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EVOLVING TOPICS IN pSS PATHOGENESIS

Poster 7

EXPLORATION OF THE CELLULAR MICROENVIRONMENT IN MINOR SALIVARY GLANDS OF PATIENTS WITH PRIMARY SJÖGREN'S SYNDROME BY IMAGING MASS CYTOMETRY

Bharaj T.*, Helgesen Y., Fromreide S., Borge H., Brokstad K., Cox R., Tornaas S., Brun J., Jonsson R., Bergum B., Appel S., Skarstein K.
Gade Laboratory for Pathology, Department of Clinical Medicine, University of Bergen, Bergen, Norway

There is a critical need to understand the immunopathogenesis in primary Sjögren's syndrome (pSS), both on a cellular and clinical level. In our previous work, we proposed an Inflammatory severity index stratification model to classify pSS patients into three distinct groups based on the grade of inflammation in their minor salivary gland (MSG) biopsies.
The advancement of inflammation was described using both the focus score (FS; number of cell infiltrates containing ≥50 mononuclear cells per 4 mm^2 of tissue) and germinal centre-like structures (GC). Patients with mild lesions (FS ≤1) were included in the first group (S1), patients with moderate lesions (FS ≥2) were included in the second group (S2), while patients displaying severe lesions (FS ≥2) and GC in their MSG tissue were classified in the third group (S3). In this study, the aim is to compare these patient groups based on cellular phenotypes and interactions in the cell infiltrates using imaging mass cytometry with the Hyperion Imaging System. MSGs of 18 patients and 8 sicca control subjects were included in a tissue microarray (TMA) block. The patients belong to a clinically and histologically well-characterised pSS cohort which has been used in our previous work.
The total antibody panel consisted of 26 metal-isotope conjugated antibodies defining different immune cell subpopulations, both characteristic cell types, and less studied populations. Furthermore, MCD Viewer (Figure 1) was used to assess the quality of the staining and determine spillover, following the data analysis pipeline using CellProfiler, Ilastik, and ImaCytE software.
Analyses are currently ongoing to determine cell-localisation within the tissue and to differentiate the patient groups. Our preliminary results are promising, and we are hopeful that this novel technology will provide new insights to map cellular interactions, especially in cell infiltrates, and further be correlated with clinical features of the patients.

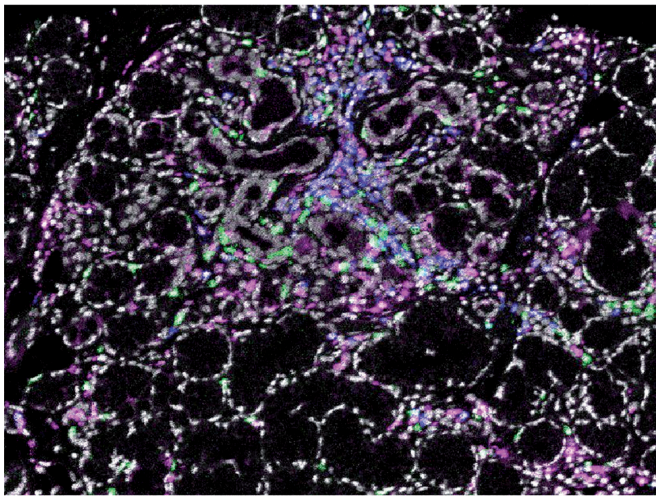

Fig. 1. Preliminary results. MSG of an S3 patient (FS=3, GC-positive) showing CD68+ cells in pink, CD8a+ cells in green, and CD20+ cells in blue. Nuclei (white) stained with Iridium. The image was generated using MCD ™ Viewer, Fluidigm, v1.0.560.6.

Poster 11

CCL5 RELEASE BY CCR9+ CD8 T CELLS: A POTENTIAL NOVEL CONTRIBUTOR TO IMMUNOPATHOLOGY OF PRIMARY SJÖGREN'S SYNDROME

Hinrichs A., Blokland S., Kruize A., Lafeber F., Leavis H., Van Roon J.*
Dept. of Rheumatology and Clinical Immunology, Center for Translational Immunology, UMC Utrecht, Utrecht, Netherlands

Introduction. Increased CCL5 expression and CD8 T cells have been shown to be pivotal regulators of immunopathology in primary Sjögren's syndrome (pSS) and pSS-like disease. Increased CCL5 expression by $CCR9^+$ CD4 T cells has previously been implicated as a contributor to immunopathology in pSS. The role of CD8 T cells and in particular CCR9+ CD8 T cells and their potential to secrete CCL5 has not previously been studied in pSS. In this study we investigated both CCR9 and CCL5 expression by CD8 T cells in pSS patients compared to healthy controls (HC).
Methods. CCR9 expression on CD8 T cells from peripheral blood was compared between patients with pSS and HC by flow cytometry. Intracellular CCL5 expression by naive, memory and effector CCR9- and $CCR9^+$ CD8 T cells was assessed. In addition, the capacity and pace of CCL5 release upon T cell activation was determined for all subsets and compared with CD4 T cells.
Results. The frequency of circulating $CCR9^+$ CD8 T cells in pSS patients is increased compared to HC. Antigen-experienced CD8 T cells, especially $CCR9^+$ effector CD8 T cells, express the highest CCL5 levels, and release the highest levels of CCL5 upon activation. Memory and effector CD8 T cells of pSS patients express significantly less CCL5 and subsequently release less CCL5 upon stimulation compared to HC. $CCR9^+$ CD8 T cells rapidly release CCL5 and significantly more than $CCR9^+$ CD4 T cells.
Conclusions. CCR9+ CD8 T cells express more CCL5 than CCR9- CD8 T cells. CCL5 is rapidly released upon activation, resulting in reduced intracellular expression. Reduced CCL5 expression by an elevated number of antigen-experienced CCR9-expressing CD8 T cells in pSS patients points towards increased release *in vivo*. This suggests that CCL5 release by CCR9+ CD8 T cells contributes to immunopathology in pSS.

Poster 12

B CELL GLYCOSYLATION IN PRIMARY SJÖGREN'S SYNDROME: A NEW POTENTIAL BIOMARKER

Morel M.[1], Pochard P.[2], Dueymes M.[2], Bagacean C.[3], Jousse-Joulin S.[4], Devauchelle-Pensec V.[4], Jamin C.*[2], Pers J.O.[1], Cornec D.[1], Bordron A.[1]
[1]Univ Brest, Inserm, LBAI, UMR 1227, Brest, France, [2]CHU de Brest, Laboratory of Immunology, Brest, France, [3]CHU de Brest, Haematology Department, Brest, France, [4]CHU de Brest, Rheumatology Department, Brest, France

Introduction. Primary Sjogren's syndrome (pSS) is an autoimmune disease characterized by the production of pathogenic autoreactive antibodies. Despite the T cell involvement, in the physiopathology of this disease, is well-documented, less information is available to describe the role of B cells. The etiology of this pathology is poorly understood. Nevertheless, some elements are pointed out including infections, epigenetic mechanisms, etc. Among them, glycosylation, as a physiological process, was also described as playing a key role in the development of various pathological disorders such as cancers. In autoimmunity, abnormal glycosylation of T cell markers takes place in SLE as well as on autoantibodies in pSS suggesting that dysregulation could occur in B cells.
Material and methods. The aim of this project was to study, by cytometry, B cell subset glycosylation in the context of primary Sjögren's syndrome, to identify any potential alteration, and to extend the glycoprofile for serum proteins including immunoglobulins using ELISA assay.
Results. We were able to demonstrate, specific glycoprofiles on B cell subsets such as N and O-glycosylation during B cell differentiation were altered in pSS. As an example of specific glycosylation, B cell hyposialylation was observed but no impairment in fucosylation was noticed. Interestingly, similar observations were obtained with the sera and immunoglobulins of these patients.
Conclusions. This clearly points out that any perturbation of natural glycosylation processes in cells especially in B lymphocytes leads to the development of pathogenic autoantibodies. The correlation between the intensity of

these alterations and the severity of autoimmune diseases could establish glycosylation as a biomarker of choice to identify the development of the pathology in patients, the physiopathology as well as the development of adapted therapeutics for them.

Poster 13

PROPROTEIN CONVERTASE SUBTILISIN/KEXIN TYPE 9 IN A COHORT OF PRIMARY SJÖGREN'S SYNDROME PATIENTS: A NOVEL MARKER OF DISEASE ACTIVITY?

Cafaro G.*[1], Bianconi V.[2], Perricone C.[1], Cosentini E.[2], Riccucci I.[1], Mannarino M.R.[2], Pirro M.[2], Gerli R.[1], Bartoloni Bocci E.[1]
[1]Rheumatology Unit. Department of Medicine and Surgery, Perugia, Italy, [2]Unit of Internal Medicine, Department of Medicine and Surgery, Perugia, Italy

Objectives. Proprotein convertase subtilisin kexin 9 (PCSK9), a serine protease, has been recently identified as key regulator of low-density lipoprotein metabolism with pro-inflammatory immunological effects. Plasma levels of PCSK9 have been demonstrated to be down-regulated in patients with systemic autoimmune diseases, especially in disease remission, to directly correlate with disease activity and to play an immunological role. Primary Sjögren's syndrome (pSS) is a chronic inflammatory autoimmune characterized by variable systemic manifestations and higher cardiovascular risk. The role of plasma PCSK9 in relation to inflammation, immune activation, disease activity and atherosclerosis risk in pSS has never been explored.
Methods. Consecutive pSS patients fulfilling the 2016 American College of Rheumatology/European League against Rheumatism (ACR/EULAR) classification criteria and age- and sex-matched healthy controls (HC) were enrolled. Demographic, disease-related clinical and immunological features and standard lipid profile were assessed. Intima-media thickness (IMT), flow-mediated dilation (FMD) and aortic pulse wave velocity (aPWV) were evaluated as measures of subclinical atherosclerosis. Plasma PCSK9 levels were determined by ELISA. Disease activity was determined by EULAR SS disease activity index (ESSDAI).
Results. Fifty-two patients with pSS (mean age 56 years ± 11, 6% males) and 26 age- and sex-matched HC (mean age 53±14 years, 6% males) were enrolled. Plasma PCSK9 levels were significantly higher in pSS patients as compared to HC [162 (79-255) versus 40 (31-91), $p<0.001$]. In pSS patients, no significant correlation emerged between plasma PCSK9 and C reactive protein, lipid profile and presence of either anti-SSA/Ro and/or anti-SSB/La antibodies. Of interest, patients with high disease activity (ESSDAI ≥5) displayed significantly higher plasma PCSK9 levels as compared to patients with low disease activity (ESSDAI <5). PCSK9 levels were not associated with IMT, FMD or aPWV in patients and HC. Finally, plasma PCSK9 levels were higher in pSS untreated patients as compared to patients treated with corticosteroid therapy ($p=0.006$). No significant difference was detected according to other immunosuppressive therapies.
Conclusions. This is the first demonstration that plasma PCSK9 is upregulated in pSS in comparison to controls subjects and is directly correlated with higher disease activity, independently from lipid profile and atherosclerotic damage. Corticosteroid anti-inflammatory therapy may reduce PCSK9 levels. Further studies are needed to investigate the complex relationship between inflammation, immunological mechanisms, lipid metabolism and atherosclerosis and PCSK9 in pSS.

Poster 18

DECIPHERING THE ROLE OF CDC2S IN SJÖGREN'S SYNDROME: TRANSCRIPTOMIC PROFILE LINKS ALTERED ANTIGEN PROCESSES WITH IFN-SIGNATURE AND AUTOIMMUNITY

Pinheiro Lopes A.*, Hillen M., Hinrichs A., Blokland S., Bekker C., Pandit A., Kruize A., Radstake T., Van Roon J.
Department of Rheumatology & Clinical Immunology/Center for Translational Immunology, Utrecht, Netherlands

Objectives. Type 2 conventional dendritic cells (cDC2s) are key orchestrators of inflammatory responses, linking innate and adaptative immunity. Here we explored the regulation of immunological pathways in cDC2s from patients with primary Sjögren's syndrome (pSS).
Methods. RNA sequencing of circulating cDC2s from pSS, non-Sjögren's sicca (nSS) patients, and healthy controls (HC) was exploited to establish transcriptional signatures. Phenotypical and functional validation was performed in independent cohorts.
Results. Transcriptome of cDC2s from pSS patients revealed dysregulation in type-I interferon (IFN), toll-like receptor (TLR), antigen processing and presentation pathways. Phenotypic validation showed increased CX3CR1 expression and decreased integrin beta-2 and plexin-B2 on pSS-cDC2s. Functional validation confirmed impaired capacity of pSS-cDC2s to degrade antigens and increased antigen uptake, including self-antigens derived from salivary gland epithelial cells. These changes in antigen uptake and degradation were linked to anti-SSA autoantibodies and the presence of type-I IFNs. In line with this, *in vitro* IFNα priming enhanced the uptake of antigens by HC-cDC2s, reflecting the pSS-cDC2 profile. Finally, pSS-cDC2s compared to HC-cDC2s increased the proliferation and the expression of CXCR3 and CXCR5 on proliferating $CD4^+$ T cells.
Conclusions. pSS-cDC2s are transcriptionally altered, and the aberrant antigen uptake and processing, including (auto-) antigens together with increased proliferation of tissue-homing $CD4^+$ T cells suggests altered antigen presentation by pSS-cDC2s. These functional alterations were strongly linked to anti-SSA autoimmunity and the presence of type-I IFNs. Thus, we demonstrate novel molecular and functional evidence for the role of cDC2s in orchestrating immunopathology in pSS. This may yield novel avenues for treatment of pSS.

Poster 19

SINGLE CELL RNA SEQUENCING POINTS TO A ROLE FOR FIBROBLASTS EARLY IN SALIVARY GLAND DYSFUNCTION IN PRIMARY SJÖGREN'S SYNDROME

Pringle S.*[1], Berg M.[2], Spijkervet F.K.[3], Vissink A.[3], Bootsma H.[1], Kroese F.G.M.[1]
[1]Rheumatology and Clinical Immunology, University Medical Center Groningen, Groningen, Netherlands, [2]Pathology and Medical Biology, GRIAC Research Institute, Groningen, Netherlands, [3]Oral and Maxillofacial Surgery, University Medical Center Groningen, Groningen, Netherlands

Background. Salivary gland (SG) dysfunction is commonly associated with the autoimmune disease primary Sjögren's syndrome (pSS). Whilst the more advanced stages of the disease are well studied, the earliest events triggering SG dysfunction remain enigmatic. We sought to elucidate the earliest events suggestive of SG dysfunction, using a non-biased single cell sequencing cell-interaction approach, and biopsies of the parotid SG.
Methods. Parotid gland biopsies were harvested from 12 SSA+ pSS patients grouped into those with with no infiltration (focus score (FS) =0, n=4), intermediate infiltration (FS 0-1, n=4) and a positive focus score (FS>1, n=4). Healthy parotid glands were also harvested (n=4). After digestion, single cell RNA sequencing was performed on all cells present in all biopsies. A total of 24,817 cells were sequenced. Every droplet with ≥500 UMIs was considered a cell. Cells with <200 expressed genes were discarded, as were cells showing mitochondrial gene expression as >25% of total genes. Data was normalized and scaled in SCTransform, and Seurat and CellChat platforms used for further analysis to identify interactions between cell types.
Results. 24 broad cell types were identified in the total sequenced cells, broadly grouped into acinar cells, ductal cells, tissue macrophages and monocytes, B cells, T cells, plasma cells and fibroblasts. 9 different subpopulations of acinar cells were identified. CellChat analysis suggested in FS=0 pSS group that there may be communication between fibroblasts and subsets of the acinar, T and B cells and monocytes. This hypothesized communication was absent or minimal in healthy control, pSS FS0-1 and pSS FS>1 groups. Further pathway analysis pinpointed CXCL12 ligand expression by fibroblasts and CXCR4 receptor by T and B cells and monocytes, in additional to the MIF pathway, as potentially active signaling pathways between the cell types. In order to validate the immunogenic role of fibroblasts early in SG damage in pSS, we are in the process of establishing fibroblast cultures from FS=0 biopsies of pSS patients and comparing their transcriptomes, immunomodulatory capabilities and effect when co-cultured with T cells, B cells and saliva producing acinar cells.
Conclusions. Theoretical analysis based on single cell sequencing data would imply that fibroblast may occupy a central role in the initiation of SG dysfunction or damage in pSS patients. Further validation of this may help us understand how to target this early disease stage, and minimize gland dysfunction.

Poster 23

ABNORMALITIES OF EXTRACELLULAR MATRIX MODELING GENE EXPRESSION IN SALIVARY GLAND EPITHELIAL CELLS OF PATIENTS WITH SJÖGREN'S SYNDROME

Rivière E.*[1], Pascaud J.[2], Letourneur F.[3], Nocturne G.[4], Mariette X.[1]
[1]Immunology of Viral Infections and Autoimmune Diseases, IDMIT, Université Paris Saclay - CEA - INSERM U1184; Rheumatology Department, Hôpital Bicêtre, Le Kremlin Bicêtre, France, [2]Immunology of viral Infections and Autoimmune Diseases, IDMIT, Université Paris Saclay - CEA - INSERM U1184, Le Kremlin Bicêtre, France, [3]Genomic, Hôpital Cochin, Université Paris Descartes, Sorbonne Paris Cité, Paris, France, [4]Le Kremlin Bicêtre, France

Background. Salivary gland epithelial cells (SGECs) are not only the target of autoimmunity in primary Sjögren's syndrome (pSS). SGECs may interact with lymphocytes and therefore participate to the over activation of the immune system (1). Moreover, SGECs may undergo TGFB mediated epithelial to mesenchymal transition during pSS (2).
Objectives. To determine whether SGECs from pSS present intrinsic abnormalities that may be involved in pSS pathogenesis, especially concerning their potential role in salivary gland microenvironment modifications.
Methods. Minor salivary gland (MSG) biopsies were obtained from patients referred for suspicion of pSS to the Rheumatology Department of Bicêtre hospital, AP-HP, Université Paris-Saclay, a tertiary reference center for systemic auto-immune diseases. pSS was defined according to the 2016 ACR/EULAR criteria. RNAseq analysis of primary SGECs (5 controls and 5 pSS) was performed after 2-3 weeks of culture (Illumina). Statistical analyses on the read counts were performed with the DESeq2 package. Absolute FC value>1.5 and p-value<0.05 was applied to identify up and down-regulated genes. Confirmation RT-qPCR were then performed on additional SGECs samples (15 controls and 13 pSS).

Table I. Enrichment pathway analysis of primary cultured SGECs from pSS compared to controls in different conditions of stimulation. Selection of the 10 most significant when more than 10 pathways were defined.

Ingenuity Canonical Pathways	-log(p-value)
Inhibition of Matrix Metalloproteases	3.85
Stearate Biosynthesis I (Animals)	3.46
Glycine Biosynthesis	I2.76
Superpathway of Serine and Glycine Biosynthesis I	2.65
y-linolenate Biosynthesis II (Animals)	2.34
Mitochondrial L-carnitine Shuttle Pathway	2.34
Folate Transformations I	2.3
Glycine Betaine Degradation	2.16
GP6 Signaling Pathway	2.06
Acyl-CoA Hydrolysis	2.03

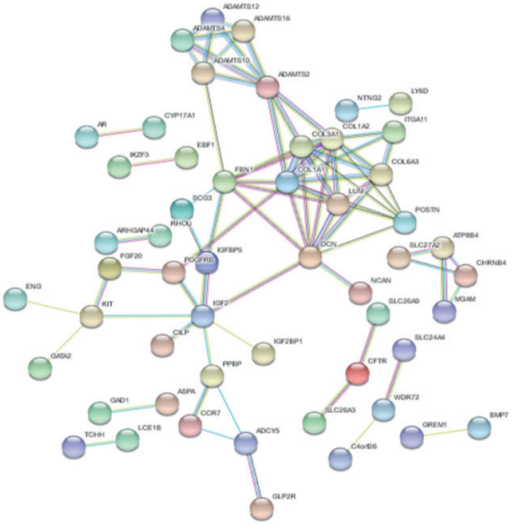

Fig. 1. Representation using String DB software of the existing links between differentially expressed genes between pSS and controls in primary cultured SGECs. Minimum required interaction score = 0.7 (high confidence)

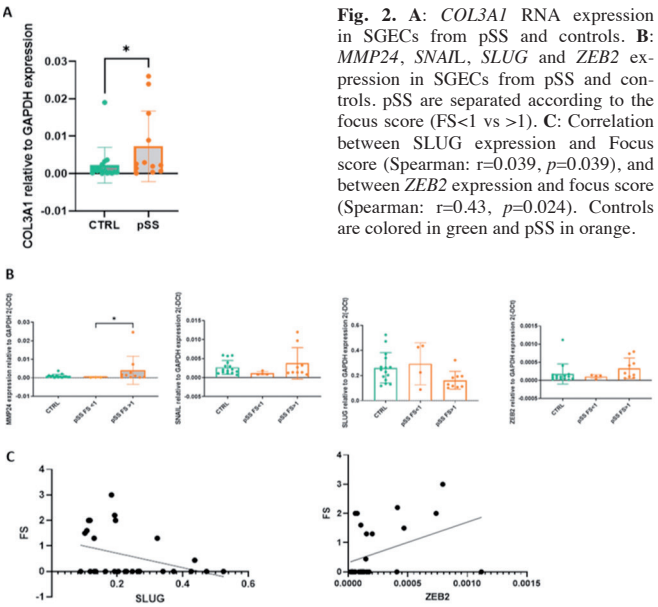

Fig. 2. A: *COL3A1* RNA expression in SGECs from pSS and controls. **B**: *MMP24*, *SNAIL*, *SLUG* and *ZEB2* expression in SGECs from pSS and controls. pSS are separated according to the focus score (FS<1 vs >1). **C**: Correlation between SLUG expression and Focus score (Spearman: r=0.039, *p*=0.039), and between *ZEB2* expression and focus score (Spearman: r=0.43, *p*=0.024). Controls are colored in green and pSS in orange.

Results. RNAseq analysis of SGECs from pSS compared to controls identified 251 upregulated and 260 downregulated genes. Functional enrichment pathway analysis highlighted an over-representation of the Inhibition of Matrix Metalloproteases signaling pathway (Table I). Among the most upregulated genes, using string DB software, we identified hubs corresponding to genes involved in extracellular matrix formation, such as collagen genes and ADAMTS genes (Figure 1). RT-qPCR allowed to confirm the upregulation of COL3A1 in SGECs from pSS compared to controls (Figure 2A). Interestingly, among the other upregulated genes in RNAseq, MMP24 was significantly higher in SGECs from pSS with a focus score (FS) >1 on MSG biopsy than pSS with a FS <1 (Figure 2B). We hypothesized that SGECs may undergo epithelial-mesenchymal transition (EMT) during pSS. We looked at EMT transcription factors, and observed a trend for an up regulation of SNAI1 (coding for SNAIL) and ZEB2, and for a down regulation of SLUG in SGECs from pSS with FS>1 compared to pSS with a FS<1 (Figure 2B). Interestingly, there was an inverse correlation between SLUG expression and the focus score in SG, and we also observed a correlation between ZEB2 expression and the focus score (Figure 2C).
Conclusions. We found an increased expression of Matrix Metalloproteases signaling pathway and a trend for increased expression of several genes involved in EMT between pSS and controls. Thus, besides a role in immune cells activation, we found another possible pathogenic role of SGECs in pSS through the induction of SG fibrosis development. The correlation between genes involved in EMT expression and lymphocytic infiltrates in the SG suggests that the crosstalk between SGECs and lymphoid cells could be bi-directional from SGECs to immune cells, but also from immune cells to SGECs.

