizer; Ely-Lilly, Speakers bureau: Novartis, Catarina Martins: None declared, Carlos Gerales: None declared, Ana Luísa Papoila: None declared, Joana Cardigos: None declared, Glória Nunes: None declared, Teresa Lopes: None declared, Nuno Alves: None declared, José Vaz-Patto: None declared, Jaime Branco: None declared, Luís Miguel Borrego Grant/research support from: MSD, Consultant for: MSD; Tecnifar, Paid instructor for: MSD; AstraZeneca, Speakers bureau: MSD; Tecnifar; AstraZeneca

DOI: 10.1136/annrheumdis-2019-eular.2614

AB0162

IMPLEMENTATION OF HYDROXYCHLOROQUINE AT THE PRE-CONCEPTIONAL STAGE IN THE TREATMENT OF ANTIPHOSPHOLIPID SYNDROME ASSOCIATED WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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Background: The problem of correcting the antiphospholipid syndrome (APS) at the planning stage of pregnancy of patients with systemic lupus erythematosus (SLE) is an important task of rheumatology.

Objectives: To study the effect of hydroxychloroquine (HC) on the level of antiphospholipid antibodies titer in women with SLE of low degree of activity at the planning stage of pregnancy.

Methods: The study included 7 women aged from 18 to 44 years with a definite diagnosis of low-level SLE (1–5 points according to the SLEDAI2K scale) and confirmed APS. All patients were characterized by a history of three or more reproductive losses in the gestational age of 10 weeks or more. According to standard laboratory tests, the level of antibodies to cardiolipin (IgM/IgG) and/or to β 2-glycoprotein I (IgM/IgG) (β 2GPI) in a titer above 99 percentile was determined twice in a 12-week interval. Before inclusion in the study, patients received methylprednisolone and acetylsalicylic acid in the recommended dosages. Other drugs potentially affecting the activity of SLE or hemostasis indicators of the patient during the observation period were not administered. At the time of inclusion, patients were prescribed with hydroxychloroquine (HC) in a dose of 400 mg per day orally, in addition to the therapy received earlier. The titer of antibodies to cardiolipin (IgM/IgG) and antibodies to β 2GPI (IgM/IgG) was determined three times: initially, after 3 and 6 months from the start of therapy. Statistical data processing was performed using the MS Excel 2010 statistical software package and MedCalc Version 17.9.7. Data of laboratory parameters are presented in the form of median (Me) and 95% confidence interval (95% CI). Comparison of dependent samples was performed using non-parametric methods (Wilcoxon Signed Ranks Test). The statistical significance of the hypotheses was accepted at a level of p < 0.05.

Results: The initial SLEDAI2K index constituted 4.0 $\pm$ 1.0 points. The median of the level of antibodies to cardiolipin is defined as 69.2 [95% CI 57.4 - 80.0] U/ml,

antibodies to β 2GPI - 69.24 [95% CI 49.7 - 87.5] U/ml. After 3 and 6 months from the start of HC administration, the SLEDAI2K index did not statistically significantly change (p=0.09). 3 months later, a statistically significant decrease in the level of antibodies to cardiolipin (IgM/IgG) by 30.4% was determined relative to the initial one [Me 21.43 (95% CI 20.2-46.1), p = 0.001]. By the 6th month of therapy, a reduced level of antibodies to cardiolipin remained unchanged; there was no statistically significant difference between the rates after 3 and 6 months of HC therapy. The level of antibodies to β 2GPI (IgM/IgG) after three months from the start of therapy remained at the level of the indicator before inclusion in the study. A statistically significant decrease in the level of antibodies to β 2GPI by 28.5% compared to the initial one was determined 6 months after the start of HC administration [Me 19.17 (95% CI 10.8-27.4), p = 0.003].

Conclusion: The study showed that, against the background of additional administration of hydroxychloroquine in patients with APS with low-level SLE, a decrease in the level of antibodies to cardiolipin (IgM/IgG) by 30.4% (p = 0.001) was observed after 3 months of therapy, to β 2-glycoprotein I (IgM/IgG) - by 28.5% (p = 0.003) after 6 months of therapy.

Disclosure of Interests: None declared

DOI: 10.1136/annrheumdis-2019-eular.4937

AB0163

THE ROLE OF IMMUNOREGULATORY MOLECULES ON FATIGUE IN PRIMARY SJÖGREN'S SYNDROME

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Background: Primary Sjögren's syndrome (pSS) is a chronic autoimmune rheumatic disease characterized by exocrine gland dysfunction. The clinical presentation of pSS can vary considerably from predominantly 'sicca' symptoms such as dry eyes and dry mouth to systemic manifestations such as arthralgia, vasculitis and fatigue^{1,2}. Previous work from our laboratory has suggested that immunoregulatory pathways might play a role in fatigue development in patients with pSS³.

Objectives: The first aim was to measure the serum levels of three candidate immunoregulatory molecules (melatonin, TGF- β and IL-10) and determine any relationship with fatigue severity. The second aim was to compare molecular profiles of the immunoregulatory mediators between pSS patients and healthy controls. The third aim was to identify key predictors of fatigue in pSS.

Methods: Serum levels of the three molecules were measured in 124 patients with pSS and 28 healthy non-fatigued controls selected from the United Kingdom Primary Sjögren's Syndrome Registry using various assays. IL-10 concentrations were measured using a cytometric bead array-based immunoassay, melatonin levels were determined using ELISA and TGF- β concentrations were quantified using a bioassay in which HKC-8 cells were stably transfected with a TGF- β inducible CAGA-luciferase reporter construct. Patient fatigue levels were evaluated with a validated self-complete questionnaire and the scores were compared with the immunoregulatory molecular levels using analysis of variance. Significance in immunoregulatory mediators between the patients and controls was determined using the Wilcoxon test. Ordinal logistic regression analysis was performed in a smaller subset of patients (N = 75) to identify the key predictors of fatigue in pSS.

Results: IL-10 was significantly higher in the sera of patients with pSS compared to the healthy controls (p<0.0001). Melatonin showed a positive correlation with fatigue levels within the patient cohort (p=0.1664) whereas IL-10 and TGF- β were inversely related to fatigue severity (p=0.1265 and p=0.0643 respectively). The regression model used the three investigated immunoregulatory molecules, disease specific, haematological and clinical parameters as well as patient reported depression, anxiety and pain as predictors. The model was able to predict fatigue levels to a 67% accuracy.

Conclusion: The study suggests that melatonin may play a role in regulating the immune response in pSS and may affect fatigue levels in patients. Dryness, anxiety, pain and melatonin appear to be the most powerful predictors of fatigue in pSS. Further research into the effects of these immunoregulatory molecules is necessary to gain a better understanding of the pathophysiology of fatigue in pSS.

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Disclosure of Interests: None declared

DOI: 10.1136/annrheumdis-2019-eular.4815