References

1. Rivière E *et al.*: *ARD* 2020.
2. Sisto M *et al.*: *Arch Immunol Ther Exp* 2020.

Oral communication 24

LONG NON-CODING RNA HCP5 IS A KEY REGULATOR OF CDC2S FUNCTION: IMPLICATIONS FOR SJÖGREN'S SYNDROME

Pinheiro Lopes A.*, Bekker C., Hillen M., Wichers C., Hinrichs A., Blokland S., Pandit A., Kruize A., Rossato M., Radstake T., Van Roon J.
Department of Rheumatology & Clinical Immunology/Center for Translational Immunology, Utrecht, Netherlands

Objectives. Long non-coding RNAs (lncRNAs) are active elements of gene regulation during immune response, as such their impaired function might lead to break of peripheral tolerance and initiation of autoimmune responses. Here, we explored the role of lncRNA HCP5 in regulating crucial functions of type 2 conventional dendritic cells (cDC2s), as key orchestrators of

T and B cell activation, with potential implication in the immune dysfunction in patients with primary Sjögren's syndrome (pSS).
Results. Functional experiments showed that immune activation, mimicked by toll-like receptor and interferon (IFN)-α stimulation, modulates HCP5 expression and that SP1, NF-kB and STAT1 transcription factors are regulators of its expression. HCP5 positively regulated regulates IFN-β, IFN–inducible genes as well as CCL2, CCL5 and CXCL13, sustaining IFN-β production and immune cell trafficking. Moreover, we showed the impact of HCP5 regulation on cDC2s, to drive B and T cell response and found reduced B cell survival in line with reduced TNFSF13B (BAFF) expression. Although limiting costimulatory molecules expression, silencing of HCP5 in cDC2s enhanced Tfh, Th1 and Th17 cytokine production by $CD4^+$ T cells associated with reduced PD-L1 expression and $CD14^+DC3$ skewing. In inflamed salivary glands of pSS patients, HCP5 expression was increased and highly correlated with immune cell infiltration and presence of cDC2s. In circulation, HCP5 expression was also increased in cDC2s of pSS patients compared with HC.
Conclusions. Our study uncovers HCP5 as an important mediator of cDC2 function, impacting type-I IFN signalling as well as mediators involved in cell recruitment affecting both arms of the immune response. Hence, perturbation of this axis in pSS suggests that HCP5 plays an important role in regulating inflammation and its targeting may yield novel avenues to halt immune activation in pSS.

Poster 37

DEFECTIVE LOCALIZATION AND INTERACTION OF AQUAPORIN-5 INTERACTING PROTEIN PARTNERS IN SALIVARY GLANDS FROM PATIENTS WITH PRIMARY SJÖGREN'S SYNDROME

D'Agostino C.*[1], Chivasso C.[1], Filipovic N.[1], Conrad L.[1], Zindy E.[1], Perret J.[1], Muhammad S.S.[1], Moscato S.[2], Baldini C.[2], Mattii L.[2], Delporte C.[1]
[1]Université Libre de Bruxelles, Bruxelles, Belgium, [2]Università di Pisa, Pisa, Italy

Primary Sjögren's syndrome (pSS), the second most prevalent rheumatic disease, is a chronic autoimmune disorder characterized by lymphoplasmacytic infiltration of the exocrine glands, particularly lacrimal and salivary glands (SG), impairing their ability to secrete fluids. The functional unit of SG consists in an epithelial parenchyma made of serous and mucous acinar cells (ACs) producing saliva connected to a network of ducts. Aquaporin-5 (AQP5) is a water channel protein belonging to the aquaporin (AQP) family. AQP5 is normally expressed at the AC apical membrane, where it ensures transmembrane water permeability and saliva formation. AQP5 may play a role in pSS pathogenesis as its expression and distribution is altered in SG acinar cells from patients suffering from pSS. Furthermore, protein-protein interactions contribute to the regulation of AQP's gating and trafficking. We hypothesize that AQP5-interacting protein partners may be involved in its altered distribution in human minor salivary gland (hMSG) acini from pSS patients. The Prolactin Inducible protein (PIP) identified, as a protein partner of AQP5 in lacrimal glands, has been involved in SS pathogenesis, showing lower level of expression in saliva and hMSGs from pSS patients. Ezrin, acting as a linker between the cytoplasmic membrane and the cytoskeleton, has been involved in pSS. Ezrin interacts with lens AQP0 and renal AQP2.
The goal of our study was to investigate a) AQP5-EZRIN, AQP5-PIP as well as PIP-EZRIN interactions in hMSG acini from pSS patients (SICCA-SS), as compared to patients with sicca without pSS (SICCA-NS), as well as in normal SG-SV40 transformed-squamous cells resembling acinar cells (NS-SV-AC), by proximity ligation assay (PLA); b) the localization of AQP5, PIP and EZRIN in hMSG from SICCA-SS as compared to SICCA-NS by double immunofluorescence. Our data revealed for the first time AQP5-PIP, AQP5-EZRIN as well as PIP-EZRIN interactions in hMSG, as well as in NS-SV-AC cells. Furthermore, SICCA-SS hMSG displayed mislocalized and decreased expression of the proteins as well as of the AQP5-EZRIN, AQP5-PIP, and PIP-EZRIN complexes. The complexes were mainly located at the basolateral side of hMSG acini in SICCA-SS instead of at the apical side of hMSG acini SICCA-NS. In conclusion, our study has shown that AQP5 is part of a multiprotein complex in which AQP5 interacting partners may play important role(s) in AQP5 regulation. Furthermore, our data have highlighted the involvement of AQP5 and several of its interacting protein partners in pSS pathogenesis.

Poster 38

EXPLORATORY IMMUNOPHENOTYPE OF THE RARE DISEASE JUVENILE SJÖGREN'S SYNDROME REVEALS A DYSREGULATION OF B AND T MEMORY CELL FREQUENCIES

Martin-Gutierrez L.*[1], Peckham H.[2], Radziszewska A.[2], Peng J.[2], Nettey O.[2], Jury L.[1], Ciurtin C.[2]
[1]Centre for Rheumatology Research, University College London, London, UK, [2]Centre for Adolescent Rheumatology Versus Arthritis, London, UK

Background. Sjögren's syndrome (SS) is an autoimmune rheumatic disease characterised by dryness resulting from chronic lymphocytic infiltration of the exocrine glands. Patients also present with other extra glandular manifestations such as arthritis, anemia and fatigue or various organ and systems involvement. The disease is more frequent in women aged 30-50. However, in rare cases, the disease starts in childhood and is known as juvenile SS (JSS) or childhood SS. Children have different clinical manifestations compared to adults, with dryness being less common, making the diagnosis very challenging.
Objectives. To investigate in depth the immune cell profile of patients with JSS for better understanding of disease pathogenesis.
Methods. Peripheral blood was collected from a cohort of patients with JSS while attending appointments at UCLH clinics. None had received B-cell depletion therapy. Immune-phenotyping of 29 immune-cell subsets, including B and T cells, in peripheral blood from patients with JSS (n=10) and age and sex-matched healthy controls (n=10) was performed using flow cytometry as we have performed previously for patients with adult-onset SS. Data were analysed using multiple t-tests and compared with the adult SS immune phenotype.
Results. Patients with JSS had an average age of 18 years (range 16-21) with an average age of disease onset at 14 years (range 12-18). 60% of patients had anti-Ro autoantibodies and 50% had anti-La autoantibodies.
Patients with JSS had an altered immune profile compared to age matched healthy controls (HCs)(mean age = 18 years, range 15-25). In the B cell compartment, JSS patients had higher frequencies of total CD19+ B cells (p=0.0044), naïve B cells ($CD19^+IgD^+CD27$-) (p=0.0183) and bm2 ($CD19^+IgD^+CD38^+$) (p=0.0490) whereas memory B cell subsets such as early bm5 ($CD19^+IgD$-$CD38^+$) and late bm5 ($CD19^+IgD$-CD38-) were significantly reduced (p=0.0249, and p=0.0117 respectively). Interestingly, in the $CD4^+$ T cell compartment, central memory ($CD4^+CD27^+CD45RA$-) T cells were significantly reduced (p=<0,0001) but effector memory ($CD4^+$CD27-CD45-) and effector memory-re-expressing-CD45RA (EMRA, $CD4^+$CD27-$CD45RA^+$) T-cell subsets were significantly elevated (p=0.0171 and p=0.0002 respectively). There was also a significant increase in $CD8^+$CD25-$CD127^+$ responders T cells (p=0.0392) in JSS patients versus HCs.
Conclusions. This is the first pilot study investigating the immunophenotype profile of patients with JSS. Our preliminary findings suggest altered immune phenotypes in the B-cell compartment in concordance with our previous immunophenotyping studies in adult SS (predominance of naïve and lower frequencies of memory B cells), suggesting an immunological rationale for the use of similar therapies. However, we also found a more specific dysregulation of the responder $CD8^+$ T cell subpopulation in JSS vs. HCs, dissimilar to the widespread $CD8^+$ T cell abnormalities described in adult-onset SS, which requires further studies.

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IMMUNE CHECKPOINT INHIBITOR TREATMENT MAY INDUCE SALIVARY GLAND PROGENITOR CELL PROLIFERATION

Pringle S.*[1], Van Der Vegt B.[2], Vissink A.[3], Bootsma H.[1], Kroese F.G.M.[1]
[1]Rheumatology and Clinical Immunology, University Medical Center Groningen, Groningen, Netherlands, [2]Pathology and Medical Biology, University Medical Center Groningen, Groningen, Netherlands, [3]Oral and Maxillofacial Surgery, University Medical Center Groningen, Groningen, Netherlands

Background. Salivary glands (SGs) can be (severely) damaged by immune checkpoint inhibitor (ICI) therapy, employed for treatment of cancer. In patients with ICI-induced SG dysfunction, 60% progress to fulfill classification criteria for primary Sjögren's syndrome (pSS), owing to immune foci in SGs and/or anti-SSA autoantibody positivity. Here we aim to understand how ICI treatment affects the SG epithelium.

Methods. Immunohistochemistry for CD4, CD8, cytokeratin 7 (CK7), AQP5, Ki67 and PD-L1 was performed in parotid SG biopsies from patients treated with anti-PD-L1 or anti-PD-1 ICIs with hyposalivation developing after commencement of ICI use. Healthy control and pSS patients were co-stained for comparison. Salivary gland organoids (SGOs) were cultured from healthy biopsies following previously published protocols, and cultured as controls, or exposed to 0.1 pg/mL IFNγ and 1ng/mL TNF-α together, or 1 ng/mL, 10 ng/mL or 100 ng/mL of the anti-PD-L1 ICI durvalumab.
Results. Dispersed and focal $CD4^+$ T cell-rich infiltrate was observed in parotid SG tissue following anti-PD-L1 and PD1 ICI treatment. $CD8^+$ T cells were also present in this infiltrate, as were limited B cells. The infiltrate did not mirror B cell rich that characterizes pSS patients. Following ICI-use, no classical $AQP5^+$ CK7- acinar cell clusters were observed (CK7 marks intercalated ducts, IDs). The parenchyma was dominated by aberrant hybrid epithelial 'structures' with ID-like morphology, containing a mixture of $AQP5^+CK7$-, AQP5-$CK7^+$ and $AQP5^+CK7^+$ cells. Hybrid structures contained both proliferative ($Ki67^+$) and senescent (p16+) cells. Healthy SG organoids exposed to IFNγ and TNF-α, mimicking the inflammatory environment following ICI treatment, did not significantly alter in growth dynamics. Exposure of SGOs to durvalumab in the absence of proinflammatory cytokines, an anti-PD-L1 ICI, induced an increase in SGO size, suggesting enhanced proliferation of SGO cells.
Conclusions. We show dramatically altered SG epithelium following anti-PD-L1 and PD-1 ICI therapy, specifically presence of aberrant ID-like structures, and lack of acinar cells with conventional appearance. Exposure of SG progenitor cells to durvalumab induced their proliferation, implying that lack of SG function post-ICI use is at least partially attributable to increased duct cell number. The reason for lack of acinar cells remains to be elucidated. Full appreciation of the mechanism behind this dysfunction remains will be critical to understand ICI induced development of sicca complaints, and development of appropriate treatment strategies.

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FINE MAPPING OF THE DDX6-CXCR5 RISK INTERVAL REVEALS SNPS IN SJÖGREN'S DISEASE WITH FUNCTIONAL SIGNIFICANCE IN IMMUNE CELLS AND SALIVARY GLAND

Wiley M.[1], Khatri B.[1], Tessneer K.[1], Joachims M.[1], Stolarczyk A.[1], Nagel A.[1], Rasmussen A.[1], Bowman S.J.[2], Radfar L.[3], Omdal R.[4], Wahren-Herlenius M.[5], Warner B.[6], Witte T.[7], Jonsson R.[8], Rischmueller M.[9], Gaffney P.[1], James J.A.[1], Rönnblom L.[10], Scofield R.H.[1], Mariette X.[11], Ng W.F.[12], Sivils K.[13], Nordmark G.[10], Tsao B.[14], Lessard C.J.*[1]

[1]Oklahoma Medical Research Foundation, Oklahoma City, USA, [2]University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK, [3]University of Oklahoma College of Dentistry, Oklahoma City, USA, [4]Stavanger University, Stavanger, Norway, [5]Karolinska Institutet, Stockholm, Sweden, [6]National Institute of Dental and Craniofacial Research, Bethesda, USA, [7]Hannover Medical School, Hannover, Germany, [8]University of Bergen, Bergen, Norway, [9]University of Adelaide, Adelaide, Australia, [10]Uppsala University, Uppsala, Sweden, [11]Université Paris-Saclay, Le Kremlin Bicêtre, France, [12]Newcastle Upon Tyne Hospitals NHS Foundation Trust, Newcastle Upon Tyne, UK, [13]The Janssen Pharmaceutical Companies of Johnson & Johnson, Spring House, USA, [14]Medical University of South Carolina, Charleston, USA

Background. Sjögren's Disease (SjD) is a complex autoimmune disease with known genetic risk intervals including the DDX6-CXCR5 locus (1).
Objectives. Identify and functionally characterize SNPs of the SjD DDX6-CXCR5 risk interval.
Methods. Fine mapping of GWAS and ImmunoChip data from 1916 SjD cases and 6893 population controls of European ancestry were imputed and tested for SNP-trait association. Bayesian statistics defined a credible SNP set. Electrophoretic mobility shift assays (EMSAs) and luciferase assays tested allele-specific protein binding affinities or regulatory activity, respectively, in immune cell lines (EBV transformed B (EBV B), Daudi, Jurkat, THP1) and A253 salivary gland epithelial cell (SGEC) line. Chromosome conformation capture with quantitative PCR (3C-qPCR) surveyed the genomic architecture of the DDX6-CXCR5 interval.
Results. SjD association signals in the DDX6-CXCR5 risk interval identified a credible set of risk SNPs. Bioinformatics analysis indicated minimal functionality of the top associated SNP, but further refinement identified 5 SNPs with strong evidence of regulatory activity: rs57494551, located in an intronic region of DDX6, and rs4938572, rs4936443, rs7117261 and rs4938573, all located in the shared promoter/enhancer region between DDX6 and CXCR5. The rs57494551 risk allele increased enhancer activity in B, A253, and THP1 cells (p<0.0001), but decreased activity in T cells (p=0.03). The rs57494551 risk allele decreased promoter activity in T (p<0.0001), THP1 (p=0.015), and A253 (p=0.009) cells. SNP rs4938572 is an eQTL of DDX6 in T cells. The rs4938572 risk allele increased protein binding, promoter (p=0.002), and enhancer (p=0.003) activity in T cells, and promoter activity in A253 cells (p=0.0007), but decreased promoter activity in THP1 (p=0.038). The rs4936443 risk allele increased promoter (p<0.002) and enhancer (p<0.007) activity in THP1 and A253 cells. The rs7117261 risk allele decreased enhancer activity in EBV B (p=0.0184), T (p=0.0252), and A253 (p=0.0007) cells, but increased promoter activity in A253 cells (p=0.0007).
The rs4938573 risk allele decreased promoter activity in EBV B, T, and A253 cells (p<0.05), but increased enhancer activity in THP1 (p=0.0432) and A253 (p=0.0031) cells. 3C-qPCR in EBV B, T, and A253 cells showed similar genomic architecture of the DDX6-CXCR5 interval with regulatory regions carrying rs4938572 or rs57494551 interacting with a region upstream of DDX6 that includes AP002954.1/4 (a reported eQTL). However, no cell type- or allele-specific changes in looping activity were observed.
Conclusions. The SjD DDX6-CXCR5 risk interval contains SNPs demonstrating immune and SGEC-specific allelic effects on protein binding and/or enhancer/promoter activity. Bioinformatic analyses and 3C-qPCR in these cell types suggest SNPs likely regulate promoter/enhancer activity and are not modulating existing chromatin architecture in the interval. Ongoing studies will use CRISPR in iPSC cells to determine how the risk alleles alter expression of these genes in differentiated cell types from a common progenitor.

Reference

1. Lessard *et al.*: *Nat Genet* 45, 1284-1292 (2013).

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CYTOKINE MRNA DETECTION IN SALIVARY GLANDS OF PATIENTS WITH PRIMARY SJÖGREN'S SYNDROME USING THE RNASCOPE® ISH TECHNOLOGY

Borge H.*[1], Fromreide S.[1], Aqrawi A L.[2], Dongre H.[4], Galtung H.[3], Liaaen Jensen J.[2], Skarstein K.[1]

[1]Gade Laboratory for Pathology, Department of Clinical Medicine, University of Bergen, Bergen, Norway, [2]Department of Oral Surgery and Oral Medicine, Faculty of Dentistry, University of Oslo, Oslo, Norway, [3]Institute of Oral Biology, Faculty of Dentistry, University of Oslo, Oslo, Norway, [4]Centre for Cancer Biomarkers (CCBIO), Faculty of Medicine, University of Bergen, Bergen, Norway

Background. RNAScope® is a method for visualization of mRNA within the cell, therefore allowing detection of gene transcripts in a single cell. This will enlighten our understanding of the specific gene expression in formalin fixed paraffin embedded tissue samples while preserving the histopathological features of the biopsy with sufficient sensitivity. This technology was chosen for its ability to detect the cellular origin of cytokines. These small, high-affinity proteins have previously been challenging to detect solely by immunohistochemistry (IHC) due to unsatisfying specificity of the antibodies available.
Objectives. To evaluate mRNA of cytokines in minor salivary gland biopsies from primary Sjögren's syndrome (pSS) patients based on our previous findings in saliva and tears.
Materials and methods. Patients were recruited at the Department of Oral Surgery and Oral Medicine, University of Oslo, Oslo, Norway and were classified according to the AECG criteria. Biopsies from non-Sjögren sicca controls were included for comparison. The paraffin embedded tissue samples were analyzed for CXCL10, CCL3 (MIP-1α), CCL4 (MIP-1β), TNFα, IL-6 and IL-1β with RNAscope® in situ hybridization (ISH) technique. In addition, a combination of ISH and IHC was performed to identify the cell source of the transcripts detected by the RNAscope® probes.
Results. Preliminary results demonstrated an upregulated expression of cytokines in the inflammatory focal infiltrates of pSS patients. Interestingly, cytokines were also observed in small clusters of inflammatory cells and interstitially close to acinar and ductal epithelium. Digital quantification utilizing Qupath software 0.3.2 and statistical analysis of the results are currently ongoing. Additionally, we were able to identify one of several cell types expressing the mRNA transcripts by combining ISH and IHC. Figure 1 illustrates the detection of a cell type expressing IL-6 mRNA. The cell sources of IL-6 were found to be both macrophages and other cells in the inflammatory areas of the salivary glands.

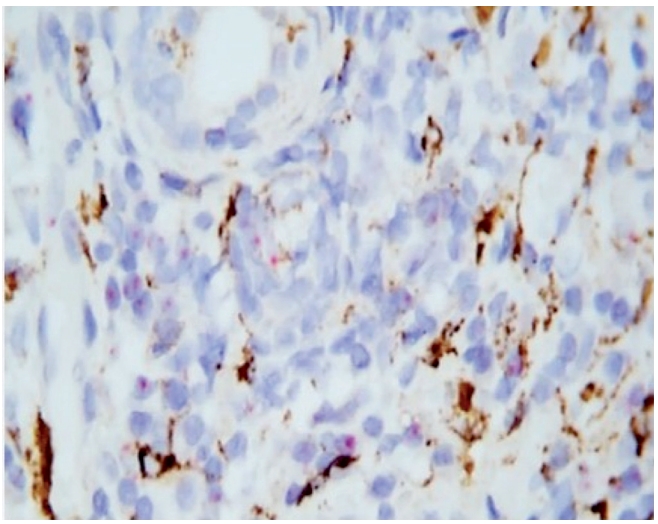

Fig. 1. Small salivary glands from a PSS patient with positive staining of macrophages by CD68 IHC (brown), and detection of mRNA of IL-6 by ISH (red dots), located in the mononuclear cell infiltrate.

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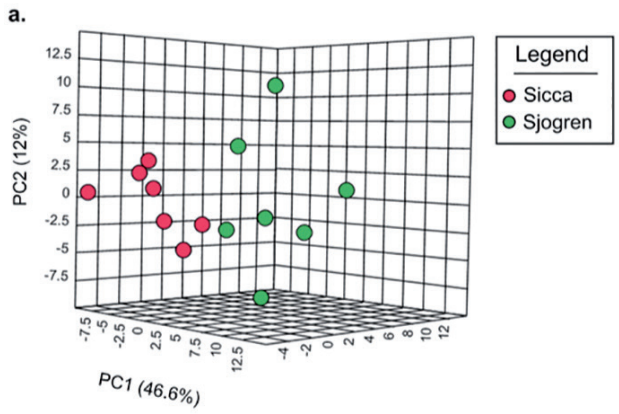
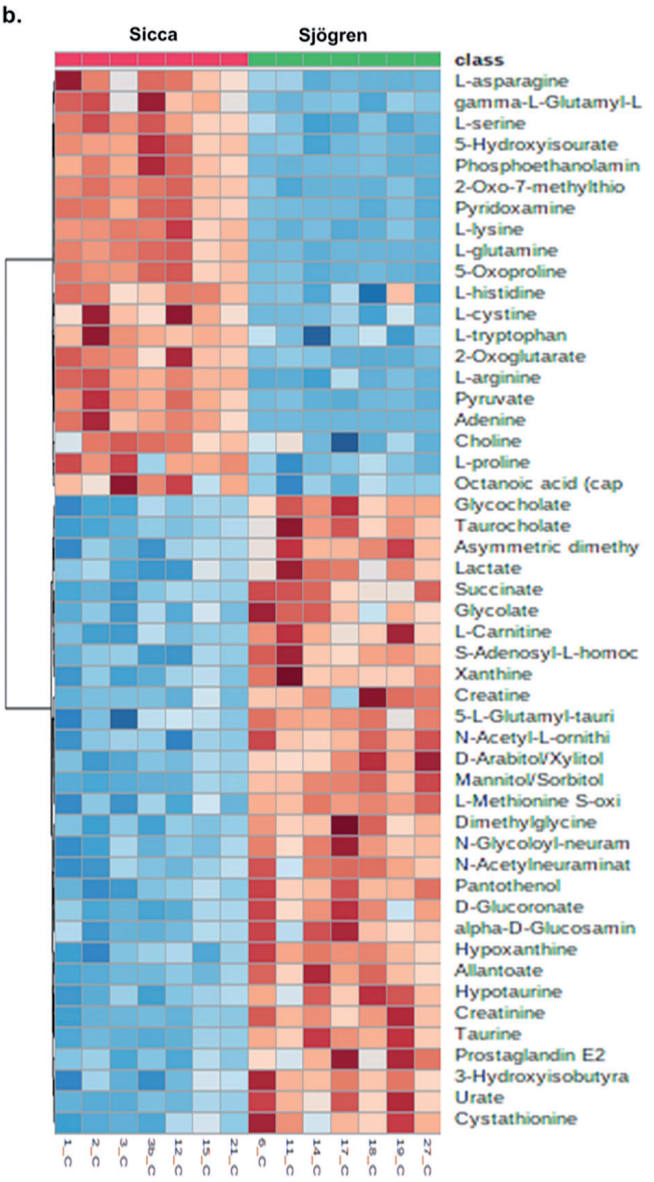
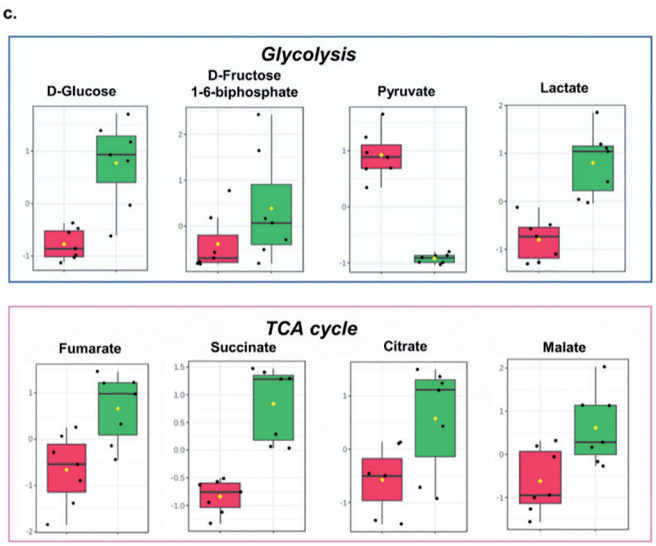
HARNESSING CELL ENERGY METABOLISM TO SUPPRESS SALIVARY GLAND INFLAMMATION IN SJÖGREN SYNDROME

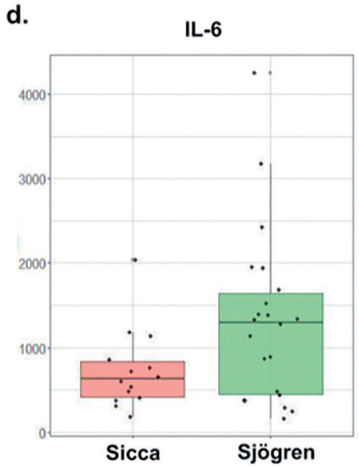
Colafrancesco S.*[1], Barbati C.[1], Stefanoni D.[2], Buoncuore G.[1], Giardina F.[1], Izzo R.[1], Gattamelata A.[1], D'Alessandro A.[3], Cavalli G.[2], Conti F.[1], Priori R.[1]
[1]Sapienza University, Rome, Italy, [2]IRCCS San Raffaele Scientific Institute and Vita-Salute San Raffaele University, Milan, Italy, [3]University of Colorado, Biochemistry and Molecular Genetics Unit, Denver, USA

Objectives. SG epithelial cells (SGEC) play a key role in sustaining inflammation in Sjögren Syndrome (SS), which is indeed termed an 'autoimmune epithelitis'. However, the mechanisms responsible for the inflammatory activation of SGEC remain largely undetermined. Our line of research indicates that SGECs in SS exhibit profound changes in cell energy metabolism as indicated by aberrant expression of autophagy (1). Inhibitions of autophagic process results in a down regulation of SGECs activation (1), thus indicating a crucial role of SGEC energy metabolism in the induction of autoimmune epithelitis. The aim of this study is to characterize metabolic changes occurring in SS SGECs and dissect the link between these changes and their acquired pro-inflammatory function.
Methods. SGECs were isolated from minor SG biopsies deriving from patients with SS and sicca. Intracellular metabolomic analysis was performed on direct ex vivo isolated primary SGECs. As read out of functional activation of SS SGECs, supernatants from SGECs coltures were collected to perform ELISA test in order to evaluate the expression of the pro-inflammatory mediator IL-6.









Metabolic and inflammatory activation of SGECs in Sjögren Syndrome. (**a**) Principal component analysis (PCA) of high-throughput metabolomics analysis of Sicca (n=7) and SS (n=7) SGECs; separation along the component 1 axis (46.6% of variance) indicated profound differences in the intracellular metabolome. SGECs from Sicca are represented as red circles, SGECs from Sjögren are represented as green circles. (**b**) Unsupervised clustering analysis of metabolites in SGECs from Sjögren (n=7) compared to Sicca (n=7). (**c**) Box plots showing statistically significant differences (p-value <0.05, Mann-Whitney) in glycolysis and TC cycle metabolites between Sicca (n=7) and Sjögren (n=7) SGECs. (**d**) Box plots showing statistically significant differences (p-value <0.05, Mann-Whitney) in concentrations of IL-6 in the supernatants of Sicca (n=14) and Sjögren (n=21) SGECs.

Results. Principal component analysis (PCA) of high-throughput metabolomics analysis of sicca (n=7) and SS (n=7) SGECs revealed a separation along the component 1 axis (46.6% of variance) indicating profound differences in the intracellular metabolome (Figure 1a). Unsupervised clustering analysis of metabolites revealed profound metabolic differences between SS and (n=7) sicca (n=7) SGECs (Figure 1b). Analysis of selected metabolites confirmed a shift towards increased glycolysis and TCA cycle activation in SS SGECs (Figure 1c). Supernatant concentrations of IL-6 were higher in SS (n=21) compared to sicca (n=14) SGECs (Figure 1d).
Conclusions. SGECs from SS patients display altered cell energy metabolism with evidence of increased glycolysis and activated TCA cycle. A metabolic driven pro-inflammatory status of SS SGECs seems confirmed by increased basal expression of IL-6. Validation of our metabolomic results, along with transcriptomic and epigenetic studies, is currently ongoing in SGECs from SS and sicca to dissect the link between changes in cell energy metabolism and their acquired pro-inflammatory phenotype.

Reference
1. Colafrancesco S *et al*.: Maladaptive autophagy in the pathogenesis of autoimmune epithelitis in Sjögren's syndrome. *Arthritis Rheumatol* 2022; 74(4): 654-64.

Poster 44

LABIAL AND PAROTID SALIVARY GLAND HISTOPATHOLOGY IN PRIMARY SJÖGREN'S SYNDROME

Nakshbandi U.*, Van Ginkel M.S., Bootsma H., Liefers S.C., Spijkervet F.K., Vissink A., Van Der Vegt B., Kroese F.G.M.
University Medical Center Groningen, Groningen, Netherlands

Background. Salivary gland involvement is a hallmark of disease in primary Sjögren's syndrome (pSS). This is reflected by the prominent role of a positive biopsy within the ACR-EULAR classification criteria, which is solely based on the focus score (FS). In pSS all salivary glands might be involved in the disease process. For this reason, both labial and parotid salivary gland biopsies can be used for diagnosis and evaluation. Although nearly all clinical centres obtain labial gland biopsies for classification and diagnosis of pSS, a parotid biopsy is also a safe and effective procedure. Furthermore, it has a comparable diagnostic potential in pSS, might be associated with less morbidity, and may even detect presence of subclinical MALT lymphomas. However, histopathological differences between both types of salivary glands should potentially be taken into account.

Objectives. The aim of this study was to get histopathological insight in minor (labial) and major (parotid) salivary glands in pSS patients in comparison with non-SS sicca patients.
Methods. Both labial and parotid salivary gland biopsies were obtained from 99 patients. According to the expert opinion of three experienced rheumatologists, 36 patients were classified as pSS patients and 63 as non-SS sicca patients. Salivary gland biopsies were formalin fixed, paraffine embedded and serially sectioned at 3-4µm. Sections were stained with H&E and for CD3, CD20, CD45, hmwCK, CD21, Bcl6, IgA/IgG and IgM. Focus score (FS), relative area of lymphocytic infiltrate, level of lymphoid organization and presence of a plasma cell shift were determined. In addition, number of lymphoepithelial lesions, germinal centers, follicular dendritic cell networks, B-cells and T-cells were analyzed.
Results. All histopathological parameters differed significantly between pSS and non-SS sicca patients in both labial and parotid salivary gland sections. Comparison of the two salivary gland types of non-SS sicca patients revealed more signs of inflammation in labial gland biopsies as shown by a significantly higher FS, $CD3^+$ T-cells, $CD20^+$ B-cells and relative area of $CD45^+$ infiltrates compared to non-SS parotid salivary gland biopsies. Other histopathological parameters were comparable between the two types of salivary glands. In pSS patients, a higher FS and relative area of $CD45^+$infiltrates was observed in labial gland biopsies compared to parotid gland biopsies. Nevertheless, relative and absolute $CD20^+$ B-cell counts, GCs/mm^2 and LELs/mm^2 were higher in parotid gland parenchyma (Table I).
Conclusions. This study shows in labial salivary gland biopsies of non-SS sicca patients more signs of (unspecific) inflammation compared to parotid biopsies. In parotid gland biopsies signs of B-cell hyperactivity, such as number of CD20+B-cells, GCs/mm^2 and LELs/mm^2, are more pronounced, compared to labial gland biopsies. These histopathological differences should be taken into consideration in diagnosis and classification of Sjögren's disease.

Table I. Histopathological data of labial and parotid salivary gland biopsies in non-SS Sicca patients and pSS patients.

	pSS patients (n=36)			Non-SS sicca patients (n=63)		
	Labial SG	Parotid SG	p-value	Labial SG	Parotid SG	p-value
Area of salivary gland section in mm^2	11.6 (9.3-16.1)	8.0 (5.2-13.8	0.01	10.6 (7.6-15.2)	10.2 (6.9-12.8	0.47
Focus score	1.4 (1.0-2.4)	1.1 (0.3-1.8)	0.06	0.2 (0-0.66)	0 (0-0.3)	*0.001*
LELs/mm^2	0 (0-0.15)	0.05 (0-0.28)	*0.03*	0 (0-0)	0 (0-0)	1.00
FDC-networks/mm^2	0.07 (0-0).20)	0 (0-0.41)	0.43	0 (0-0)	0 (0-0)	0.01
GCs/mm^2	0 (0-0)	0 (0-0.11)	0.02	0 (0-0)	0 (0-0)	1.00
CD3*cells/mm^2	560 (261-1199)	470 (177-1334)	0.29	266 (187-453)	94 (65-176)	*<0.001*
CD3* cells (%)	10.2 (4.8-18.6)	7.7 (2.7-21.1)	0.76	4.7 (3.4-7.5)	1.8 (1.2-3.0)	*<0.001*
CD20*cells/mm^2	257 (160-529)	365 (61-877)	*0.05*	59 (34-124)	16 (7-24)	*<0.001*
CD20*cells (%)	4.7 (2.8-8.5)	6.1 (1.0-16.3)	*0.03*	1.0 (0.6-2.2)	0.3 (0.1-0.5)	*<0.001*
CD3(CD20 segregation, n (%)*	20 (55.6)	18 (50.0)	0.72	7 (11.1)	4 (6.3)	0.45
CD45*cells (%)	21.5 (12.9-31.5)	7.9 (1.5-22.2)	*<0.001*	8.5 (4.7-12.1)	0.5 (0.2-0.9)	*<0.001*
IgA/IgG plasma cell shift, n (%)*	25 (69.4)	19 (52.8)	0.23	3 (4.8)	1 (1.6)	0.63
IgM plasma cells/mm2	88 (29-217)	35 (14-89)	*<0.001*	11 (5-22)	8 (4-21)	0.34

Data is reported as median (IQR) or n (%). LEL: lymphoepithelial lesion; FDC: follicular dendritic cell; GC: germinal center.

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USE OF SALIVARY AUTOANTIBODIES IN SICCA PATIENTS TO DETECT DISEASE

Tsaliki M.*[1], Cavett J.[2], Kurien B.[2], Bruxvoort C.[1], Scofield R.H.[3], Koelsch K.A.[2]
[1]University of Oklahoma Health Sciences Center, Department of Pathology, Oklahoma City, USA, [2]University of Oklahoma Health Science Center, Department of Medicine, Section of Diabetes and Endocrinology, Oklahoma City, USA, [3]Department of Veteran Affairs, Medical Research, Oklahoma City, USA

Introduction. Diagnosis of Sjögren's Syndrome (SS) depend on clinical manifestations that can take a long time to develop resulting in undiagnosed patients. Clinic examination involves invasive tests and measurement of serum levels of anti-Ro\SSA, anti-La\SSB, and rheumatoid factor antibodies; the former is part of EULAR/ACR research classification criteria. Antibody secreting cells accumulate in the salivary glands of SS patients and produce autoantibodies, which may be present in the saliva prior to the sera of sicca patients. Several patients present to the clinic with Sjögren's-like symptoms

but do not meet the classification criteria, hence are characterized as non-SS (NSS) sicca. These subjects are commonly understudied and excluded from clinical trials. We hypothesize that there is a significant presence of autoantibodies in the saliva of SS and NSS sicca subjects and that there is a correlation between IgG/IgA levels and clinical characteristics.
Methods. We screened frozen whole unstimulated saliva samples from SS (n=200), NSS (n=200), and healthy controls (HCs; n=46) to detect salivary autoantibodies using ELISA. All subjects in this study have been clinically evaluated at the OMRF Sjögren's Syndrome clinic (OSSCORT). We validated our ELISA results using a capillary western blot method (Jess by ProteinSimple). We compared and correlated disease manifestations among those with, and without, salivary antibodies.
Results. Our analysis showed that salivary anti-Ro antibodies were significantly more prevalent among pSS (38.7%; IgG, 36.5%; IgA) compared to NSS sicca subjects (5.55%; IgG, 3.19%; IgA) and HC (0%; IgG, 4.76%; IgA). Similarly, salivary anti-La antibodies were significantly more common in pSS patients (25.2%; IgG, 39.6%; IgA) compared to NSS sicca subjects (5.5%; IgG, 15.2%; IgA), which in turn had significantly higher anti-La IgA antibody levels compared to HCs (0%; IgG, 2.32%; IgA). A similar pattern holds for RF which were more common in saliva of pSS (10%; IgG, 27%; IgA) and NSS sicca subjects (7.9%; IgG, 11.5%; IgA) compared to HCs (2.22%; IgG, 4.35%; IgA). NSS subjects with salivary anti-Ro/La were not statistically distinct in terms of disease manifestations compared to pSS subjects. In this cohort, 24 SS and 29 NSS sicca subjects were seronegative, but saliva positive, for anti-Ro antibodies. Lastly, NSS sicca subjects with salivary autoantibodies have similar ocular and oral dryness to that of SS subjects.
Conclusions. One of the hallmarks of SS is persistent mouth dryness that could be caused by damage, lymphatic infiltrations, and/or inflammation in salivary glands. Salivary glands in SS patients are sites where antibody-secreting cells accumulate and secrete autoantibodies that are then detected in saliva. Thus, salivary autoantibodies could be used as a diagnostic tool to detect patients with early disease onset and assist in the prognosis of SS. Our results indicate a subset of NSS sicca subjects who may have early disease onset and will eventually seroconvert or will remain seronegative as a distinct phenotype of the disease.

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TRANSCRIPTOME-WIDE ASSOCIATION STUDY OF SJÖGREN'S DISEASE RISK ALLELES IDENTIFIES NOVEL GENES WITH ALTERED EXPRESSION IN MINOR SALIVARY GLAND AND OTHER TISSUES

Radziszewski M.[1], Wiley M.[1], Khatri B.[1], Tessneer K.[1], Rasmussen A.[1], Bowman S.J.[2], Radfar L.[3], Omdal R.[4], Wahren-Herlenius M.[5], Warner B.[6], Witte T.[7], Jonsson R.[8], Rischmueller M.[9], Gaffney P.[1], James J.A.[1], Rönnblom L.[10], Scofield R.H.[1], Mariette X.[11], Alarcón-Riquelme M.E.[12], Ng W.F.[13], Sivils K.[14], Nordmark G.[10], Deshmukh U.[1], Farris A.D.[1], Lessard C.J.*[1]
[1]Oklahoma Medical Research Foundation, Oklahoma City, USA [2]University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK, [3]University of Oklahoma College of Dentistry, Oklahoma City, USA, [4]Stavanger University, Stavanger, Norway, [5]Karolinska Institutet, Stockholm, Sweden, [6]National Institute of Dental and Craniofacial Research, Bethesda, USA, [7]Hannover Medical School, Hannover, Germany, [8]University of Bergen, Bergen, Norway, [9]University of Adelaide, Adelaide, Australia, [10]Uppsala University, Uppsala, Sweden, [11]Université Paris-Saclay, Le Kremlin Bicêtre, France, [12]Genyo, Center for Genomics and Oncological Research, Pfizer/University of Granada/Andalusian Regional Government, Granada, Spain, [13]Newcastle Upon Tyne Hospitals NHS Foundation Trust, Newcastle Upon Tyne , UK, [14]The Janssen Pharmaceutical Companies of Johnson & Johnson, Spring House, USA

Background. Sjögren's disease (SjD) is an autoimmune disease characterized by reduced function of exocrine glands, but also has systemic manifestations affecting multiple organs (1). How genetic and epigenetic changes influence epithelial-immune cell interactions in SjD pathogenesis remain understudied.
Objective. Evaluate the role of SjD risk loci in minor salivary gland (MSG) tissue to identify genes potentially involved in salivary gland dysfunction.
Methods. SNPs from 16 regions with SNP-SjD associations (P<5x10-8) in our GWAS (2) were interrogated for eQTLs in Genotype-Tissue Expression (GTEx) MSG data. Further analyses identified genes that were eQTLs in the MSG and significantly expressed in RNA-seq and ATAC-seq data from the submaxillary salivary gland epithelial cell line, A253. Pathway enrichment analysis was performed using gProfiler on genes where coalescence of eQTL, RNA-seq, and ATAC-seq data was observed. Transcriptome-wide association study (TWAS) analysis was performed using GWAS summary statistics and MSG eQTL GTEx data.
Results. In total, 5884 genome-wide significant SNPs were identified as MSG eQTLs using two discovery thresholds: p(FDR)<0.05 provided by eQTL study (3566 SNPs) and p(FDR)>0.05 and p<0.05 in eQTL study (2318 SNPs). Ten SjD risk loci carried SNPs that were MSG eQTLs for a total of 155 unique genes with coalescence of RNA- and ATAC-seq data in A253 cells. Many SNPs altered the expression of the nearest gene to the risk allele (*i.e.*, index gene), such as IRF5 and TNPO3 on chromosome 7 at 128Mb. This locus also had 12 additional genes that were eQTLs in MSG. In contrast, other loci had no reported eQTLs for the index gene, but several reported eQTLs for other genes, such TYK2 on chromosome 19 at 10Mb that showed no change in TYK2 expression but eQTLs for 8 distant genes, including ICAM1. Pathway enrichment analysis revealed an enrichment in Butyrophilin (BTN) family interactions (R-HSA-8851) (PAdj=1.564x10-5), including the BTN2A1, BTN2A2, BTN3A1, BTN3A2 and BTN3A3 gene cluster in the MHC region. Further, TWAS of MSG and the SjD GWAS summary statistics (after Bonferroni correction) showed association between SjD and BTN3A2 (p=3.52e-54), as well as many other loci in the MHC region. Several long non-coding RNAs on chromosome 17 were also observed in TWAS of lung, spinal cord, and liver. LINC02210 (p=3.58x10-10). LINC02210 was also observed in TWAS of lung, spinal cord, and liver. LINC02210 had a positive z-score in liver (6.02), opposite of the negative z-scores reported in MSG (-6.27), lung (-5.99), and spinal cord (-6.27).
Conclusions. SjD risk alleles influence disease by altering gene expression in MSG. Interestingly, we observed MSG eQTLs for several BTN family genes, which act as cell-surface binding partners to regulate cell-cell interactions, including interactions between epithelial cells and activated T cells (3). Additional transcriptional studies of SjD MSG tissues and other tissues will provide further insights into SjD pathology.

References
1. Verstappen: *Nat Rev Rheumatol* 2021;17(6): 333-48.
2. Khatri *et al*.: *Ann Rheum Dis* 2020; 79: 30-31.
3. Arnett HA, Viney JL: *Nat Rev Immunol* 2014; 14: 559-69.

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(withdrawn by authors)

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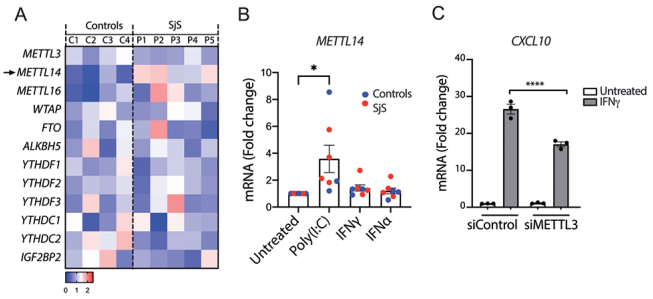
M6A METHYLATION OF RNA IN SALIVARY GLAND EPITHELIAL CELLS: ROLE IN SJÖGREN'S SYNDROME

Shalabi H., Riviere E., Pascaud J., Nocturne G., Mariette X., Bechara R.*
Université Paris-Saclay, Inserm UMR1184, Le Kremlin Bicêtre, France

Background. Finding an efficient treatment of Sjögren's syndrome (SjS) will require a comprehensive understanding of molecular pathways that regulate inflammation within salivary gland epithelial cells (SGEC). Whereas regulation at the level of gene transcription is well established, post-transcriptional control of mRNA is also a vital component in immune responses. Several immune mRNAs were shown to carry a methylation at the N6 position of adenosine, called m6A. m6A is added to specific RNA by methyltransferases termed 'writers', which can be reversed by demethylases 'erasers'. Diverse 'readers' can bind to m6A and impact RNA stabilization and/or translation. These features gave rise to the field of epitranscriptomic and much is yet to be learned, including whether m6A marks are implicated in SGEC function.
Methods. To assess whether m6A machinery components are differentially expressed in SjS vs controls, we retrieved RNA-seq data from SGEC sorted from minor salivary gland biopsies. We specifically looked at the expression of the m6A machinery (writers, erasers, readers). Simultaneously, we stimulated cultured SGEC from controls and SjS with different cytokines and evaluated the expression of the m6A machinery. We finally determined the functional role of m6A writer in SGEC by performing knockdown experiments using small interfering RNA.
Results. Among the differentially expressed genes in sorted SGEC from controls and SjS, we noticed a significant increase in METTL14 expression (component of the m6A writer complex), whereas other component of the m6A machinery were similarly expressed (Fig A). METTL14 mRNA total counts positively correlated with the lymphocytic infiltration. We then investigated whether inflammatory triggers (Poly(I:C), IFNα/γ) similarly increase METTL14 expression in primary SGEC cultured in vitro. Poly(I:C)-stimulated SGEC increased the expression of METTL14 mRNA in both controls and SjS (Fig B). Interestingly, METTL14 was not differentially expressed in cultured SGECs from SjS and controls without any stimulation. These findings suggest that the abnormal increase in METTL14 observed in SGEC sorted from SjS is the consequence of a pro-inflammatory microenvironment present in the glandular epithelia of SjS rather than an intrinsic activation of these cells. To further assess how pro-inflammatory triggers contribute to SGEC activation through m6A modification, we performed knockdown experiments of the catalytic activity of the m6A writer (METTL3) and evaluated the expression of CXCL10, a well-known chemokine involved in the accumulation of T cells in salivary glands. Interestingly, knockdown of METTL3 decreased CXCL10 expression upon SGEC activation by pro-inflammatory triggers (Fig C).
Conclusions. SGEC, whether directly sorted from SjS or activated in vitro, overexpress METTL14, component of the m6A writer complex. Such alterations may affect the whole RNA methylome and hence differentially regulate the expression of genes implicated in SjS which is under evaluation. Collectively, post-transcriptional regulation in SGEC via m6A marks represents a previously unidentified paradigm of inflammation in SjS.



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1) ABNORMALITY OF TYPE I INTERFERON SIGNALLING IN B CELLS IN PRIMARY SJÖGREN'S SYNDROME AND THE IMPACT ON LABORATORY AND CLINICAL FINDINGS

Ritter J.[1], Szelinski F.*[1], Aue A.[2], Stefanski A.[1], Schrezenmeier E.[2], Lino A.[3], Dörner T.[1]
[1]Department of Rheumatology and Clinical Immunology, Charité - Universitätsmedizin Berlin, Berlin, Germany, [2]Department of Nephrology and Intensive Care, Charité - Universitätsmedizin Berlin, Berlin, Germany, [3]German Rheumatism Research Center (DRFZ), a Leibniz Institution, Berlin, Germany

B cell hyperactivity, manifested by autoantibody production (anti-SS-A, anti-SS-B) and hypergammaglobulinaemia as well as interferon (IFN) signature play a central role in the pathogenesis of primary Sjögren's Syndrome (pSS). The link between these hallmarks is still elusive. While treatment of pSS remains limited, an improved understanding of the interrelation between IFN and JAK/STAT signalling within B cells may hold promise to improve potential treatment targets and related biomarkers for specific pSS subgroups. Peripheral blood from 47 pSS patients and 36 matched healthy controls (HC) were stained with B cell markers together with intracellular Signal Transducers and Activators of Transcription 1 (STAT1), STAT2, pSTAT1 and 2, Interferon Regulatory factor 9 (IRF9) and IRF1 and analysed by using flow cytometry. Cell subsets and correlations with all markers and clinical information were subjected to statistical analyses.
Compared to HC, the pSS group showed significantly elevated STAT1 expression among all B cell subsets (p>0.0001) including naïve (CD27-IgD$^+$), pre-switched (CD27$^+$ IgD$^+$), switched-memory (CD27+IgD-), double negative (CD27- IgD-) B cells and plasmablasts (CD20low CD27++).
Furthermore, IRF9 and STAT2 were increased among most B cell subsets. Positive correlations were found between STAT1 and IRF9 in B cells with Siglec-1 (CD169), an IFN signature marker expressed and measured on the surface of CD14$^+$ monocytes (p>0.0001; r=0.633). Notably, increased levels of IRF9 positively correlates with STAT1 in all B cell subsets.
Upregulated STAT1 and IRF9 within pSS B cells were associated to subgroups of patients especially with high immunoglobulins, high anti-nuclear antibody titers (ANAs), high rheumatoid factors (IgA, IgM) as well as positive high anti-SS-A and anti-SS-B autoantibodies.
In addition, high STAT1 was found in subgroups of patients with extraglandular manifestations, as well as in pregnant patients with the risk of development a congenital heart block (CHB).
The current data provide evidence of a type I IFN signature by B cell subsets in pSS indicating that both key pathogenic findings are interrelated. Elevated STAT1, STAT2 and IRF9 expression suggest transcriptionally activity, which was evident in subgroups of patients with extraglandular manifestations or increased risk of development a CHB and in serologically active patients. Targeting intracellular pathways under the control of type I IFN as well as B cell activation may lead to improved treatment options in Sjögren's.

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IMMUNIZATION IN PRIMARY SJÖGREN'S SYNDROME - THE IMPORTANCE OF THE CYTOKINE PROFILE IN RESPONSE TO DISEASE-MODIFYING THERAPY

Sebastian A.[1], Madej M.[1], Gajdanowicz P.[2], Sebastian M.[3], Luczak A.[1], Zemelka-Wiacek M.[2], Jutel M.[2], Wiland P.*[1]
[1]Department of Rheumatology and Internal Medicine, Wrocław, Poland, [2]Department of Clinical Immunology, Wroclaw Medical University, Wrocław, Poland, [3]Department of General, Minimally Invasive and Endocrine Surgery, Wroclaw Medical University, Wrocław, Poland

The pathomechanism of pSS is similar to that of other autoimmune diseases and is multifactorial (genetic predisposition, environmental trigger, initiation and maintenance of the autoimmune process). Many cytokines take part in this process, including interferon.
Understanding the individual contributions of all interacting cell types and their interactions is of paramount importance in understanding disease pathogenesis and developing effective therapeutic approaches. Most published research papers usually analyze single cells and cytokines in the context of disease pathogenesis. Only in the literature review publications can we find a summary of the entire cytokine pathways involved in the pathomechanism

of pSS; therefore, there are still difficulties in the clinical diagnosis of pSS. The study aimed to simultaneously assess the distribution of cytokines involved in the pathomechanism of pSS (IL5, IL13, IL 2, IL 6, IL 10, TNF-α, IFNγ) and determine their common clinical correlation and discuss the potential use of anti-cytokine drugs in therapy.
The study group consisted of patients over 18 years of age with a confirmed diagnosis of pSS based on the current ACR-EULAR Classification Criteria of 2016. The study group consisted of 40 pSS patients (37 women and 3 men). The most frequently detected cytokines in the studied population were: IFNγ (82% of patients), TNF-α (70%), IL6 (50%), and IL2 (42.5%). In all patients, except for one patient (32 out of 33 subjects), IFN gamma was found with the presence of other specific cytokines. There was no difference in clinical symptoms, age, and laboratory test results between the group of patients Il-6 + TNF-α + IFNγ positive cytokine, and the group of patients in whom they were not detected. There was no correlation between the presence of IL5, IL13, IL2, IL6, IL10, TNF-α and musculoskeletal symptoms, skin lesions, glandular domains, pulmonary neurological, lymphadenopathy, biological and haematological domains in ESSDAI (p>0.05).
IFNγ most likely plays a central role in the pathomechanism of the disease. We have not noticed a clinical correlation between the three most common cytokines (IL6, IFNγ and TNF-α), preliminary research results open up the possibility of searching for new treatments for pSS; and a lower percentage of patients with detectable levels of TNF-α and IL6 may explain the ineffectiveness of drugs targeting them cytokines in clinical trials to date.

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SSA-REACTIVE B CELLS ESCAPE PERIPHERAL TOLERANCE CHECKPOINTS IN PATIENTS WITH PRIMARY SJÖGREN'S SYNDROME

Chriti N., Tison A., Porchet E., Marec N., Devauchelle-Pensec V., Pers J.O., Hillion S., Cornec D.*
LBAI, UMR1227, Univ Brest, Inserm, Labex IGO, CHRU Brest, Brest, France

Background and objectives. Little is known about the auto-reactive B cells that secrete autoantibodies against SSA in primary Sjögren's syndrome (pSS). Here, we aimed to characterize the circulating SSA-specific B cells (SSA+ B cells), in order to better understand the mechanisms leading to the breakdown of self-tolerance in patients with pSS.
Patients and methods: Using a flow-cytometry-based method, we detected and phenotypically characterized SSA+ B cells among peripheral blood mononuclear cells (PBMCs) collected from patient with pSS and from healthy controls (HCs). We tested, by ELISPOT, their ability to secrete SSA-specific immunoglobulins in vitro following stimulation.
Results. We included 51 patients with pSS and 44 HCs. pSS patients had a higher frequency of SSA+ B cells (3.2% [1%-7.45%]) compared to HCs (2.5% [0.7%-5.27%]), p<0.05. Sorted SSA+ B cells from HCs were able to secrete in vitro IgM but not IgG anti-SSA immunoglobulins. While the proportion of SSA+ B cells among transitional and naïve B cells were similar in patients and HCs, their proportion within the memory compartment was higher in pSS patients. Expansion of a $CD19^+IgD^+CD27^-CD21low/-CD11c^-$SSA+ naïve B-cell subset was observed in pSS patients. SSA+ B cells were also enriched within the IgMlow unswitched memory B-cell subset in patients, as well as in double negative (IgD-CD27-) and switched memory B cells of the different isotypes.
Conclusions. In pSS patients, autoreactive SSA+ B cells maturate and reach the memory compartment, suggesting that they escape to the different layers of peripheral tolerance checkpoints and differentiate in vivo into anti-SSA antibody-secreting cells. Further analyses are currently ongoing in our group in order to compare the transcriptional program of these autoreactive B cells between HCs and patients with pSS using single-cell RNAseq of sorted SSA+ B cells. The study of their BCR repertoire will also lead to a better understanding of the generation of anti-SSA antibodies in the patients.

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TARGETED METABOLOMICS IN LABIAL SALIVARY GLANDS HIGHLIGHTS NEW POTENTIAL BIOMARKERS TO PREDICT PRIMARY SJÖGREN'S SYNDROME.

Urbanski G.*[1], Chabrun F.[1], Lacout C.[1], Lozac H P.[2], Blanchet O.[1], Chao De La Barca J.[1], Simard G.[1], Lavigne C.[1], Reynier P.[1]
[1]Angers University Hospital, Angers, France, [2]Le Mans Hospital, Le Mans, France

The diagnosis of primary Sjögren's syndrome (pSS) is currently based on the highlighting of late consequences of the exocrinopathy. A better understanding of its pathogenesis would enable discovering new biomarkers and promoting earlier diagnosis. The analysis of labial salivary glands (LSG) is of major interest in pSS diagnosis, notably in absence of anti-SSA antibodies, to testify the immune origin of the exocrinopathy and could be an interesting target for a better understanding of pSS pathogenesis. We analyzed the LSG from a prospective cohort of 40 newly-diagnosed pSS and 40 non-pSS Sicca patients through a standardized targeted metabolomic approach using liquid chromatography coupled with mass spectrometry. A metabolomic signature predictive of the pSS status was sought out using linear (logistic regression with elastic-net regularization) and non-linear (random forests) machine learning architectures. The pSS and control groups were composed of 36/40 (90%) and 35/40 (87.5%) females respectively (p>0.99). The median age was 63 [51.8-67] years for pSS patients versus 58.5 [46.8-66.3] years for non-pSS sicca patients (p=0.45). Among the pSS group, 20 (50%) participants presented anti-SSA antibodies. None had anti-SSA or anti-SSB antibodies in the control group. The focus score on LSG was ≥1 in 35 (87.5%) and 0 in the pSS and control groups respectively. Among the 126/188 metabolites accurately measured, we identified a discriminant signature composed of six metabolites including the kynurenine (increased concentration in pSS samples) and five phospholipids (all with decreased concentration in pSS samples) with robust performances (ROC-AUC = 0.86) for predicting the pSS status. Dimensional reduction through principal component (PC) analysis revealed two main PCs explaining 91.1% of model variance. The kynurenine carried almost all the information contained in the second PC whereas all the phospholipids mainly expressed in the first PC. This first PC (phospholipids) was associated with the intensity of the lymphocytic infiltration whereas the second PC (kynurenine) was positively correlated to the presence of anti-SSA antibodies. Previous studies reported a link between the phospholipid concentration in saliva and the risk of caries. Moreover, it seems that salivary concentration of lipids is positively correlated to the salivary flow rate. However, those results were produced in saliva analysis and not directly within salivary glands, contrary to our findings. The kynurenine is a biogenic amine well-known to be involved in the imbalance between tolerance and inflammation in immune diseases and pSS. This metabolite is produced by the action of the indoleamine-2,3-dioxygenase, which is itself under the influence of type I and II interferons. However, to the best of our knowledge, we firstly highlight this implication directly within the LSG in human samples from pSS patients. This metabolomics study enabled to identify potential new biomarkers in early involvement of salivary tissue, while revealing new metabolic pathways potentially involved in pSS pathogenesis within LSG.

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THE TUBARIAL GLANDS RESEMBLE THE PALATAL SALIVARY GLANDS BASED ON FURTHER HISTOLOGICAL CHARACTERIZATION, AND MAY REPRESENT AN ORGAN OF INTEREST IN PRIMARY SJÖGREN'S SYNDROME

Pringle S.*[1], Bikker F.[3], Vogel W.[4], Hofland I.[2], Van Der Vegt B.[5], Bootsma H.[1], Kroese F.[1], Vissink A.[6], Valstar M.[7]

[1]Rheumatology and Clinical Immunology, University Medical Center Groningen, Groningen, Netherlands, [2]Core Facility Molecular Pathology & Biobanking, Division of Pathology,, Amsterdam, Netherlands, [3]Oral Biochemistry, Academic Centre Dentistry Amsterdam, University of Amsterdam and VU University Amsterdam, Amsterdam, Netherlands, [4]Dept. of Nuclear Medicine, Netherlands Cancer Institute (NCI), Amsterdam, Netherlands, [5]Department of Pathology and Medical Biology, University of Groningen, University Medical Center Groningen, Groningen, Netherlands, [6]Oral and Maxillofacial Surgery, University Medical Center Groningen, Groningen, Netherlands, [7]Dept. of Head and Neck Oncology and Surgery, Netherlands Cancer Institute, Amsterdam, Netherlands

Background. Primary Sjögren's syndrome (pSS) often results in dysfunction of the salivary glands (hyposalivation and xerostomia) and substantial decrease in patient quality of life. High label uptake on 68Ga-PSMA-11 PET-CT imaging identified a bilateral structure in the nasopharynx as a potential salivary gland (SG)-like additional 'area of interest', to be considered in conditions affecting the SGs. This structure was termed the 'tubarial gland'. We aimed to better understand the histological and immunohistochemical position of the tubarial glands compared to other salivary glands and their potential role in hyposalivation, xerostomia development and swallowing problems in pSS.

Methods. Characterization of tubarial gland tissue was performed using standard immunohistological techniques, in comparison with tissue from the parotid, submandibular, sublingual, palatal and labial SGs.

Results. Acinar cells in SGs are responsible for saliva manufacture. Expression of the acinar cell-associated aquaporin-5 was detected in tubarial glands, in an apical location associated with polarized, secretory acinar cells. α-amylase expression, associated with SGs containing serous acinar cells, was not observed in tubarial glands. Expression of serous/serous demilune (SeD) acinar cell markers PIP and PRH2 was observed in tubarial acinar cell clusters, although SeD cells themselves were not clearly evident. Mucins within putative acinar cells, as inferred from alcian blue labeling, were detected in tubarial glands, similar to the sublingual, palatal and labial mucous-producing SGs. Expression of adrenergic receptor-β1 by acinar-like cells of the tubarial gland suggests ability to transduce a sympathetic neuronal signaling. Tubarial gland tissue also contained keratin 14$^+$ (KRT14$^+$) cells associated with acini and localized to a position suggestive of myoepithelial cells. In terms of ductal architecture, tubarial glands contained bi-layered KRT14$^+$ Keratin7$^+$ (KRT7$^+$) large excretory ducts (similar to all other SGs), and simple/stratified squamous ducts, comprised of intermingled KRT14$^+$ and KRT7$^+$ cells (not previously reported, and similar to palatal, sublingual and labial SGs). These simple/stratified ductal cells in tubarial tissue expressed the sodium iodide transporter NIS, implying potential functionality ability to modify saliva ion content. No striated or intercalated ducts were observed in tubarial gland tissue, similar to the palatal SGs.

Conclusions. Based on histological analyses and, in comparison to parotid, submandibular and sublingual palatal and labial salivary glands, tubarial glands resemble most convincingly palatal SGs. We draw this conclusion based on the acinar cell morphology (namely lack of notable serous demilune acinar cells, presence of mucins and expression of acinar cell marker proteins), and ductal compartment architecture (absence of intercalated or striated ducts, presence of squamous epithelial cells). Functional analysis is necessary to confirm the involvement of tubarial glands in moistening the pharyngeal mucosa. Imaging modalities incorporating the SGs may be critical to compiling a total picture of SG dysfunction in pSS.

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DOES ANCESTRY INFLUENCE PRIMARY SJÖGREN'S SYNDROME PHENOTYPE OR SEVERITY?

Beydon M.*[1], Seror R.[1], Desmoulins F.[1], Mariette X.[2], Nocturne G.[1]

[1]Department of Rheumatology, Assistance Publique - Hôpitaux de Paris, Hôpital Le Kremlin-Bicêtre, Paris, France, [2]Université Paris-Saclay, Centre for Immunology of viral Infections and Autoimmune Diseases, CEA, INSERM UMR1184, Le Kremlin Bicêtre, France

Background. It is well established that in systemic lupus erythematous (SLE), disease burden is higher in patients from African ancestry (AA) than in Caucasian patients. Although primary Sjögren's syndrome (pSS) and SLE vary by their clinical presentation, they share common pathogenic mechanisms. Data focusing on ethnicity and its impact in pSS are scarce. Our objectives were to compare demographic and biological parameters as well as disease activity and therapeutic management between patients of African Ancestry (AA) and Caucasians.

Materials and methods. We conducted a retrospective case-control study. Ethnicity was classified retrospectively asking the patient or relatives, if necessary. We included all pSS patients referred in a single national referral center for Sjögren's disease since 1990 of AA including sub-Saharan and Afro-Caribbean origins. Each AA pSS patient was matched to two Caucasians patients from the same center based on follow-up duration. Patients were excluded if they met diagnostic criteria for SLE, rheumatoid arthritis or any other connective tissue disease. We calculated a cumulative ESSDAI (cumESSDAI) score during follow-up defined as the sum of each category maximum score during follow-up. Characteristics of patients were compared between patients of African Ancestry (AA) and Caucasians.

Results. We included 48 patients of AA matched to 96 Caucasians with a median follow-up of 5 years [IQR 2-10]. Patients of AA were younger with a median age at diagnosis of 40 [IQR 28–48] vs. 53 [IQR 38–60] (p<0.001). Anti-SSA antibodies were more frequently positive in AA patients (83% vs. 67%, p=0.06) as well as anti-Sm (8% vs. 0%, p=0.01) and anti-RNP (17% vs. 4%, p=0.02). Mean serum titers of gammaglobulins was markedly higher in patients of AA (18.8g/L [IQR 15-24] vs. 12.6g/L [IQR 9.7-16.2], p<0.001) as was any occurrence of cryoglobulinemia during follow-up (10% vs. 2%, p=0.041). Rheumatoid factor positivity, low C3 or C4 and β2-microglobulin titers during follow-up were similar between both groups. Median cumESSDAI score was higher in AA patients (9.5 [IQR 4-19] vs 4.0 [IQR 2-8] p<0.001) with a higher prevalence of arthritis (27% vs 14%,

Table I. Patients characteristics according to ancestry.

	AFRICAN ANCESTRY N = 48[1]	CAUCASIAN N = 96[1]	p-value[2]
Age at symptoms onset	40.0 (28.0, 48.0)	53.0 (37.8, 60.0)	**<0.001**
Age at Sjogren diagnosis	44.0 (33.0, 51.0)	56.0 (44.8, 66.0)	**<0.001**
Sex (Female)	45 / 48 (94%)	89 / 96 (93%)	>0.9
Arthritis	13 / 48 (27%)	13 / 96 (14%)	**0.046**
Myositis	5 / 48 (10%)	0 / 96 (0%)	**0.004**
Pulmonary involvement	12 / 48 (25%)	5 / 96 (5.2%)	**<0.001**
IPD	9 / 48 (19%)	2 / 96 (2.1%)	**<0.001**
Bronchiectasis	2 / 48 (4.2%)	3 / 96 (3.1%)	>0.9
Pulmonary hypertension	3 / 48 (6.2%)	0 / 96 (0%)	**0.035**
Lymphadenopathy	15 / 48 (31%)	7 / 96 (7.3%)	**<0.001**
Splenomegaly	0 / 48 (0%)	2 / 96 (2.1%)	0.6
Cutaneous involvement	4 / 48 (8.3%)	12 / 96 (12%)	0.5
Purpura	3 / 48 (6.2%)	8 / 96 (8.3%)	0.8
CNS involvement	1 / 48 (2.1%)	1 / 96 (1.0%)	>0.9
PNS involvement	2 / 48 (4.2%)	9 / 96 (9.4%)	0.3
Renal involvement	4 / 48 (8.3%)	2 / 96 (2.1%)	0.10
Lymphoma	5 / 48 (10%)	5 / 96 (5.2%)	0.3
Gammaglobulins (median)	18.8 (15.0, 24.2)	12.6 (9.7, 16.2)	**<0.001**
IgG titer (median)	18.8 (14.0, 24.3)	13.0 (10.3, 16.9)	**<0.001**
Beta2microglobulin titer (median)	2.4 (2.0, 2.8)	2.2 (1.7, 2.8)	0.2
RF	18 / 48 (38%)	47 / 96 (49%)	0.2
SSA	40 / 48 (83%)	64 / 96 (67%)	**0.035**
SSB	16 / 48 (33%)	36 / 96 (38%)	0.6
SM	4 / 48 (8.3%)	0 / 96 (0%)	**0.011**
RNP	8 / 48 (17%)	4 / 96 (4.2%)	**0.021**
Cryoglobulin positivity	5 / 48 (10%)	2 / 96 (2.1%)	**0.041**
Low C3	0 / 47 (0%)	4 / 88 (4.5%)	0.3
Low C4	13 / 47 (28%)	23 / 88 (26%)	0.8
CumESSDAI total	9.5 (4.0, 19.0)	4.0 (2.0, 8.0)	**<0.001**
Cum-ClinESSDAI total	10.5 (3.8, 20.2)	4.0 (2.0, 8.0)	**<0.001**
Steroid prescription	17 / 48 (35%)	27 / 96 (28%)	0.4
Methotrexate prescription	7 / 48 (15%)	10 / 96 (10%)	0.5
Rituximab	9 / 48 (19%)	8 / 96 (8.3%)	0.068
Patients with immunosuppressors	13 / 48 (27%)	14 / 96 (15%)	0.070

[1]Median (IQR); n / N (%)

[2]Wilcoxon rank sum test; Fisher's exact test; Pearson's Chi-squared test

p=0.046), myositis (10% vs 0%, p=0.004), interstitial lung disease (19% vs 2.1%, p<0.001) and lymphadenopathy (31% vs 7.3%, p<0.001). CumESSDAI constitutional domain was more frequently increased in AA patients (p=0.01). Lymphomas occurred in five patients in both groups (10% vs 5.2% p=0.3). When evaluating disease activity with clinESSDAI rather than ESSDAI, results were unchanged.
Patients of AA were more often prescribed immunosuppressors, particularly Rituximab, without overall statistical significance.
Conclusions. Patients of AA seemed to have a distinct phenotype of pSS compared to Caucasian, with earlier disease onset, higher gammaglobulin titers, more frequent anti-SSA positivity and higher systemic disease activity.

Poster 91

CCR9/CXCR5 CO-EXPRESSING CD4 T CELLS ARE INCREASED IN PRIMARY SJÖGREN'S SYNDROME AND ENRICHED IN PD-1/ICOS EXPRESSING EFFECTOR T CELLS

Hinrichs A., Leavis H., Kruize A., Lafeber F., Van Roon J.*
Dept. of Rheumatology & Clinical Immunology, Center for Translational Immunology, UMC Utrecht, Utrecht, Netherlands

Objectives. Primary Sjögren's syndrome (pSS) is an autoimmune disease characterized by B cell hyperactivity. CXCR5+ follicular helper T cells (Tfh), CXCR5-PD-1hi peripheral helper T cells (Tph) and CCR9$^+$ Tfh-like cells have been implicated in driving B cell hyperactivity in pSS. These cell types are typified amongst others because of their elevated expression of PD-1 and ICOS, markers expressed on "true" Tfh cells found in lymph nodes. Our aim was to study the potential overlap between the two CXCR5-negative cell subsets and to study their PD-1/ICOS expression as compared to CXCR5$^+$ Tfh cells that has not been previously evaluated.
Methods. Tph and CCR9$^+$ Tfh-like cell populations from peripheral blood mononuclear cells (PBMCs) of pSS patients (n=12) and healthy controls (HC, n=12) were compared by flow cytometry. PD-1/ICOS (co-)expression from these cell subsets was compared to each other and to CXCR5-expressing Tfh cells, taking into account the differentiation status as defined by CD27 CD45RO differentiation markers.
Results. Tph cells and CCR9+ Tfh-like cells, both in pSS patients and HCs have limited overlap. PD-1/ICOS expression is higher in memory cells expressing either chemokine receptor CXCR5 or chemokine receptor CCR9. However, the highest expression is found in CXCR5/CCR9 co-expressing memory effector CD4 T cells, which are enriched in the circulation of pSS patients. Increased frequencies of Tph (memory CXCR5negPD1hi), Tfh-like (CXCR5negCCR9$^+$) and classical Tfh cells (memory CXCR5$^+$ICOS$^+$PD1$^+$) were associated with autoimmunity in pSS patients.
Conclusions. Tph and CCR9$^+$ Tfh-like cells are two distinct cell populations that lack CXCR5 expression that both could drive B cell hyperactivity in pSS as both are enriched in pSS patients as compared to HC. Considering the highest frequencies of PD-1/ICOS positive cells on CXCR5$^+$CCR9$^+$ T cells and the upregulated expression at pSS inflammatory sites of both CCL25 and CXCL13, ligands of CCR9 and CXCR5, our results also suggest a significant contribution of these co-expressing effector T cells in immunopathology of pSS.

Poster 93

IL-1 ALPHA AND IL-1 BETA EXPRESSION IN PRIMARY SJÖGREN'S SYNDROME SALIVARY GLAND EPITHELIAL CELLS

Izzo R.*[1], Colafrancesco S.[1], Barbati C.[1], Buoncore G.[1], Gattamelata A.[1], Giardina F.[1], Simoncelli E.[1], Mastromanno L.[1], Villa M.[1], Conti F.[1], Priori R [2].
[1]Division of Rheumatology, Department of Clinical Internal, Anaesthesiologic and Cardiovascular Sciences, Sapienza University, Rome, Italy, [2]Saint Camillus International University of Health Science, UniCamillus, Rome, Italy

Objectives. Primary Sjögren's Syndrome (pSS) is an "autoimmune epithelitis" due to the crucial role played by 'activated' salivary gland epithelial cells (SGECs) in disease pathogenesis[1]. Despite evidences demonstrating a role of innate immunity in pSS onset and maintenance, the exact role of IL-1 pathway has still to be determined. IL-1α and IL-1β are two major players in IL-1 family cytokines. The alarmin IL-1α is released by damaged cells following inflammatory insults, conversely, IL-1β is actively expressed by different cell types upon inflammasome activation. Although a role of IL-1 pathway in pSS has been described[2], the expression of IL-1β and IL-1α by pSS SGECs has never been investigated. The aim of this study is to investigate the expression IL-1α and IL-1β by SGECs of pSS in basal conditions.
Methods. Minor salivary glands (MSG) biopsies from consecutive patients with pSS (AECG criteria) and sicca syndrome (controls) referring to the Sjögren's Clinic of Sapienza University were collected. After collection, MSG were cultured in appropriate culture medium for SGECs growth. Supernatants from SGECs cultures were collected in order to determine the expression of IL- 1α and IL- 1β by ELISA.
Results. Forty MSG were cultured, 24 from pSS and 16 from sicca patients. The main clinical, laboratory and histological features are reported in table. No significant differences were detected in IL-1α and IL-1β levels between pSS and sicca (p=0.95, median 27.5 vs 25.8 pg/ml; p=0.35, median 20.5 vs 19 pg/ml, respectively). Despite not significant, in samples from pSS patients with positive rheumatoid factor (RF) and anti-SSA antibodies, supernatants levels of IL-1α were higher compared to pSS patients with no positive antibodies (p=0.90, median 63 vs 22.4 pg/ml; p=0.31, median 63.2 vs 35.4 pg/ml). No correlation was observed between IL-1α and IL-1β levels and the focus score (p=0.68, r -0.11; p=0.33, r -0.16).

Table.

	pSS	Controls
ANA, n (%)20 (83)	8 (50)	
Anti-SSA, n (%)	16 (66)	0 (0)
Anti-SSB, n (%)	7 (29)	0 (0)
RF, n (%)	8 (37.5)	2 (12.5)
FS, median (IQR)	1.9 (2.2)	0 (0.67)
CD21+, n (%)	13 (54)	-
ESSDAI, median (IQR)	0 (3.5)	0 (2)
Swollen salivary glands, n	4 (16)	1 (6)
Arthritis, n (%)	3 (12.5)	1 (6)
Purpura, n (%)	2 (8)	1 (6)
lymphoma, n (%)	0 (0)	0 (0)
Lymphadenopathy, n (%)	6 (25)	0 (0)
HypoC3/C4, n (%)	4 (16)	1 (6)
Hyper Y, n (%)	12 (50)	1 (6)
Leukopenia, n (%)	4 (16)	0 (0)

Conclusions. Our data, do not show a differential basal expression of IL-1Beta and IL-Alpha in SGECs from patients with pSS and sicca syndrome. However, in patients with more severe laboratory features, preliminary data suggest a higher concentration of IL-1Alpha. Functional experiments are currently ongoing to further investigate IL-1 expression in pSS SGECs.

References
1. Manoussakis 2010.
2. Khalafalla 2017.

Poster 96

IDENTIFYING POTENTIAL PATHOGENIC MECHANISMS IN PRIMARY SJÖGREN'S SYNDROME USING METABOLOMICS AND MACHINE LEARNING APPROACHES

Martin-Gutierrez L.*[1], Zhang S.[1], Peng J.[2], Robinson G.[1], Butt M.[2], Ciurtin C.[2], Jury E.[1]
[1]Centre for Rheumatology Research. University College London, London, UK, [2]Centre for Adolescent Rheumatology Versus Arthritis, London, UK

Background. Primary Sjögren's syndrome (pSS) is a chronic autoimmune rheumatic disease characterized by widespread immune system activation leading to exocrine gland damage and functional impairment of the salivary and lachrymal glands as well as systemic damage to various organs and tissues. Despite clear evidence supporting an immune-mediated pathogenesis there are no disease modifying treatments for pSS patients.
Objectives. This project investigated the serum metabolomic profile of pSS patients compared to healthy controls (HCs) to improve understanding of pathogenic mechanisms.
Methods. Serum metabolomic quantification of more than 150 metabolites in female pSS patients (n=41) and matched female healthy controls (HCs) (n=77) was performed using nuclear magnetic resonance spectroscopy. Data were analysed using logistic regression, multiple t-tests, and five supervised machine learning (ML) approaches for classification: neural network, Decision trees, support vector machine and random forest, adjusting for age, and ethnicity. To determine whether pSS patients could be stratified according to their metabolic profile unsupervised hierarchal clustering was also performed.
Results. All five ML models differentiated pSS patients from HCs with an accuracy (area under the curve) >0.75. Strikingly, amino acids involved in immune cell metabolic processes were amongst the top differentially expressed metabolites in pSS patients. Eleven metabolites were identified in at least 3 of the 5 models: histidine, isoleucine, leucine, total concentration of branched-chain amino acids, alanine, tyrosine, glycine, acetone (ketone), lactate (glycolysis- product of pyruvate), concentration of HDL particles, and linoleic acid (fatty acid). Differential expression of these metabolites was confirmed using T-test analysis and univariate logistic regression which additionally identified valine, glucose, and pyruvate (ketone-important intermediate of glycolysis). Glycine and lactate were elevated in pSS and while the other metabolites had reduced expression suggesting ongoing active metabolic processes. Interestingly, unsupervised hierarchal clustering of the pSS patients alone identified two groups based on metabolomic profile. In this case the top differentially expressed metabolites identified were lipid based and included high, low and very low lipoprotein particle subsets and Apolipoprotein-A1 concentration.
Conclusions. Our study shows that amino acid metabolism and other metabolic processes are altered in pSS. Since amino acid metabolism and lipid metabolism play a key role supporting various immune cell functions, these processes could be targeted to improve immunity in pSS which lacks current effective therapies. Future work will focus on correlating with clinical information, such as disease activity and disease damage, across patient groups determine the possible relationship between clinical features and differentially expressed metabolites.

Poster 98 (withdrawn by authors - late withdrawal)

DEFINING CELL-TYPE-SPECIFIC MOLECULAR AND TRANSCRIPTOMIC PROFILES OF CHILDHOOD SJÖGREN'S DISEASE BY SINGLE-CELL RNA-SEQUENCING

Kim M.*[1], De U.[1], Borcherding N.[2], Paek J.[6], Winn N.[6], Schrepfer T.[3], Bhattacharyya I.[6], Kolb R.[1], Thatayatikom A.[4], Zhang W.[1], Cha S.[5]
[1]Department of Pathology, Immunology, and Laboratory Medicine, University of Florida, Gainesville, USA, [2]Department of Pathology and Immunology, Washington University, Washington, USA, [3]University of Florida College of Medicine, Gainesville, USA, [4]AdventHealth Medical Group, Orlando, USA, [5]University of Florida College of Dentistry and Center for Orphaned Autoimmune Disorders, Gainesville, USA, [6]University of Florida College of Dentistry, Gainesville, USA

Objectives. A recent discovery of the childhood Sjogren's disease (cSjD) cohort at the University of Florida demonstrates that cSjD shares some clinical, pathological, and histological features with adult SjD. However, the etiology, natural history, and pathogenesis of cSjD are poorly defined. This study characterizes peripheral immune cells that contribute to cSjD pathogenesis by applying high-throughput NGS.
Methods. Single-cell RNA-sequencing (scRNA-seq) was performed on PBMC samples isolated from 4 patients with cSjD, non-cSjD, healthy controls (HC), and biopsy-positive non-cSjD with or without recurrent parotitis (RP). cSjD patients were diagnosed based on the 2016 ACR/EULAR SjD criteria for adults. A total of 52,571 immune cells were sequenced and subjected to cell type identification and functional characterization. The Seurat package was used to create a multimodal Seurat object and perform essential analyses, including QC/pre-processing, normalization, dimension reduction, cell clustering, and visualization, with default statistical methods available within the package. Differentially expressed genes (DEGs) were determined based on the log-fold change threshold >0.36 and p-value <0.05. DEGs presented herein indicate comparisons between cSjD and HC, unless otherwise specified.
Results. Sub-clustering of CD79A+ B cells identified a phospholipase D4 (PLD4)+ B cell subset in cSjD, which revealed Ro60, CD19, and other DEGs associated with immunoglobulin production and antigen presentation via MHC-II. Mucosal-associated invariant T (MAIT)-like $CD8^+$ T cells were significantly expanded in cSjD whereas there was little to no enrichment for activation gene signatures in $CD8^+$ T cell and KLRF1+ NK cell subsets. Furthermore, effector memory $CD4^+$ T cells in cSjD patients strongly upregulated genes associated with inflammation and cytolytic responses such as granzyme A. CLEC2C and KLRB1, a pair of ligand and receptor, were differentially upregulated between $PLD4^+$ B and effector memory $CD4^+$ T subsets. Interestingly, regulatory T cells in cSjD appear to be functionally more suppressive than the cells in HC based on the DEG profile, which requires further validation. Sub-clustering of $CD68^+$ myeloid cells in cSjD identified a distinct subset of proinflammatory-CD14+ monocytes enriched with gene signatures involving interferon (IFN) signaling as well as costimulation and antigen processing/presentation. Interestingly, this subset was absent in a published study on scRNA-seq of PBMCs from adult SjD. More importantly, IFN-related $CD14^+$ and effector memory $CD4^+$ T subsets were preferentially activated in patients with RP.
Conclusions. Our current study with the unbiased NGS approach revealed that the activation of the regulatory feedback loop among effector memory $CD4^+$ T cells, IFN-related $CD14^+$ monocytes, and $PLD4^+$ B cells may play a critical role in cSjD immunopathogenesis.

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SINGLE-CELL RNA SEQUENCING DATA FROM THE SICCA COLLECTION DIFFERENTIATE SJÖGREN'S DISEASE AND ELUCIDATE CELLULAR PATTERNS OF COMPOSITION AND EXPRESSION

Taylor K.E.*[5], Urbanski G.[3], Patel R.K.[1], Flynn E.R.[1], Ghosh A.[2], Norouzi A.[2], Davidson B.[2], Poon A.[2], Chu C.[2], Nititham J.[4], Fragiadakis G.[1], Eckalbar W.L.[2], Criswell L.A.[4], Ye C.J.[7], Shiboski C.[3]
[1]Data Science CoLab and Division of Rheumatology, Dept. of Medicine, UC San Francisco, UC San Francisco, USA, [2]Genomics CoLab, UC San Francisco, San Francisco, USA, [3]Dept. of Orofacial Sciences, UC San Francisco, San Francisco, USA, [4]National Human Genome Research Institute, NIH, Bethesda, USA, [5]Division of Rheumatology, Dept. of Medicine, UC San Francisco, San Francisco, USA

Over the last twenty years, the Sjögren's International Collaborative Clinical Alliance (SICCA) has built a large cohort of 3514 patients who have undergone deep phenotyping, enabling a new international consensus for classification criteria for Sjögren's disease (SjD), and, more recently, genome-wide DNA typing. However, many questions remain about the phenotypic and molecular heterogeneity of this multi-faceted disease and its initiation. Thus, the newly funded SICCA-NextGen project represents a second phase with the aim to provide new insights into pathogenic mechanisms of SjD through the generation of rich multi-comics data from peripheral blood mononuclear cells (PBMCs) from 370 participants of the SICCA biorepository. Single-cell RNA-Sequencing (scRNA-Seq) enables the analysis of gene expression from PBMCs at the cellular level.
We hereby present preliminary results of the scRNA-Seq from PBMCs from 88 participants of the SICCA-NextGen cohort, the first batch to be sequenced. The population was exclusively composed of females with a median age of 54 years [47-62]. Forty-five (51.1%) participants were classified as having SjD according to 2016 ACR/EULAR criteria (median score 8 [5-9], among whom 28 (62%) had anti-SSA antibodies. The 43 participants used as controls had a median 2016 ACR/EULAR score of 1 [1-2].
scRNAseq was performed using 10x Genomics' Chromium Single Cell 5'

V1.1 chemistry and processed using the 10x Cell Ranger pipeline. After the development of a fully automated pipeline for pre-processing, quality control, and demultiplexing of pooled samples, we generated and analyzed the transcriptomes of 220,974 cells. Within Seurat, batch adjustment was performed using Harmony and cells were clustered using the Louvain method. Cell types were determined using Azimuth and via the expression of marker genes. MAST was used to perform differential expression (DE) analysis.
In SjD participants, we observed a lower proportion of T cells, more monocytes and dendritic cells, and more B cells in PBMCs, as well as more T regulatory cells within T cells and fewer B memory cells within B cells (all FDR-adjusted $p<0.05$). In the largest cell cluster ($CD14^+$ Monocytes) we observed 530 DE genes between SjD positive and negative participants, with a large representation of interferon pathway and antiviral genes. Similar gene types were highly represented in 142 DE genes in T regulatory cells and 1026 DE genes in B memory cells.
Considering SSA positive versus SSA negative SICCA participants, we observed 1218 DE genes in the largest $CD14^+$ monocyte cluster.
This first batch of 88 samples enabled SICCA-NextGen to set up an extensive scRNAseq pipeline from PBMC processing to the transcriptome analysis of cell clusters. Moreover, it brings encouraging preliminary results and we anticipate that the complete data will significantly further our understanding of the pathogenesis of SjD.

Poster 118

MITOCHONDRIAL DYSFUNCTION IN SJÖGREN'S SYNDROME

Kurien B.T.*[1], Pharaoh G.[2], Cavett J.[1], Lewis V.[4], Chambers A.[1], Bhaskaran S.[3], Anjum J.[1], Karfonta B.[1], Radfar L.[1], Rasmussen A.[3], Lessard C.J.[3], Farris A D.[3], Sivils K.[3], Koelsch K.A.[1], Van Remmen H.[3], Scofield R.H.[4]
[1]University of Oklahoma Health Sciences Center, Oklahoma City, USA, [2]University of Washington, Seattle, WA, USA, [3]Oklahoma Medical Research Foundation, Oklahoma City, USA [4]Department of Veterans Affairs Medical Center, Oklahoma City, USA

Introduction. Sjögren's disease (SjD) is a chronic inflammatory, autoimmune illness characterized by reduced lacrimal and salivary gland secretion resulting in keratoconjunctivitis sicca and xerostomia, respectively. In addition, SjD patients have higher rates of metabolic syndrome and experience significant fatigue, often their most disabling symptom. Fatigue and metabolic syndrome are associated with chronic low-level inflammation. We have previously reported oxidative damage in systemic lupus erythematosus and oxidative modification of proteins in SjD. Free radical-mediated oxidative damage, mitochondrial dysfunction, and metabolic syndrome have been examined only sporadically in SjD, and their associations have not been studied. We hypothesized that SjD subjects have mitochondrial dysfunction and that fatigue and oxidative damage will be present in a subset of subjects with SjD.
Materials and methods. We enrolled 17 SjD subjects and seven age and sex-matched subjects at the Oklahoma Shared Clinical and Translational Resources for this study. Subjects underwent a fasting blood draw, lipid and glucose testing, BMI measurement, and completed a fatigue questionnaire. PBMCs were isolated from blood by density gradient centrifugation. B cells were isolated through positive selection, while T cells were isolated through negative selection using Miltenyi Biotech B and T cell isolation kit. We plated one million T cells/well on Cell Tak coated plate to make the cells adherent. The cells were analyzed for mitochondrial oxygen consumption rate (OCR) and extracellular acidification rate (glycolysis) using the Seahorse XF24 assay. SDS-PAGE analysis of plasma proteins followed by immunoblotting of 4-hydroxynonenal (HNE) modified proteins using anti-HNE antibody were also performed.
Results. Our previous studies confirmed oxidative damage in SjD demonstrated by an HNE-modified plasma protein migrating at ~16 kD. In the present study, we did not find significant differences in non-mitochondrial respiration between controls and SjD [17.67±2.77 Standard Error (SE) vs. 17.95±3.1 SE pmol/min/million cells]. However, basal OCR was significantly higher ($p<0.0001$) in controls compared to SjD (114.94±16.13 SE vs. 70±5.69 SE pmol/min/million cells). ATP-linked respiration was also significantly higher ($p<0.001$) in controls than in SjD (116.07±16.79 SE vs. 66.93±4.71 SE pmol/min/million cells). The biggest differences were in the maximal respiration ($p<0.0005$) (controls- 421.3±88.35 SE; SjD- 173.97±17.21 SE pmol/min/million cells) and reserve capacity ($p<0.0002$) (controls- 310.93±74.37 SE; SjD- 105.01±12.34 SE pmol/min/million cells). There was no significant difference in basal glycolysis or glycolytic stressed levels in controls and SjD. Our next steps will be to determine which of these SjD subjects have metabolic syndrome and oxidative damage and whether mitochondrial dysfunction, metabolic syndrome and oxidative damage occur in a sub-set of these SjD subjects.
Conclusions. Mitochondrial dysfunction appears to be a significant problem in SjD. We will analyze if it is associated with the metabolic syndrome and fatigue that frequently accompany SjD.

Poster 121

INVOLVEMENT OF INTERFERON IN THE PATHOPHYSIOLOGY OF VAGINAL DRYNESS IN PRIMARY SJÖGREN'S SYNDROME

Visser A.*, Nimwegen J., Bootsma H., Van Der Tuuk K., Mourits M., Van Kempen L., Kroese F., Verstappen G.
UMCG, Groningen, Netherlands

Background. In female patients with primary Sjögren's syndrome (pSS), vaginal dryness is a frequent complaint that negatively impacts sexual function and quality of life. Little is known about the pathogenesis of vaginal dryness in pSS. A histopathological case-control study in premenopausal women showed a higher degree of inflammation in vaginal biopsies from pSS patients compared to controls1. Inflammation of the salivary glands, *i.e.* the main target tissue of pSS, is associated with increased expression of interferon (IFN)-stimulated genes (ISG). Whether IFNs are also involved in the pathology of vaginal dryness in pSS patients is unknown.
Objectives. To explore the relation between vaginal dryness complaints and molecular- and histopathology of vaginal tissue from pSS patients.
Methods. Vaginal punch biopsies of 8 premenopausal pSS patients with vaginal dryness complaints and 7 age-matched non Sjögren individuals were included. Expression of genes involved in IFN signaling were measured using nCounter PanCancer IO 360™ Panel (NanoString) and results validated using TaqMan Real-Time PCR. Vaginal tissue sections were stained by immunohistology for Myxovirus resistance protein 1 (MxA) protein expression. Vaginal dryness was reported by patients using a numeric rating scale (NRS, range 0-10) and experienced gynaecologists assessed the 5 domains (elasticity, pH, moisture, fluid, mucosa) of the vaginal health index (VHI).
Results. The IFN signaling pathway was enriched in vaginal biopsies from pSS patients compared to controls. This difference could be mostly attributed to 4 pSS patients showing strong expression of ISGs. Increased expression of ISGs in pSS patients was confirmed by PCR. The 4 patients with the highest ISG expression in their vaginal biopsy also showed the strongest MxA protein staining. ISG expression levels, as measured using Nanostring technology, positively correlated with NRS scores for oral, ocular and vaginal dryness, and negatively with the VHI domains mucosa and fluid. Expression levels of ISGs also correlated with the amount of CD45+ cells in the vaginal biopsies and with anti-SSA positivity.
Conclusions. We showed upregulation of ISGs in vaginal biopsies from pSS patients. Importantly, this IFN activity is associated with both the histopathology and clinical presentation of vaginal dryness in pSS. Apparently, IFN also plays an important role in the pathogenesis of extraglandular manifestations, such as vaginal dryness.

Reference

1. Van Nimwegen *et al*.: Vaginal dryness in primary Sjögren's syndrome: a histopatho logical case–control study, *Rheumatology* 2020; 59(10): 2806-15.

Poster 124

DEEP SPATIAL PROFILING OF SJÖGREN SYNDROME PATIENTS BY IMAGING MASS CYTOMETRY: PRELIMINARY RESULTS

Chatzis L.*[1], Hemon P.[2], Scuiller Y.[2], Goules A.V.[1], Tzioufas A.G.[1], Pers J.O.[2]
[1]Department of Pathophysiology, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece, [2]LBAI, UMR1227, Univ Brest, INSERM, Brest, France

Introduction. Imaging mass cytometry (IMC) is a powerful high throughput technique that enables in situ multiparametric analysis of a single fixed tissue section while preserving spatial architecture. Sjögren Syndrome (SS), despite being one of the most common systemic autoimmune diseases, has still unclear pathogenetic mechanisms involved and no effective treatment.

Objectives. In the present study, we aimed to redefine by IMC the glandular architecture and the inflammatory infiltrate of minor salivary gland (MSG) biopsies of SS patients at different levels of histologic involvement and SS related mucosa-associated lymphoid tissue (MALT).
Methods and results. For this purpose, we collected 5 MSG biopsies from sicca controls [(Focus Score (FS):0-1, Anti – Ro/SSA (-), Anti-La/SSB (-)], five from SS patients with mild infiltration [FS:1-2, Tarpley Score (TS):1], five with intermediate (FS:2-4, TS:2) and five with severe (FS: 4-12, TS: 3-4). All participants were newly diagnosed patients having received no previous immunomodulary treatment. In addition, four MSG biopsies from patients with SS associated MALT lymphomas were also collected. Patients' demographic, clinical and serologic data were recorded. Formalin-fixed, paraffin-embedded (FFPE) tissue sections were prepared and stained using 2 panels of metal conjugated antibodies. The first (38 antibodies) aims to define the main cell populations and describe the glandular architecture of the tissue (Table I) and the second (27 antibodies) focuses on the different subtypes of infiltrating B cells (Table II). Serial FFPE tissue sections were used for the 2 panels. The acquisition process was performed using the Hyperion system. Hyperion data processing and analysis necessitated the use of several software in a labour-intensive pipeline. For cell segmentation, a validated proprietary artificial intelligence software was exploited. One hundred and four regions of interest (ROIs) for each panel were analyzed. Each ROI represented an inflammatory infiltrate, and a new stratification of the ROIs was created based on the number of T and B cells. The cell subpopulations comprising the inflammatory infiltrates varied between patients with different lesion severity as reflected by the focus score and intriguingly, between the different ROIs in the same patient.
Conclusions. Analyzing the variety of infiltrating cell subpopulations and their cell-to-cell interactions within the target tissue, previously limited by the low dimensionality of the available histologic techniques, may provide novel pathogenetic insights for the disease and potential therapeutic targets for Sjögren syndrome.

Table 1: Antibodies used in the first (Global) Panel

CD38	Bcl6
CD204	CD20
Vimentin	CD8a
CD14	CD138
T-bet	MPO
CD34	Flt3Ligand
CD163	CD56
Pan-Keratin	CD106 (VCAM1)
TSLP	CD127
CD31	Collagen type 1
Ki-67	CD3
IgD	CD27
IgM	Caspase-3
FoxP3	Podoplanin
CD4	HLA-DR
cKit	pS6
CD68	Flt-3 Receptor
IgA	CXCL13
IgG	CXC3

Table 2: Antibodies used in the second (B cell) Panel

CD45RB	Podoplanin
Vimentin	SMA
T-bet	CD38
Pan-Keratin	CD21
Ki-67	CD23
IgD	CXCL13
FoxP3	AID
CD4	PD-1
CD68	Collagen Type I
Bcl6	CCR6
CD20	CD3
CD8a	CD27
CD138	PD-1
MPO	

Poster 129 (withdrawn by authors - late withdrawal)

MOLECULAR-GENETIC PROGNOSIS FOR THE DEVELOPMENT OF DRY KERATOCONJUNCTIVITIS IN PRIMARY SJÖGREN'S SYNDROME AND RHEUMATOID ARTHRITIS

Safonova T.*[1], Zaitseva G.[2]
[1]Rheumacenter, Moscow, Russian Federation, [2]Research Institute of Eye Diseases, Moscow, Russian Federation

The contribution of polymorphic markers of the THBS1, GTF2I, MUC1, TRIM21, STAT4, PTPN22 genes to the development of primary Sjögren's syndrome (pSS) and rheumatoid arthritis (RA) has been established.
To identify the association of gene markers with ophthalmic manifestations, 254 patients with pSS and RA were examined: Schirmer's test I, II; NIBUT, HRT III, impression cytology of the conjunctiva, isolation of predisposing genotypes of the TRIM21, MUC1, THBS1, GTF2I, STAT4, PTPN22 genes by the analysis of DNA melting curves.
Predisposing genotypes of TRIM21, MUC1, THBS1, GTF2I, STAT4, PTPN22 gene markers have been identified. Associations of rs915956, rs7947461, rs4144331 of the TRIM21 gene with a predisposition to the development of RA were established ($p<0.05$); genes: TRIM21 rs4144331, THBS1 rs1478604; STAT4 rs7582694 to pSS, trend ($p\leq0.1$) of PTPN22 genes rs2476601, rs33996649 ($p\leq0.001$); TRIM21 rs7947461, GTF2I rs117026326, STAT4 rs7574865. Genotypes AG and GG rs4072037 of the MUC1 gene correlated with the Schirmer's test I, II; NIBUT and decompensated changes in the conjunctival epithelium ($p<0.05$). Predisposing genotypes GG rs1478604, rs2228262 of the THBS1 gene are associated with changes in the course and structure of corneal nerve fibers and the severity of keratoconjunctivitis sicca (KCS) ($p<0.05$) in pSS. The prognostic value of the TRIM21 rs915956 and rs7947461 genes with the risk of developing KCS against the background of RA ($p\leq0.001$), the trend ($p\leq0.1$) of the TRIM21 rs4144331, MUC1 rs4072037, THBS1 rs2292305 genes was determined. The risk of developing KCS against the background of pSS is associated with the TRIM21 rs4144331, PTPN22 rs33996649 genes ($p\leq0.001$), the trend ($p\leq0.1$) of the THBS1 rs2228262, STAT4 rs7574865 genes; GTF2I rs117026326.
To predict the development of KCS in patients with RA and pSS in the absence of clinical and functional changes in the ocular surface, it is recommended to analyze the status of the genes: TRIM21, MUC1, THBS1, STAT4, PTPN22. With probable pSS, a complex molecular genetic analysis is required. When identifying predisposing genotypes of gene markers: TRIM21, MUC1, THBS1, STAT4, PTPN22 to the development of KCS, the use of tear replacement therapy is indicated.

Poster 130

TLR7 REGULATES X-LINKED TLR ADAPTOR ENDOLYSOSOMAL SLC15A4 (TASL) EXPRESSION IN SJÖGREN'S DISEASE SUBJECTS

Harris-Lewis V.*[2], Bruxvoort C.[1], Lawrence S.[1], Cavett J.[1], Kurien B.[1], Scofield R.H.[2]
[1]University of Oklahoma Health Science Center, Oklahoma City, USA, [2]Veterans Affairs Medical Center-OKC, Oklahoma City, USA

Background. Sjögren's disease (SJD) and systemic lupus erythematosus (SLE) are complex autoimmune disorder related by B cell hyperactivity resulting in autoantibody and cytokine production. Approximately 90% of patients are female. We propose the number of X chromosomes increases susceptibility. Therefore, our objective is to functionally describe TASL, the X-linked protein encoded by the SLE risk gene CXorf21, to uncover any role this protein may have in the pathogenesis or susceptibility to SJD. Studies show that TASL directly interacts with another SjD associated risk allele, Slc15A4. SLC15a4, a lysosomal proton-oligopeptide symporter, is necessary for lysosomal antigen processing, inflammatory cytokine and antibody production in various immune cells. The function of TASL has yet to be characterized, however, our data show that knockdown of TASL regulates lysosomal pH and publicly available data suggest TASL functions as a short chain dehydrogenase/reductase. We predict TASL works with a network of endolysosomal-resident proteins including TLR7, NOX2 (Ncf1; a SjD risk variant), and SLC15A4 to regulate inflammatory (auto)immune responses.

Methods. Monocytes and plasma were collected from 15 primary (pSjD) and 15 incomplete Sjögren's disease (iSjD) and 15 healthy control subjects. Cells were plated and stimulated with TLR7 agonist, Imiquimod, (5µg/ml) for 24 hours. Gene expression and protein analysis were evaluated using quantitative PCR and Protein Simple JESS™ . Cell culture media and plasma were examined for cytokine profiles using Protein Simple ELLA™ . TASL dehydrogenase/reductase activity was evaluated using an NAPDH enzyme activity kit.
Results. Our qPCR and protein data confirm TASL (CXorf21) expression is increased pSjD and iSjD subjects compared to healthy controls. This response is exacerbated following TLR7 activation. Both Tlr7 and CXorf21 expression levels increase 3- and 5-fold, respectively following TLR7 stimulation. Protein analysis supported the gene expression data with an increase in TASL and TLR7 protein levels in pSjD and iSjD compared to healthy controls. Additionally, we found an increase in proinflammatory cytokines in pSjD and iSjD when compared to the control group. Using purified TASL protein to assess enzymatic activity, we found TASL has dehydrogenase activity and this enzymatic activity was further enhanced in the presence of SLC15A4 purified protein.
Conclusions. This is the first study to assess the potential function of TASL in SjD. We have shown that TASL is over-expressed in primary and incomplete SjD, compared to healthy controls. Additionally, we show that TLR7 activation of these subject's cells resulted in an increased inflammatory cytokine production compared to healthy controls. These data along with our previous studies lead us to predict that TASL functions as a dehydrogenase that breaks down NADPH. This putative enzyme activity potentially inhibits the lysosomal NADPH oxidase complex (NOX2) from producing superoxides in the endolysosome lumen. This would result in lower endolysosomal pH which is necessary for TLR7 activation and subsequent inflammatory responses.

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SINGLE CELL AND SPATIAL TRANSCRIPTOMICS IDENTIFIES ALTERED CELLULAR NEIGHBORHOODS IN THE SALIVARY GLANDS OF SJÖGREN'S DISEASE PATIENTS

Warner B.*[1], Pranzatelli T.[1], Perez P.[1], Martin D.[1], Jang S.[1], Dominick K.[1], Yamada E.[1], Byrd K.[1], Abed M.[1], Nidcr Genomics and Computational Biology Core N.[1], Beach M.[1], Pelayo E.[1], Khavandgar Z.[1], Lessard C.J.[2], Farris D.[2], Sakai S.[3], Barber D.[3], Oliver A.[4], Bartolome-Casado R.[4], Dominguez Conde C.[4], Baer A.[1], Chiorini J.[1]
[1]National Institute of Dental and Craniofacial Research, Bethesda, USA, [2]Oklahoma Medical Research Foundation, Oklahoma City, USA, [3]National Institute of Allergy and Infectious Disease, Bethesda, USA, [4]Wellcome Sanger Institute, Cambridge, UK

Introduction. Sjögren's Disease (SjD) is a systemic autoimmune disorder with especial targeting of lacrimal and salivary glands. Complex gene-environment interactions lead to pathogenic glandular infiltration of lymphocytes and autoantibody generation. High-throughput transcriptional analyses have helped define mechanisms of immune dysfunction in SjD. Yet, 'bulk' approaches cannot resolve disease-specific changes in tissue composition or the transcriptional state of each cell and lacks spatial context. We hypothesize that single-cell (sc) and spatial transcriptomics can pinpoint effector immune cells and pathogenic cell-cell interactions leading to glandular dysfunction.
Methods. SjD (n=15) and healthy (HV, n=18) minor salivary glands (SG) and peripheral blood mononuclear cells (PBMC, n=18) were used for 10X scRNAseq (~450k cells); SjD (n=25) and HV (n=25) SG were used for 10X Visium spatial transcriptomics (~15k spots). These datasets were used to define SjD-specific changes in cell populations and transcriptional states. Altered utilization of pathways in single cells was assessed across annotated pathways (KEGG, GO, Reactome, and mSigDB). Flow cytometry and ex vivo T cell activation assays were used to show the cytotoxicity of infiltrating SG immune cells. Spatial transcriptomics was used to quantify the altered cell-cell interactions and cellular networks using Cell2location based on cellular identities from scRNAseq. Cellular co-occurrence and cellular neighborhoods were measured.
Results. SjD SG exhibited greater cellularity and transcriptional state alterations than PBMC. SjD SG had proportionately more inflammatory cells (T and B cells, dendritic cells [DC]) and less acinar cells. SjD-specific differentially expressed genes (DEG) were identified in all cell types, however, generally MHC class I transcripts (*e.g.*, B2M and HLA-B), and interferon (IFN) stimulated genes (ISG) were increased in all cell types in SjD. These phenomena correlated with anti-SSA positivity, but not focus score. While many DEG were identified in acinar cells (*e.g.*, ISGs), secretory marker expression was lower. T cell clusters in SjD showed enrichment of CD8GZMA$^+$GZMK$^+$T-cells (>6-fold; q<0.0001). Functional annotation analysis revealed enriched T cell pathways: 'Type I IFN response', 'T cell receptor signaling', and 'IFNγ signaling'. Using lymphocytes from SjD and HV SGs, SjD CD8$^+$T-cells were significantly more cytotoxic *ex vivo*. Spatial transcriptomics confirmed cellularity-dependent architectural and transcriptional alterations in the glands and disease-specific cell-cell interactions (T cells:DC, T cells:acinar cells) and neighborhoods.
Conclusions. This study is one of the first to use single cell and spatial transcriptomics to disentangle the highly complex disease-dependent disorganization, cellular alterations, and transcriptional state changes in the SG of SjD patients. Our findings directly link the loss of acinar cells with the presence of cytotoxic CD8$^+$T-cells and illustrates disease-specific immune cell interactions. In summary, these data pinpoint pathogenic cell populations and cell-cell communications that may be directly targetable for therapeutic intervention.

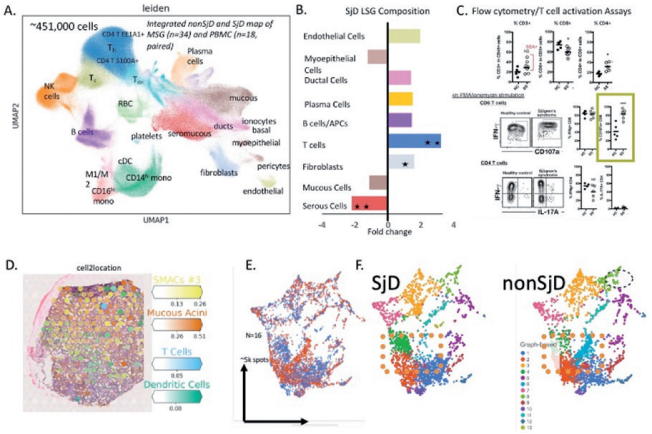

Figure. scRNAseq and spatial transcriptomics were used to understand compositional and transcriptional alterations in SG and PBMC from SjD and nonSjD subjects: **A**. UMAP and leiden clustering of ~451,000 cells from 34 LSG and 18 paired PBMC. **B**. SjD exhibits loss of secretory cells and increased in inflammatory cells (adj. q-val. *<0.05, **<0.01), as well as profound effects on per-cell gene expression (data not shown). **C**. Flow cytometric analysis and PMA/ionomycing stimulation confirmed increased T cell infiltration with an emphasis on increased activated T$_c$ cells in SjD. **D**. Spatial transcriptomics revealed altered tissue organization at the transcriptional, cell: cell, and transcriptional level (data not shown). Cell2location was used to infer the cellularity of spatially-resolved spots. Leiden clustering of spots reveals shifts in SjD and reveals not only changes in cellularity and transcriptome, but that higher-order arrangement and the signaling neighborhoods of the gland profoundly affected.

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REGULATION OF STAT4 EXPRESSION BY GROWTH FACTOR SUPPLEMENTATION IN SJÖGREN'S SYNDROME CELL CULTURE MODELS

Mougeot J.*, Noll B., Thornburg T., Noll J., Cathleen P., Lizano M., Brennan M., Mougeot F.
Atrium Health, Charlotte, USA

Objectives. Our goal was to investigate the effects of Epidermal Growth Factor (EGF) and Vascular Endothelial Growth Factor (VEGF) on STAT4 expression in Sjögren's syndrome cell culture models and whether these growth factors would affect the p38-MAPK inhibitor-mediated suppression of STAT4 expression. We also determined the effects of IFN-γ treatment on expression of the active forms of STAT1 and STAT4 to investigate the role of IFN-γ suppression in the immune response.
Study design. iSGECs (immortalized salivary gland epithelial cells) and A253 cell lines were treated with EGF, VEGF, IFN-γ or p38-MAPK inhibitor for 0, 24, 48 and 72 hours. Expression of STAT4 mRNA was quantified by qRT-PCR. Relative fold changes were normalized to GAPDH and fold-change differences between untreated and treated cells were determined using the ΔΔCT method. Presence of Phospho-STAT4 and Phospho-STAT1 proteins was determined by Western Blot.
Results. We observed a decrease in STAT4 mRNA expression after 48-hours of stimulation with EGF in iSGECs derived from a sicca patient (iSGEC-

nSS2) and from a patient with primary Sjogren's syndrome (iSGEC-pSS1), and A253 cells. P38 inhibition had a greater effect on decreasing STAT4 mRNA expression in iSGECs compared to A253 cells. VEGF supplementation led to a decrease in A253 STAT4 mRNA levels which was comparable to p38 inhibition. Dual supplementation by EGF and p38 inhibitor led to a larger decrease in STAT4 mRNA compared to p38 inhibition alone in both iSGECs and A253 cells. Phospho-STAT4 protein was expressed at higher basal levels in iSGEC-pSS1 compared to iSGEC-nSS2 and A253 cells. EGF supplementation increased Phospho-STAT4 protein levels in A253 and both iSGECs. IFN-γ supplementation significantly increased Phospho-STAT1 protein in iSGEC-pSS1 cells but did not increase Phospho-STAT4. Combined IFN-γ and EGF supplementation further increased Phospho-STAT4 protein expression in iSGEC-nSS2 and A253 cells but did not change Phospho-STAT4 expression in iSGEC-pSS1 cells, compared to EGF supplementation alone. Basal levels of Phospho-STAT1 protein expression were not detected before and after EGF supplementation in iSGEC-nSS2 and A253 but were detected in iSGEC-pSS1 cells. Supplementation with EGF and IFN-γ led to increased Phospho-STAT1 expression in all three cell lines.
Conclusions. Investigation of EGF and VEGF mediated pathways will help identify new means to regulate STAT4 expression in salivary gland epithelial cells. The effects of EGF on p38 inhibitors might be beneficial to correct for STAT4 dysregulation in pSS salivary gland. Interferons are important regulators of active Phospho-STAT1 expression and may facilitate STAT1/STAT4 interactions, which are critical to the immune response in Sjogren's syndrome. Suppression of IFNs can occur via downregulation of the JAK/STAT pathway, resulting in loss of inflammatory response.

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AUTOPHAGY-RELATED PRDM1-ATG5 RISK LOCUS IN SJÖGREN'S DISEASE

Nagel A.[1], Khatri B.[1], Radziszewski M.[1], Wiley M.[1], Stolarczyk A.[1], Joachims M.[1], Tessneer K.[1], Rasmussen A.[1], Bowman S.J.[2], Radfar L.[3], Omdal R.[4], Wahren-Herlenius M.[5], Warner B.[6], Witte T.[7], Jonsson R.[8], Rischmueller M.[9], Gaffney P.[1], James J.A.[1], Rönnblom L.[10], Scofield R.H.[1], Mariette X.[11], Alarcón-Riquelme M.E.[12], Ng W.F.[13], Nordmark G.[10], Farris A.D.[1], Lessard C.J.*[1]

[1]Oklahoma Medical Research Foundation, Oklahoma City, USA, [2]University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK, [3]University of Oklahoma Health Sciences Center, Oklahoma City, USA, [4]Stavanger University Hospital, Stavanger, Norway, [5]Karolinska Institutet, Stavanger, Norway, [6]National Institute of Dental and Craniofacial Research, Bethesda, USA, [7]Hannover Medical School, Hannover, Germany, [8]University of Bergen, Bergen, Norway, [9]University of Adelaide, Adelaide, Australia, [10]Uppsala University, Uppsala, Sweden, [11]Université Paris-Saclay, Le Kremlin Bicêtre, France, [12]Genyo, Center for Genomics and Oncological Research, Pfizer/University of Granada/Andalusian Regional Government, Granada, Spain, [13]Newcastle Upon Tyne Hospitals NHS Foundation Trust, Newcastle Upon Tyne, UK

Background. Dysregulation of autophagy has been implicated in Sjögren's disease (SjD). ATG5 is reportedly overexpressed in SjD (1, 2).
Objectives. To identify and characterize autophagy-related SjD risk variants in PRDM1-ATG5 risk locus.
Methods. GWAS of 3,232 SjD cases and 17,481 population controls of European ancestry were imputed with HRC panel version 1.1 and tested for SNP-trait association. Single marker SNP-Sjögren's associations were tested using logistical regression models in PLINK (3). Bayesian statistics defined a credible SNP set in the PRDM1-ATG5 locus. Bioinformatic analyses (RegulomeDB, promoter capture Hi-C, eQTLs, etc.) further prioritized SNPs. Luciferase assays tested allele-specific enhancer function in neutrophil-like PLB985 cells. Functional significance of autophagy gene ATG5, and its binding partner ATG16L1, were tested by Western blotting and confocal microscopy in CRISPR knockout (KO) in PLB-985 myeloid cell line.
Results. Fine-mapping of PRDM1-ATG5 locus identified a peak at rs-526531positioned 10kb downstream of PRDM1. Seven variants in the 95% credible set clustered in an intergenic region enriched with enhancer regulatory marks. Of these, four were eQTLs for PRDM1 and ATG5 in immune cell types. SNPs rs526531 and rs533733 were eQTLs for ATG5 in monocytes, minor salivary gland, and neutrophils (p<5x10-2 - 5x10-4). Epigenetic chromatin marks analysis showed enhancer marks for rs533733 in monocytes, and promoter/TSS marks for neutrophils. These data suggest that risk SNPs on the PRDM1-ATG5 locus may modulate ATG5 expression and, thereby, autophagy in SjD relevant cell types by modulating the local chromatin regulatory network. To assess the roles of ATG5 and its binding partner, ATG16L1, in autophagy, PMA/I-induced hallmarks of autophagy, LC3-I and LC3-II conversion and p62 protein aggregation, were assessed by Western blotting and confocal microscopy in homozygous and heterozygous ATG5 or ATG16L1 CRISPR KO PLB 985 cells. Loss of ATG5 or ATG16L1 impaired PMA/I-induced autophagosome formation in differentiated, neutrophil-like PLB-985 cells.
Conclusions. Functional characterization of SNPs on the PRDM1-ATG5 provides new insights into the mechanisms that regulate autophagy in health and disease. Ongoing studies will focus on *in vitro* validation of predicted functional SNPs in A235 salivary gland epithelial cell line.

References
1. Byun YS *et al.*: *Sci Rep* 7.1 (2017): 1-11.
2. Colafrancesco S *et al.*: *Arthritis Res Ther* 22.1 (2020): 1-8.
3. Khatri B *et al.*: *Ann Rheum Dis* 2020; 79(Suppl1): 30. OP0047.

Poster 153 (withdrawn by authors - late withdrawal)

WHOLE EXOME SEQUENCING OF TWO RARE FAMILIAL COHORTS IDENTIFIES PUTATIVE GENETIC VARIANTS IN CHILDHOOD SJÖGREN'S DISEASE

Winn N.*[1], Kim S.[2], Mun S.[2], Khan Z.[1], Thatayatikom A.[3], Han K.[2], Cha S.[1]

[1]University of Florida, Gainesville, USA, [2]Dankook University, Cheonan, Korea, Republic of Korea, [3]AdventHealth Medical Group, Orlando, USA

Objectives. This study aims to investigate genetic variants for childhood Sjögren's disease (cSjD) in five sisters and two monozygotic twin brothers enrolled in the University of Florida cohort.
Methods. Whole exosome sequencing (WES) was applied to a total of nine individuals across two families. Family 1 consisted of the SMALL sisters (the first initials of 5 sisters in the birth order) and their mother. Three older sisters were diagnosed with cSjD (ages 14, 15, and 17 at the time of diagnosis) based on the 2016 ACR/EULAR primary SjD criteria. Two younger sisters (ages 9 and 12) and their mother were symptomatic, but did not fulfil the SjD criteria, thus classified as undefined autoimmune disease (UAD). Family 2 consisted of 10-year-old cSjD monozygotic twins who present almost identical disease phenotypes, and their mother with no health concerns. WES was performed by genomic DNA extraction, sequence library construction, and functional annotation of sequence variants. Pathogenicity analysis of the prevalence of the variants identified in the cohort was compared to the general population using four control databases: The Exome Aggregation Consortium, 1000 Genomes Project phase three database, National Heart, Lung, and Blood Institute Exome Sequencing Project, and the Genome Aggregation Database. Finally, gene ontology (GO) enrichment analysis was performed to classify the biological function of the genes into three classes (biological process, molecular function and cellular component) as well as to identify pathways through the KEGG database.
Results. WES of both cSjD and UAD patients found 1661 cSjD-associated variants in 1104 genes with 790 of these variants being non-synonymous and found in 570 genes. Further analysis illustrated 7 of these genes with sizable quantities of nonsynonymous variants (ZNF568, HLA-DRB1, OR51Q1, OR4C5, HLA-DRB5, OR6J1, and CCDC57). Comparison of the cSjD patients revealed 12 cSjD-associated variants (notably 8 nonsynonymous and 1 frameshift mutation) observed in 9 genes (ZNF568, HLA-DRB1, OR51Q1, OR4C5, HLA-DRB5, OR6J1, and CCDC57). GO enrichment analysis found that of the 790 variants found in 570 genes, the highest number of genes were associated with detection of stimulus, olfactory receptor activity, the MHC protein complex, and olfactory transduction within the biological processes, molecular functions, cellular components, and KEGG pathways, respectively. Pathogenicity function analysis showed 5 variants (rs61734341, rs150361978, rs143693332, rs35271262, rs11557577, rs142987478) predicted to be deleterious and possibly damaging, and 2 variants (p.I387V and p.Q114H) predicted to possibly be either deleterious or benign.
Conclusions. Our novel findings from WES revealed the identification of multiple pathogenic variants and genes present in the cSjD patients of both families as well as the UAD family members, suggesting a genetic linkage to the disease etiology of cSjD. Whether the identified variants serve as functional variants that impact onset and progression of cSjD is under active investigation.

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ELEVATED LEVELS OF IL-9 FAIL TO SUPPRESS PATHOGENIC TH17 CELLS IN SJÖGREN'S SYNDROME

Voigt A.*, Shen Y., Nguyen C.
University of Florida, Gainesville, USA

Introduction. Sjögren's Syndrome (SjS) is an autoimmune disorder, with a strong predisposition for occurring in women; T helper (Th)17 cells play a strong role perpetuating SjS disease state. Th17 cells have a close, but not well-understood, relationship with the cytokine IL-9, which has the ability to enhance regulatory T (Treg) cells suppressive function. Here, we aim to elucidate the function of IL-9 producing cells in SjS.
Methods. Th9 and their associated cytokines were determined on the sera of SjS patients and SjS-susceptible mice (B6.NOD-Aec1Aec2). Cellular sources of IL-9 were examined via flow cytometry and single-cell analysis. B6.NOD-Aec1Aec2 mice were treated with an anti-IL-9 antibody (n=11) or an isotype antibody control (n=12) five times per week. Mice were examined for alterations in saliva flow rate, antinuclear antibodies, and focal score. *In vitro* Treg suppression assay was performed to study effector T cell proliferation in response to IL-9 and anti-IL-9.
Results. The correlation analysis of SjS patient sera against serology and symptomology showed a significant relationship between IL-9 and IgG, ANA, ESSDAI, Ro52, Ro60, and La. The main cellular sources of IL-9 in mice are macrophages, NK cells, and T cells. Interestingly, blocking IL-9 made the focal scores significantly worse in the female mice, while slightly improving the ANA staining patterns in the males, indicating a sexually dimorphic mechanism with this cytokine. Given the ability of IL-9 to enhance Tregs, a suppression assay was performed in which it was determined that the overall proliferative T cell profile was not significantly altered between the control and SjS-susceptible mice. However, addition of anti-IL-9 resulted in the loss of Tregs suppressive function specifically of Th17 cells in SjS-susceptible mice.
Conclusions. Elevated levels of IL-9 in the sera of SjS patients and susceptible mice correlates to disease state. Efforts to diminish circulating IL-9 to a normal level resulted in a more severe disease phenotype in mice due to misregulation of Th17 cells by Tregs. This indicates that the observed increase in IL-9 is an internal attempt to increase Tregs suppression of pathogenic Th17 cells.

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UNIQUE BIOLOGICAL PROFILE OF GERMINAL CENTRES WITHIN TERTIARY LYMPHOID STRUCTURES IN THE SALIVARY GLANDS OF PATIENTS WITH SJÖGREN'S SYNDROME

Nayar S.*[1,2], Turner J.D.[1], Asam S.[1], Colfrancesco S.[3], Berardicurti O.[4], Iannizzotto V.[1], Smith C.G.[1], Flint J.[2], Teodósio A.[2], Gardner D.H.[2], Bowman S.J.[1,5], Ng W.F.[6], Croft A.P.[2], Filer A.[1,2], Fisher B.A.[1,5], Buckley C.D.[7], Barone F.[8]
[1]Rheumatology Research Group, Institute of Inflammation and Ageing, University of Birmingham, Birmingham, UK, [2]Birmingham Tissue Analytics, Institute of Translational Medicine, University of Birmingham, Birmingham, UK, [3]Rheumatology Unit, University of Rome, Sapienza, Rome, Italy, [4]Rheumatology Unit, Department of Biotechnological and Applied Clinical Science, University of L'Aquila, L'Aquila, Italy, [5]National Institute for Health Research (NIHR) Birmingham Biomedical Research Centre and Department of Rheumatology, University Hospitals Birmingham NHS Foundation Trust, Birmingham, [6]Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, UK, [7]Kennedy Institute of Rheumatology, University of Oxford, Oxford, UK, [8]Candel Therapeutics, Needham, Massachusetts, USA

Introduction. Tertiary lymphoid structures (TLS) are accumulations of lymphoid cells that share similar cellular compartments, organization and function when compared to secondary lymphoid organs (SLOs) such as tonsil. TLS germinal centres (GC) provide a local hub for maturation and proliferation of auto-reactive B-cells and expansion of malignant B-cell clones. TLS that form within salivary glands (SGs) of Sjögren's syndrome (SjS) patients are clearly associated with poor disease outcome, autoantibody production and lymphoma development. The phenotypical and functional features supporting TLS pathogenic properties are largely unclear.
Methods. Frozen SGs were obtained from SjS patients and selected for presence of germinal centre (GC)+ TLS. SG and tonsil were stained, microdissected. Isolated RNA from SG TLS and tonsil GC were used for RNAseq using ClonTech SMARTseq v4 kit. Nanostring GeoMx Digital Spatial Profiler (DSP) and Multiplex IHC (Lunaphore Comet) were used for proteomic validation.
Results. Transcriptomic analysis revealed 3836 significantly differentially expressed genes in SG TLS as compared to tonsil GC. Predominant expression of the lymphoid chemokines/cytokines (CCL19, CCL21, CXCL13 and BAFF) and costimulatory molecules (CD40, ICOS, ICOSL, PD1, PDL1, PDL2) was identified in both TLS and tonsil GCs. Interestingly, CCL19, BAFF, PDL2 expression was higher in SjS TLS than tonsil GCs. Conversely, CCL21 expression was greater in tonsil GCs. Gene expression for CXCL12 was enriched in TLS GC as compared to tonsil, suggesting a potential association of this molecule with the highly inflammatory ectopic setting of TLS. Importantly, TLS GC showed significantly increased expression of STING1, IFNG and TNF along with other cytokines (IL33, IL23). Inflammatory genes encoding for the chemokines CXCL10, CXCL9 and their receptor CXCR3, were detected in TLS GC, but absent in tonsil GCs, suggesting that TLS GCs are defined by a different pro-inflammatory profile signature compared to tonsil GC. Transcriptomic and proteomic analysis of TLS GC unveiled an altered cell-proliferation/apoptosis profile with down-regulation of BCL6 and AICDA, the enzymes responsible for B cell affinity maturation. Moreover, spatial proteomic analysis on Geomx and multiplex IHC revealed differences in abundance of immune cell populations. The TLS GC showed presence of GranzymeB+ CD8 T cells along with T follicular and peripheral helper cells. Furthermore, high expression of CD27, CD127, GITR and TNFSF9 was enriched in TLS GC.
Conclusions. Our study provides the first comprehensive transcriptomic and proteomic overview of the mechanisms regulating the local pathogenic microenvironment in TLS and demonstrate that these differences diverge from SLOs. We demonstrated that, although characterised by similar anatomical organization, TLS pathogenic cytokines, and cellular signature is associated with low levels of bcl6, and AID, aberrant apoptosis and costimulation, compared to GC in tonsil. Our findings unveil impaired regulation of the B cell cycle, responsible for the survival of auto-reactive, poorly selected B cell clones as a key feature of SS.

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IDENTIFICATION OF SJÖGREN'S DISEASE-ASSOCIATED T CELL RECEPTORS THROUGH DEEP SEQUENCING AND SINGLE-CELL APPROACHES

Jupudi A.A.*[1], Joachims M.[1], Lawrence C.[1], Lopez-Davis C.[1], Khatri B.[1], Rasmussen A.[1], Radfar L.[2], Grundahl K.[1], Scofield R.H.[1], James J.A.[1], Guthridge J.[1], Lessard C.J.[1], Thompson L.F.[1], Farris A.D.[1]
[1]Oklahoma Medical Research Foundation, Oklahoma City, USA, [2]University of Oklahoma Health Sciences Center, Oklahoma City, USA

Introduction. Sjögren's disease (SjD) is a chronic rheumatic autoimmune disorder with hallmark focal lymphocytic infiltrates in the lacrimal and salivary glands (SG). A pathogenic role for $CD4^+$ T cells is implied by the association of SjD with HLA DR3/DQ2 and dominance of $CD4^+$ T cells in SG infiltrates. In this study, we aim to identify T cell receptors (TCRs) with shared antigen-specificity in SjD cases.
Methods. Peripheral blood (PB) samples were collected from 19 cases (16 $DR3^+DQ2^+$, 2 $DR3^-/DQ2^-$, 1 $DR3^+DQ2^-$) meeting the 2016 ACR/EULAR classification criteria for SjD and 19 DR3+DQ2+ matched healthy controls (HC). $CD3^+CD4^+CD45RA^-$ antigen-experienced T cells were bulk-sorted from all subjects followed by RNA extraction and cDNA synthesis using the SMARTSeq system. A two-stage PCR amplification approach was adopted to generate TCRβ libraries for TCR deep sequencing. We implemented the 'Molecular Identifier Guided Error Correction pipeline' (MIGEC) to extract CDR3 sequences, V/J segment usage, and clonotype information from raw sequencing data, while also correcting for amplification bias and sequencing errors. In addition to the PB data, we included paired TCR α and β sequences derived from the SG of 20 SjD cases in this study (n=10 by TCR RT-PCR, n=10 by single-cell RNAseq). The resultant curated metadata was used to identify TCRs with shared antigen specificity using the 'GLIPH2' (Grouping of Lymphocyte Interactions by Paratope Hotspots) algorithm.
Results: PB-TCR deep sequencing data from 12 SjD cases and 12 HC passed quality control. We analyzed 1,877,614 CDR3β chain sequences using GLIPH2 and identified over 55,000 shared antigen-specificity groups found exclusively in the patient TCR repertoire and not in HCs. Of these, 215 groups contained TCRs from ≥3 SjD cases and had significant GLIPH2 scores for clonal expansion, cluster size, V enrichment, and conserved CDR3 length. Furthermore, we identified six shared specificity groups with

significant GLIPH2 scores for the same features containing TCRs that were commonly enriched in both the PB and SG tissue of patients. Notably, three TCRs were found to be enriched both in the blood and SG of the same patient. One of these was part of a clonal expansion in the SG, over-represented in PB, and expressed dual TCRα chains.
Conclusions. This study presents evidence of the occurrence of clonally-expanded T cells containing dual TCRα chains in the affected SG tissue and peripheral blood of the same patient. Such TCRs have been proposed to contribute to autoimmunity in several studies. We discovered a SjD-associated TCR repertoire shared between the SG and PB across multiple patients. Furthermore, we found disease-associated TCRs enriched in the PB of cases. These data corroborate the systemic nature of SjD and enable the discovery of shared SjD T cell epitopes.

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ANTI-N-METHYL-D-ASPARTATE RECEPTOR (NMDAR) AUTOANTIBODIES AS POTENTIAL BIOMARKER OF FATIGUE IN PATIENTS WITH SJÖGREN SYNDROME

Marinoska T.*[1], Möckel T.[2], Dreher M.[2], Schwarting A.[2]
[1]Center for Rheumatic Disease Rhineland-Palatinate GmbH, Bad Kreuznach, Germany, [2]Division of Rheumatology and Clinical Immunology, University Medical Clinic, Mainz, Germany

Introduction. Up to 67-85% of patients with Sjögren's syndrome suffer from fatigue, an overwhelming feeling of exhaustion with motor and cognitive components as well as social and economic consequences. Since fatigue has so far only been understood as a subjective perception of the patient, not feasible to objective measurements, the diagnosis is only based on patient-related questionnaires. On the other hand, fatigue is often the decisive factor for quality of life. Therefore, an extended diagnosis for objective determination of fatigue is long awaited. The presence of different, mostly disease-typical autoantibodies is a feature of autoimmune diseases. We recently published a correlation between anti-N-methyl-D-aspartate receptor (NMDAR) antibodies and fatigue in patients with SLE (systemic lupus erythematosus). In the present study, it was examined whether the described association between circulating anti-NMDAR antibodies and the fatigue symptoms also applies to patients with Sjögren's syndrome and other rheumatic diseases.
Methods. Serum samples of total 100 patients with rheumatic diseases, from which 26 patients with Sjögren's syndrome, 39 patients with SLE and 35 patients with other rheumatic diseases (such as rheumatic arthritis, psoriatic arthritis, spondyloarthritis, scleroderma, osteoarthritis and fibromyalgia) were analyzed for the presence of antibodies to the NR2 subunit of the NMDAR by ELISA (Enzyme-Linked Immunosorbent Assay). In addition, the severity of fatigue was determined according to the FSMC questionnaire (Fatigue Scale for Motor and Cognitive Functions) and correlated with the antibody titer.
Results. Primary analyzes showed that
1. Anti-NR2 antibodies can also be found in 50% Sjögren patients with fatigue
2. Sjögren patients with positive anti NR2 antibodies suffer mostly from severe fatigue
Conclusions. The presence of anti-NR2 antibodies in patients with fatigue associated with Sjögren's syndrome could be a helpful diagnostic tool for the objective determination of this complex set of symptoms.

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BAFF-VAR IS A NEW PREDISPOSING FACTOR FOR PSS AND IMPACTS DISEASE ACTIVITY

Dulin M.*[1], Ly B.[1], Le Guern V.[2], Seror R.[1], Mariette X.[1], Nocturne G.[1]
[1]Department of Rheumatology, Assistance Publique - Hôpitaux de Paris, Hôpital Le Kremlin-Bicêtre, Le Kremlin Bicêtre, France, [2]Department of Internal Medicine, Hopital Cochin, Paris, France

Background. Chronic B cell activation plays a key role in primary Sjögren's syndrome (pSS) pathogeny. BAFF (B-cell activating factor) is largely involved in this process and positive results of therapies targeting this pathway highlight its involvement. BAFF serum level has shown to be increased in pSS patients and the reasons for this increase remain partially understood. A functional polymorphism within TNFSF13B locus coding for BAFF and called BAFF-var has been recently described. Since it associates a 4 bp deletion and a substitution (GCTGT>A), its presence was not assessable in the GWAS studies. It leads to a shorter transcript that escapes microRNA inhibition of BAFF translation resulting in increased serum BAFF level. BAFF-var has been shown to be more frequent in patients with lupus and multiple sclerosis and was first described in Sardinia. More recently, it has been shown to be associated with lupus activity and with the risk of lupus nephritis. Our objective was to assess BAFF-var prevalence among pSS patients and to test the association of this variant with disease characteristics.
Materials and methods. We conducted a retrospective and bicentric study on a French cohort from one national referral center for Sjögren's disease (Cochin and Bicêtre hospitals, Paris, France). Patients who met the 2016 ACR/EULAR diagnostic criteria for pSS with available DNA and/or sera were included. We performed Taqman allelic discrimination assay on DNA samples for genotyping BAFF-var. Soluble BAFF was measured by enzyme-linked immunosorbent assay (ELISA). Clinical and biological data were collected at diagnosis and during follow up. Disease activity was assessed by a cumulative ESSDAI score (EULAR Sjögren's syndrome Disease Activity Index) which was calculated by considering for each domain the highest value reached by the patient during follow-up.

Tab. I. Disease characteristics in pSS patients according to BAFF-var genotype.

	BAFF-VAR (n= 37)	BAFF-WT (n= 185)	p
Demographic data			
Men	4/37 (10,8%)	14/185 (7,5%)	0,5114
Afro-Caribbean ethnicity	**2/37 (5,4%)**	**37/185 (20%)**	**0,0334**
Age of symptom onset	48 yo [37 ; 55]	48 ans yo [34 ; 56]	0,9905
Age at diagnosis	53 yo [44 ; 62]	51 yo [42 ; 61]	0,6870
Follow-up time	60 months	62 months	0,7998
Clinical features			
Asthenia	27/37 (73%)	157/185 (85%)	0,0946
Joint pains	30/37 (81%)	130/185 (70%)	0,2297
Pathological Schirmer	21/33 (64%)	112/176 (64%)	0,9999
Pathological salivary flow	12/34 (35%)	84/164 (51%)	0,1307
Paraclinical features			
Chisholm ≥ 3 on MSGB	25/37 (68%)	144/178 (81%)	0,0807
Lymphocytes count (/mm3)	1710	1495	0,4387
Gammaglobulins (g/L)	14,7 [11,7 ; 17,8]	13,7 [11,3 ; 18,9]	0,7175
Monoclonal component	3/37 (8%)	22/185 (12%)	0,7754
Beta 2 microglobulin (mg/L)	2,4	2,2	0,4631
Anti SSA	27/37 (73%)	138/185 (75%)	0,8383
Anti SSB	17/37 (46%)	60/185 (32%)	0,1317
RF	21/37 (57%)	88/185 (48%)	0,3688
Cryoglobulinemia	2/37 (5,4%)	8/185 (4,3%)	0,6744
BAFF serum level (pg/ml)	**1845 [1393 ; 1965]**	**1335 [1069 ; 1962]**	**0,0137**
Activity and complications			
Cumulative ESSDAI on follow up	**6** [3 ; 14]	**4** [2 ; 10]	0,0923
General symptoms	2/37 (5,4%)	9/185 (4,9%)	0,9999
Lymphadenopathy	**10/37 (27%)**	**25/185 (14%)**	**0,0490**
Glandular involvement	17/37 (46%)	76/185 (41%)	0,5894
Joint involvement	19/37 (51%)	76/185 (41%)	0,2776
Skin involvement	4/37 (11%)	20/185 (11%)	0,9999
Lung damage	3/37 (8,1%)	22/185 (12%)	0,7754
Kidney damage	2/37 (5,4%)	6/185 (3,2%)	0,6231
Muscular impairment	1/37 (2,7%)	7/185 (3,7%)	0,9999
Peripheral Neurological Impairment	3/37 (8,1%)	8/185 (4,3%)	0,3985
Central Neurological Impairment	0/37 (0%)	2/185 (1%)	0,9999
Hematological disorder	5/37 (14%)	48/185 (26%)	0,1390
Biological domain	21/37 (57%)	109/185 (59%)	0,8559
Low activity: ESSDAI < 5	**13/37 (35%)**	**99/185 (54%)**	**0,0482**
Moderate – High activity: ESSDAI 5	24/37 (65%)	86/185 (46%)	
History of MZL	**6/37 (16,2%)**	**9/185 (4.8%)**	**0,02**

Results are presented as number (%) or median [interquartile range]

Results. We included 431 pSS patients. DNA and sera samples were available for 408 and 383 patients, respectively. Among the 408 patients tested, we found that 37 patients were BAFF-var carriers (36 heterozygotes and 1 homozygote) representing a variant prevalence of 9% in pSS population compared to a prevalence of 2% in the general population (1000 Genomes Project). Focusing on the 222 patients for whom DNA and serum were available, we found that BAFF-var was significantly associated with higher soluble BAFF level (median 1845 vs 1335 pg/ml), a more active disease and a more frequent lymph node involvement (Table I). Interestingly, we also observed an increased risk of marginal zone lymphoma (MZL) in BAFF-var carriers (16.2% in patients with BAFF-var versus 4.8% in others, p=0.02)). We observed a correlation between BAFF serum level and cumulative disease activity (r = 03881, p<0.0001).
Conclusions. We found an increased prevalence of BAFF-var in patients with pSS compared with what is known in the European population. Gentotyping of controls from the same geographic area is on-going and will be presented at the symposium. This variant is associated to increased serum BAFF level, more B-cell activation, higher cumulative disease activity and higher risk of MZL.

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ONSET OF PAROTID SWELLING AND SUBSEQUENT PRIMARY SJÖGREN'S SYNDROME AFTER RUBELLA VACCINE

Manfrè V.*[1], Fabro C.[1], Longhino S.[1], Rizzo M.T.[1], Giovannini I.[1], Pegolo E.[2], Zabotti A.[1], Quartuccio L.[1], De Vita S.[1]
[1]Rheumatology Clinic, ASUFC, Udine, Italy, [2]Institute of Anatomic Pathology, ASUFC, Udine, Italy

Sjögren's syndrome (pSS) is a chronic autoimmune disease characterized by lymphocyte infiltration and destruction of exocrine glands, mainly salivary and lacrimal glands, resulting in their functional impairment (sicca syndrome), with systemic extraglandular manifestations in up to 30-50% of cases and lymphoproliferative complications in 5-10% of cases, where parotid swelling (PSW) and cryoglobulinemia are the major risk factors (1). Pathogenesis of pSS is multifactorial: genetic, exogenous and endogenous factors contribute to trigger abnormal autoimmune responses. Between exogenous factors, infectious agents, mainly viral infections (*e.g.* EBV) have known alleged roles in pSS development. The role of vaccines as triggers of autoimmune disease in the contest of ASIA syndrome has also been object of debate, and few cases of pSS after vaccinations (*e.g.* HBV, H1N1) have been described (2). Herein we present the case of a female Caucasian patient, who reported recurrent episodes of painful bilateral episodical short duration (<2 months) [*i.e.*, maximum of 15 days and generally every 3-6 months] PSW, without other clinical manifestations. Of note, the first episode occurred 2 weeks after rubella vaccine inoculation, at 30 years old. No other known infectious triggers or specific clinical events were related to the onset of PSW. The patient came to our attention 12 years after the first episode of PSW, due to the recurrence of short duration PSW episodes, progressive onset of mild dry mouth symptoms; detection of diffuse parotid inhomogeneity and volume increase and multiple intraparenchymal lymph nodes at salivary gland ultrasound (SGUS) requested by her general practitioner, and the identification of histological features of autoimmune chronic sialadenitis on histological samples of labial tissue examined due to mucocele exeresis.
No clinical extraglandular manifestations were reported at our first and following visits. In the clinical suspect of pSS further analysis were requested, with the following results: ANA, anti-SSA, anti-SSB and RF positivity; polyclonal hypergammaglobulinemia, mild leuco-neutropenia; no cryoglobulinemia. Objective tests were negative. SGUS performed at our Clinic confirmed volume increase, diffuse parenchymal inhomogeneity (OMERACT score grade 3) and enhanced vascularization of parotid glands, which raised the suspicion of a lymphoproliferative evolution. Therefore, the patient underwent US-guided core needle biopsy of the most swollen gland, with histological result of focal lymphocytic sialadenitis (Focus Score=1,35) and initial MALT acquisition, further supporting our final pSS diagnosis. This case supports a causal connection between exogenous triggers as viral infections and vaccinations (in this proper case a live attenuated vaccine) and pSS development. Moreover, it delineates a rational diagnostic application of US-guided core needle biopsy to pSS patients with recurrent parotid swelling.

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ANALYSIS OF IFN-REGULATED CHEMOKINES AND B CELL SUBSETS IN PEDIATRIC SJÖGREN'S SYNDROME

Boni A.[1], Pires Marafon D.[2], Caiello I.[3], Matteo V.[3], Marasco E.*[2], Prencipe G.[3], Nicolai R.[2], Bracaglia C.[2], De Benedetti F.[2]
[1]Maternal-Infantile and Urological Science Department, Sapienza University of Rome, Rome, Italy, [2]Division of Rheumatology, Department of Pediatrics, IRCCS Bambino Gesù Children's Hospital, Rome, Italy, [3]Laboratory of Immuno-Rheumatology, IRCCS Ospedale Pediatrico Bambino Gesù, Rome, Italy

Background. Pediatric Sjögren's syndrome (pSS) is a rare disorder that is often diagnosed late due to the lack of validated diagnostic criteria and validated biomarkers. The pathogenesis is largely unknown, but there is evidence of involvement of both the innate and adaptive branch of the immune system. Immunological overactivity is central in the pathogenesis of pSS. Several studies showed the presence of B cells abnormalities in patients with SS with an expansion of naïve B cells and a decrease in the frequency of memory B cells. Interferons (IFNs) play a key role in activating innate and adaptative immune cells, and showed increased biological activity in patients with SS.
Objectives. We set out to investigate the activation of the interferon pathway and of B cell subsets and B cell cytokines in patients with pSS at disease onset and at follow up visits.
Materials and methods. A monocentric retrospective cohort study was conducted on 23 patients with pSS enrolled at the department of Rheumatology of Bambino Gesù Children's Hospital. The IFN score was calculated by the expression of 6 IFN-inducible genes (IFI27, IFI44L, IFIT1, ISG15, RSAD2, SIGLEC1) evaluated by quantitative PCR (qPCR). Serum levels of CXCL9, CXCL10, CXCL13, and BAFF were analyzed by ELISA. B-cell phenotype was assessed on peripheral blood mononuclear cells (PBMCs) by flow cytometry. Systemic disease activity was evaluated by ESSDAI (EULAR Sjogren's syndrome disease activity index) and Clinical-ESSDAI score (Clin-ESSDAI), according to 2020 EULAR recommendations; active disease was defined by ClinESSDAI ≥1 and remission by ClinESSDAI=0. As controls we selected age-matched people with no diagnosis of pSS or any other systemic autoimmune disease.

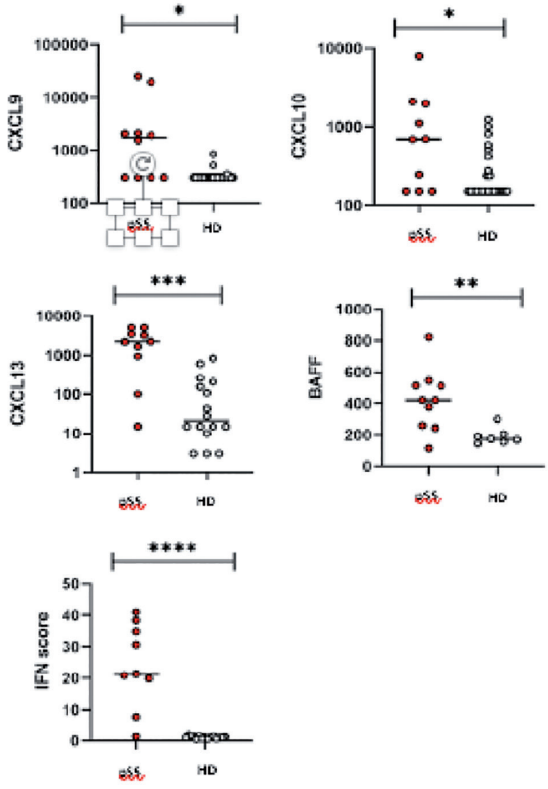

Fig. 1.

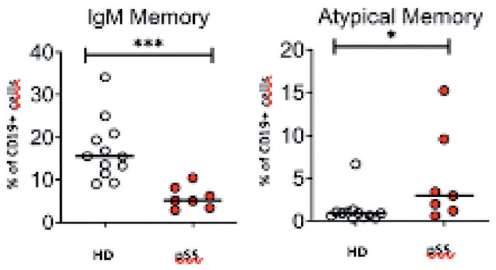

Fig. 2.

Results. Serum levels of CXCL9, CXCL10, CXCL13 and BAFF were significantly higher in patients with pSS than the control group (p<0.05) (Figure 1). The IFN score was significantly higher in patients with pSS than the control group (p<0.05) (Figure 1). We correlated levels of biomarkers with clinical and laboratory parameters: we observed a positive correlation between titer of anti-La antibodies and IFN score (rho=+0.85); a positive correlation between hypergammaglobulinemia and BAFF (rho=+0.80) and CXCL9 (rho=+0.82) and CXCL10 (rho=+0.80). We observed a negative correlation between lymphocytopenia and CXCL9 (rho=-0.74) and CXCL10 (rho=-0.75). Analysis of B-cell subsets at disease onset revealed the expansion of a population of atypical memory B cells (p=0.013) and reduction of IgM memory B cells (p=0.0002) compared to the control group (Figure 2). We compared levels of metabolites and distribution of B cell subpopulations at disease onset with samples obtained at follow-up for each patient: no significant differences were observed.
Conclusions. High levels of CXCL9, CXCL10, CXCL13, BAFF and IFN score at disease onset are present in patients with a diagnosis of pSS. Alteration in B cell subsets are present in patients with pSS compared to controls. Our data confirm an hyperactivation of chemokines and B cells in patients with pSS and provide evidence for their development as biomarkers.

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(withdrawn by authors)

EVOLVING TOPICS IN PSS STRATIFICATION

Poster 1

ALTERED CELL FREQUENCIES IN PATIENTS WITH SJÖGREN'S SYNDROME

Sarkar I.[1], Aarebrot A.K.[1], Solberg S.M.[2], Petrovic A.[1], Davies R.[1], Joshi A.M.[3], Brith B.[1], Brun J.G.[4], Hammenfors D.[4], Jonsson R.[1], Appel S.*[1]
[1]Broegelmann Research Laboratory, Department of Clinical Science, University of Bergen, Bergen, Norway, [2]Department of Dermatology, Haukeland University Hospital, Bergen, Norway, [3]Computational Biology Unit, Department of Clinical Science, University of Bergen, Bergen, Norway, [4]Department of Rheumatology, Haukeland University Hospital, Bergen, Norway

Primary Sjögren's syndrome (pSS) is a systemic chronic inflammatory and lymphoproliferative autoimmune disease of unknown etiology. 90% of the patients are female. It is characterized by, but not limited to, dysfunction of the salivary and lacrimal glands, leading to dryness of the mouth (xerostomia) and the eyes (keratoconjunctivitis sicca). Sjögren's syndrome is also associated with chronic fatigue and muscle and joint pain. Other extraglandular manifestations such as involvement of the skin, lungs, liver, and kidney, are observed in 30-50% of the patients. In addition, the risk of developing B cell lymphomas is increased 10 to 20-fold. In order to find potential biomarkers for patient stratification, we used mass cytometry to phenotype peripheral blood mononuclear cells in patients with Sjögren's syndrome and healthy controls. Frequencies of memory B cells ($CD19^+CD20^+CD27^+$), $CD8^+$ T central ($CD27^+CD45RO^+$) and effector memory cells ($CD27^-CD45RO^+$) and terminally differentiated $CD4^+$ T cells ($CD27^-CD45RO^-$) were altered between healthy donors and patients. In addition, HLA-DR and CD38 were upregulated in many cell subsets in the patients in both, myeloid and lymphoid cell compartments. Most of the observed differences were more prominent in patients with autoantibodies present, indicating greater disease severity. Increased activation status of several immune cells may predispose pSS patients to produce autoantibodies and might be a new target for therapy.

Poster 20

SJÖGREN'S AND NON-SJÖGREN'S SICCA SHARE A SIMILAR SYMPTOM BURDEN BUT WITH A DISTINCT SYMPTOM-ASSOCIATED PROTEOMIC SIGNATURE

Pucino V.*[1], Jason D T.[1], Nayar S.[1], Florian K.[2], Rauz S.[3], Richards A.[4], Poveda-Gallego A.[4], Higham J.[4], Bowman S.J.[1], Barone F.[5], Fisher B.A.[1]
[1]Institute of Inflammation and Ageing, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK, [2]Department of Rheumatology and Immunology, Inselspital University Hospital Bern, Bern, Switzerland, [3]Academic Unit of Ophthalmology, Birmingham and Midland Eye Centre, Birmingham, UK, [4]Department of Oral Medicine, Birmingham Dental Hospital, Birmingham, UK, [5]Candel Therapeutics, Boston, USA

Objectives. Given the similarity in symptoms between primary Sjogren's syndrome (SjS) and non-SjS sicca syndrome (sicca), we sought to characterise clinical and proteomic predictors of symptoms in both groups in order to better understand disease mechanisms and help guide development of immunomodulatory treatments. These have not, to date, unequivocally improved symptoms in SjS clinical trials.
Methods. Serum proteomics was performed using O-link Inflammation and Cardiovascular II panels. SjS (n=53) fulfilled 2016 ACR/European Alliance of Associations for Rheumatology (EULAR) criteria whereas sicca (n=60) were anti-Ro negative, displayed objective or subjective dryness, and either had a negative salivary gland biopsy or, in the absence of a biopsy, it was considered that a biopsy result would not change classification status. Linear regression analysis was performed to identify the key predictors of symptoms. Cluster analysis was completed using protein expression values.
Results. EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI), EQ-5DEuroQoL-5 Dimension utility values, and anxiety and depression did not differ between SjS and sicca. Correlations between body mass index (BMI) and ESSPRI were found in sicca and to a lesser extent in SjS. Twenty proteins positively associated with symptoms in sicca but none in SjS. We identified two proteomically- defined subgroups in sicca and two in SjS that differed in symptom burden. Within hierarchical clustering of the

SjS and sicca pool, the highest symptom burden groups were the least distinct. Levels of adrenomedullin (ADM), soluble CD40 (CD40) and spondin 2 (SPON2) together explained 51% of symptom variability in sicca. ADM was strongly correlated with ESSPRI (spearman's r=0.62; $p<0.0001$), even in a multivariate model corrected for BMI, age, objective dryness, depression and anxiety scores.
Conclusions. Obesity-related metabolic factors may regulate symptoms in sicca. Further work should explore non-inflammatory drivers of high symptom burden in SjS to improve clinical trial outcomes.

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SYSTEMIC INVOLVEMENT IN SJÖGREN SYNDROME: CAN WE PREDICT IT?

Bandeira M.*, Silvério-António M., Khmelinskii N., Eurico Fonseca J., Romão V.C.
[1]*Rheumatology Department, Centro Hospitalar Universitário Lisboa Norte, Centro Académico de Medicina de Lisboa (CAML), Lisboa, Portugal;* [2]*Rheumatology Research Unit, Instituto de Medicina Molecular, Faculdade de Medicina, Universidade de Lisboa, CAML, Lisboa, Portugal*

Background. Sjögren's Syndrome (SS) is a systemic autoimmune disease targeting mainly exocrine glands. Its hallmark is ocular and oral dryness. Systemic extra-glandular involvement including neurological, renal, vascular or pulmonary manifestations are present in one third of patients. Stratification of SS patients is a growing need and predictors for systemic disease are a useful tool for differentiating patients with exclusive glandular involvement from patients with systemic involvement, which may occur years after disease onset.
Methods. Retrospective cohort study based on Reuma.pt, including SS patients followed in our center until March 2022. Only patients who fulfilled the 2016 ACR/EULAR classification criteria for SS were included. Data from univariate analysis was performed using chi-square, Kruskal-Wallis or ANOVA, as appropriate. Independent predictors of systemic involvement were identified through binomial logistic regression modelling.
Results. 216 patients were included; 96.8% females, with a mean age at diagnosis of 51.32±14.85. The most common clinical manifestations were oral dryness (n=203/216, 94.0%) and ocular dryness (n=198/216, 91.7%). Patients were divided into three groups based on both ESSDAI at diagnosis and ESSDAI during follow-up: group A with no systemic involvement (ESSDAI=0 at diagnosis and throughout follow-up), group B with no systemic involvement at diagnosis that developed throughout follow-up (ESSDAI at diagnosis=0 and ESSDAI throughout the patient's follow-up≥1) and group C with systemic involvement from the beginning (ESSDAI at diagnosis≥1).

Table. I.

	Patients with no systemic involvement (ESSDAI=0 at diagnosis and throughout follow-up)	Patients with no systemic involvement at diagnosis that developed throughout follow-up (ESSDAI at diagnosis=0 and ESSDAI throughout the patient's follow-up≥1)	Patients with systemic involvement from the beginning (ESSDAI at diagnosis≥1)	Univariate analysis
Age at diagnosis, median ± SD (N)	**58.16±13.90 (31)**	**52.09±11.51 (23)**	**49.90±13.90 (162)**	**p=0.017**
Disease duration (in years), median ± SD (N)	**5.90±5.78 (31)**	**10.96±9.39 (23)**	**9.25±7.71 (162)**	**p=0.036**
Females, n/N (%)	30/31 (96.8)	22/23 (95.7)	157/162 (96.9)	p=0.950
Deceased patients, n/N (%)	2/31 (6.5)	4/162 (2.5)	2/23 (8.7)	p=0.228
Ocular dryness, n/N (%)	29/31 (93.5)	22/23 (95.7)	147/162 (90.7)	p=0.669
Oral dryness, n/N (%)	30/31 (96.8)	22/23 (95.7)	151/162 (93.2)	p=0.701
Schirmer's test < 5mm in 5 minutes, n/N (%)	19/26 (73.1)	13/19 (68.4)	97/141 (68.8)	p=0.906
Unstimulated salivary flow < 1.5mL in 15 minutes, n/N (%)	5/17 (29.4)	4/12 (33.3)	43/92 (46.7)	p=0.323
Positive salivary biopsy, n/N (%)	**12/27 (44.4)**	**16/20 (80.0)**	**94/132 (71.2)**	**p=0.012**
Positive anti-SSA/Ro, n/N (%)	27/31 (87.1)	21/23 (91.3)	150/162 (92.6)	p=0.597
Positive anti-SSB/La, n/N (%)	16/31 (51.6)	13/22 (59.1)	88/162 (54.3)	p=0.864
Positive antinuclear antibodies, n/N (%)	27/31 (87.1)	20/23 (87.0)	154/162 (95.1)	p=0.133
Positive rheumatoid factor, n/N (%)	**7/28 (25.0)**	**92/160 (57.5)**	**11/21 (52.4)**	**p=0.006**
Hematologic neoplasia, n/N (%)	0/31 (0.0)	10/162 (6.2)	1/23 (4.3)	p=0.353

Abbreviations: ESSDAI – EULAR Sjögren's syndrome disease activity index

Disease duration was significantly lower in patients with ESSDAI=0 at diagnosis and throughout follow-up (5.90±5.78 years, n=31), intermediate in the group who had systemic involvement at diagnosis (9.25±7.71 years, n=162), and higher in the group with no systemic involvement at diagnosis that developed throughout follow-up (10.96±9.39 years, n=23). Age at diagnosis was significantly higher in patients with no systemic involvement (58.16±13.90 years, n=31), intermediate in patients who developed systemic involvement during follow-up (52.09±11.51 years, n=23) and lower in patients with systemic involvement at diagnosis (49.90±13.90 years, n=162). Both rheumatoid factor (RF) and salivary gland biopsy were more frequently positive in patients with systemic involvement. In the multivariate analysis, age at diagnosis (OR 0.956, 95%CI: 0.918-0.996, $p=0.032$), positive biopsy (OR 3.800, 95%CI: 1.330-10.861, $p=0.013$) and RF (OR 3.853, 95%CI: 1.336-11.114, $p=0.013$) were identified as predictors of systemic involvement (ESSDAI≥1 at some point during follow-up) in SS patients independently of sex, disease duration, presence of anti-SSA or anti-SSB and sicca symptoms.
Conclusions. Patients with systemic involvement are more likely to have a lower age at diagnosis, positive salivary gland biopsy and positive RF compared to patients with no systemic disease during the disease course. Age at diagnosis, positive salivary gland biopsy and RF were identified as independent predictors of systemic involvement in SS. Its presence may require a closer follow-up.

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AUTOANTIBODIES AGAINST AQUAPORIN-5 IN PRIMARY SJÖGREN SYNDROME AS POTENTIAL DISEASE ACTIVITY AND PROGNOSTIC BIOMARKER

Stano S.*, Natuzzi D., Rinaldi A., Bizzoca R., Iannone F., Cacciapaglia F.
Rheumatology Unit; Department of Emergency and Transplantation of Organs (DETO) University of Bari, Bari, Italy

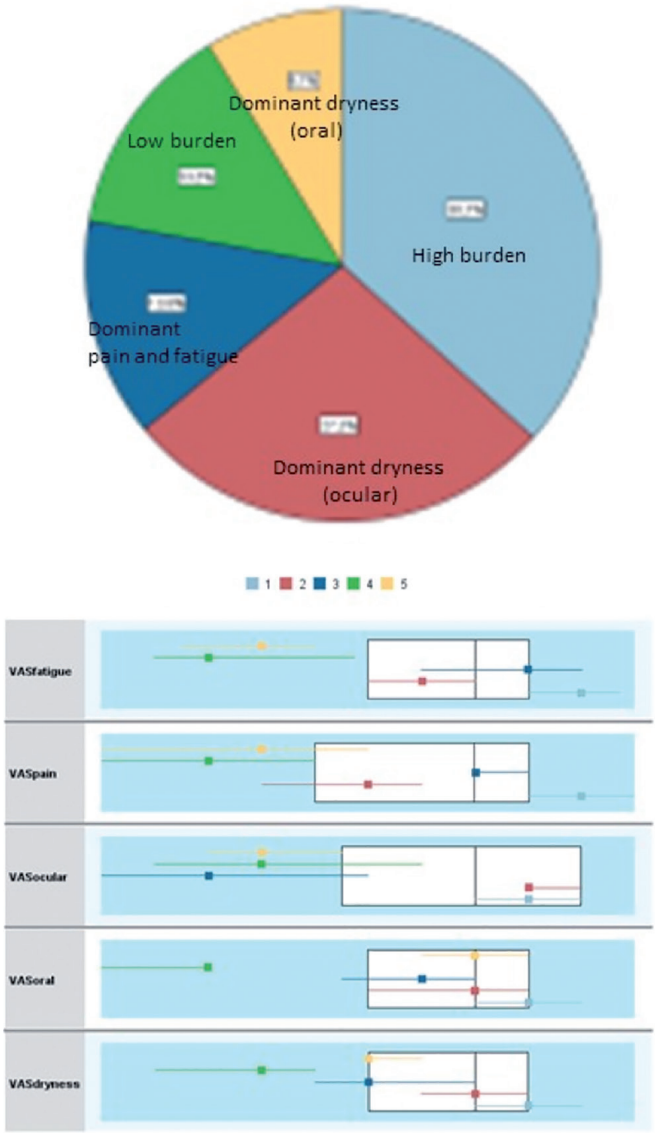
Introduction. Primary Sjögren Syndrome (pSS) is a systemic autoimmune disease characterized by lymphocytes activation and infiltration of exocrine glands with inflammatory damage and consequent secretory dysfunction. The molecular mechanism of the secretive physiological process is critically regulated by aquaporin-5 (AQP5), a small integral membrane protein which regulates water and small solutes passage through formation of highly selective pores in the apical membrane of acinar cells within salivary glands.
Objectives. To assess the presence of anti-AQP5 antibodies (Abs) in pSS patients and evaluate their utility as a biomarker of disease activity.
Methods. Blood samples from pSS patients, diagnosed according to American-European Consensus Group (AECG) criteria and healthy donors (HD), as control group, were collected and stored at -80°C until assay. For pSS patients age, sex, disease duration, disease activity expressed as EULAR SS Disesase Activity Index (ESSDAI) and EULAR SS Patient Reported Index (ESSPRI), DAS28, ongoing treatment and comorbidity, were registered. Moreover, ANA, anti-SSA, anti-SSB, RF, cryoglobulinemia, ESR, CRP, C3, C4, hypergammaglobulinemia and vitamin D status, were collected from clinical records. A commercial ELISA kit for anti-AQP5 Abs detection was used according to manufacturer's instructions (SEA583Hu, humans, CloudClone, Katy, Texas, USA). The GraphPad Prism software was used for the statistical analysis.
Results. Fifty pSS patients and 10 HD were enrolled, and no statistically significant differences in mean anti-AQP5 antibodies titer between the two groups were observed (1 ng/ml - 95%CI 0.7-1.3 vs 0.9 ng/ml - 95%CI 0.7-1.1, respectively; $p=0.76$). After the ROC curve construction, 0.92 ng/mL was identified as the most accurate cut-off value for assessing the presence of anti-AQP5 Abs (sensibility 70% and specificity 68%). Stratifying patients according to disease activity we observed higher anti-AQP5 Abs titer in those patients with ESSDAI>14 (OR 19 95%CI 3.4-89; $p=0.007$) and ESSPRI>5 (OR 5 95%CI 1.2-19; $p=0.04$). Furthermore, those patients identified positive for anti-AQP5 Abs had higher ESR and higher prevalence of hypergammaglobulinemia, skin manifestations and renal involvement.
Conclusions. We observed that anti-AQP5 Abs positivity was associated to high ESSDAI and ESSPRI, and were related to some recognized features of lymphoproliferative evolution in pSS patients.
These autoantibodies open new scenarios in our understanding of SS pathophysiology, and may also serve as disease activity and prognostic biomarker. Further studies are needed to confirm our findings.

Oral communication 70

SYMPTOM-BASED CLUSTERING IN SJÖGREN'S SYNDROME: A CLUE FOR INVESTIGATING PATHOBIOLOGICAL NON-INFLAMMATORY MECHANISMS OF THE DISEASE

Baldini C.*[1], Elefante E.[1], Ferro F.[1], Fulvio G.[1], La Rocca G.[1], Fonzetti S.[1], Navarro Garcia I.C.[1], Signorini V.[1], Donati V.[2], Izzetti R.[3], Mosca M.[1]
[1]Rheumatology Unit, University of Pisa, Pisa, Italy, [2]Pathology Unit, Pisa, Italy, [3]Odontostomatology Unit, Pisa, Italy

Background. Symptom-based cluster analysis has recently appeared as a useful tool to identify homogeneous subgroups of patients with Sjögren's syndrome (SS). These clusters incorporate relatively common symptoms also detected in patients without SS. Thus, it is not clear whether symptom-based cluster stratification may help in differentiating SS patients from SS-like subjects.
Objectives. 1. To compare sicca symptoms, pain and fatigue in patients with and without SS and to perform an exploratory clustering analysis of symptom scores for pain, fatigue, dryness in the cohort.
2.To investigate determinants associated with patients' reported outcomes (PROs) and their distribution in different clusters.
Methods. Patients undergoing a minor salivary gland biopsy (MSB) for suspected SS were prospectively included from January 2018 and January 2022. A standardized diagnostic work-up was performed in all patients including anti-Ro/SSA antibody detection, salivary flow measurement (UWS) and ocular tests. At diagnosis, the following PROs were collected in all the cases: ESSPRI, VAS ocular, oral and global dryness, VAS fatigue, VAS pain, OSDI and OHIP. The presence of fibromyalgia (FM) was recorded. For statistical analysis, we used the chi-square test for categorical data and the ANOVA t-test or Mann-Whitney test for continuous data. Bivariate correlations were assessed using Pearson's or Spearman's correlation coefficient. Two-steps cluster analysis was used to reveal natural clusters within the cohort.
Results. We included 312 subjects (289 F:23 M). Of them, 172 fulfilled the ACR/EULAR 2016 criteria for SS and 160 represented the "non-SS" control group. Gender distribution, age, Schirmer's test, UWS and prevalence of FM were similar in the two groups. The VAS ocular dryness, OSDI and OHIP scores were significantly lower in SS patients than in patients without SS (p<0.05) whereas the ESSPRI, VAS global dryness, VAS oral dryness, VAS fatigue and VAS pain were similarly altered in the two groups. The ESSPRI slightly correlated with the UWS (r=-0.249**) but not with the ocular tests. By contrast, patients' perception of dryness assessed by OHIP, OSDI, VAS oral, ocular and global dryness significantly correlated with objective lachrymal and salivary gland dysfunction. Patients with FM presented higher ESSPRI, VAS pain, fatigue and OHIP scores than patients without FM independently from SS diagnosis (p<0.001). In patients with SS the ESSDAI did not correlate with any of the PROs. Symptom-based cluster analysis identified 5 subgroups in our cohort (Fig. 1). Patients with and without SS were equally distributed among the clusters; however, each cluster had distinct clinical phenotypes (Fig. 1).
Conclusions. In patients undergoing a MSB for suspected SS, PROs are not disease specific but significantly correlate with objective tests for dryness and FM. Symptom-based clustering stratification may help to identify common pathobiological non inflammatory mechanisms in SS and SS-like disorders for the development of future therapies.



Clustering distribution and comparison in SS and SS-like disorders

	cluster1	cluster2	cluster3	cluster4	cluster5	p-value
SS	58 (50.9%)	47 (55.3%)	25 (58.1%)	29 (69%)	13 (48.1%)	0.307
Anti-Ro/SSA	47 (41.2%)	37 (43.5%)	17 (39.5%)	26 (61.9%)	11 (40.7%)	0.180
FS	0.79±0.96	1.39±2.18	0.95±1.15	1.17±1.65	0.57±0.67	0.316
Gender	111 (97.4%)	79 (92.9%)	40 (93%)	35 (83.3%)	23 (85.2%)	**0.02**
UWS	1.92±2.14	2.61±2.56	2.85±2.87	3.02±2.29	3.23±2.49	**0.008**
Schirmer	5.99±4.14	5.00±3.47	8.36±4.59	9.04±5.21	8.33±5.80	**0.007**
ESSDAI	2.91±3.66	3.88±5.51	5.21±5.15	3.89±4.70	1.52±2.33	**0.04**
ESSPRI	8.30±8.32	5.89±0.98	6.77±1.31	2.69±1.36	3.64±1.21	**<0.001**
OHIP	6.89±5.16	4.12±3.87	4.81±4.05	2.05±2.96	3.24±2.89	**<0.001**
OSDI	49.04±22.72	43.58±23.31	23.25±20.80	19.41±16.33	21.81±18.28	**<0.001**
Fibromyalgia	56 (58.3%)	14 (20.3%)	23 (59%)	8 (25.8%)	4 (18.2%)	**<0.001**

Fig. 1.

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ANTI-SSA/RO PROFILING IN PATIENTS WITH NEWLY DIAGNOSIS OF SJÖGREN SYNDROME: IMPACT ON "SICCA" AND "NON-SICCA" DISEASE ONSET

Fonzetti S.*[1], Ferro F.[1], Fulvio G.[1], La Rocca G.[1], Navarro Garcia I.C.[1], Donati V.[2], Mosca M.[1], Baldini C.[1]
[1]Rheumatology Unit University of Pisa, Pisa, Italy, [2]Pathology Unit, Pisa, Italy

Background. Recently, a growing interest has arisen in investigating the clinical significance of anti-Ro52 and anti-Ro60 serologic profiles in patients with primary Sjögren's syndrome (SS). However, little is known regarding the association between anti-SSA/Ro specificities and pSS clinical presentation.
Objectives. to evaluate glandular and extra-glandular manifestations of pSS at the time of disease diagnosis in patients stratified according to the anti-SSA/Ro serologic profile.
Methods. this is a cross-sectional study including consecutive newly diagnosed pSS patients (ACR/EULAR 2016 criteria) enrolled prospectively from January 2017 to March 2022. Patients were stratified in 4 groups according to the anti-SSA/Ro serologic status: seronegative, isolated anti-Ro52, isolated anti-Ro60, and both anti-Ro60 and anti-Ro52. Demographics, clinical, biological, histological and instrumental data were collected. ESSPRI and ESSDAI were assessed in all the patients. Data were presented as mean±SD, or percent frequency as appropriate. Intergroup comparisons were made using the t-test/Mann-Whitney test for continuous variables and Fisher's exact test for categorical variables.
Results. We included 176 pSS patients (F:M 158:18; mean age (s.d.): 56 (13) yrs). Of them 91 (51.7%) presented anti-Ro60 and anti-Ro52, 8 (4.5%) anti-Ro60 alone, 46 (26.1%) anti-Ro52 alone and 31 (17.6%) were seronegative. No differences were observed in gender distribution among the 4 groups; seronegative patients were significantly older than patients with both anti-Ro60 and anti-Ro52 (62(10) yrs vs 53(12) yrs, p=0.01). Sicca symptoms represented the most frequent complaints for the vast majority of the patients with no differences among the groups in terms of VAS oral, ocular, and global dryness. Similarly, VAS fatigue and pain were equally distributed among the groups. However, patients with the double positivity for anti-Ro60 and anti-Ro52 tended to present a higher complexity in the glandular infiltrate (p=0.09) and presented significantly higher SGUS score in their major salivary glands (0.002). As far as extra-glandular manifestations, seronegative patients presented a lower ESSDAI than seropositive patients (p=0.03). The highest scores in the biological domain of the ESSDAI were observed in patients with both anti-Ro60 and anti-Ro52 positivity. These patients also presented the highest frequency of Rheumatoid factor, antibodies anti-SSB and hyper-IgG. Regarding systemic extra-glandular manifestations lung involvement was significantly more common in patients with isolated anti-Ro52 with respect to the other groups (p=0.03). More specifically, in 12/176 (7%) pSS patients, ILD was the presenting feature of pSS: of them 7/12 (58.3%) presented isolated anti-Ro52 (p=0.07).
Conclusions. anti-SSA/Ro status influences the glandular, biological and lung domain of the ESSDAI at the onset of the disease and may help to identify different SS phenotypes. The relationship between anti-Ro52 and ILD in pSS deserve further investigations.

	Seronegatives	Ro52	Ro52/Ro60	Ro60	p-value
Constitutional	3	13	6	0	ns
Lymphadenopathy	13	20	26	13	ns
Salivary Gland Enlargement	0	13	13	0	ns
Articular	26	35	35	38	ns
Cutaneous	3	7	8	0	ns
Pulmonary	3	20	7	0	**0.03**
Interstitial lung disease	3	15	4	0	0.07
Renal	3	2	3	0	ns
Muscular	0	0	0	0	ns
PNS	0	0	0	0	ns
CNS	0	0	2	0	ns
Hematological	7	22	10	12	**ns**
Lymphopenia	0	13	6	10	ns
Neutropenia	6	13	5	0	ns
Biological	19	44	50	25	**0.02**
Hyper-IgG	3	9	36	13	**< 0.001**
anti-La/SSB	0	0	51	13	**< 0.001**
Rheumatoid factor	21	12	48	0	**< 0.001**
SGUS≥ 2	29	32	59	14	0.002

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SJÖGREN'S SYNDROME ILD PREVALENCE AND ASSOCIATED RISK FACTORS, A MONOCENTRIC COHORT STUDY

La Rocca G.*, Ferro F., Fulvio G., Fonzetti S., Navarro Garcia I.C., Elefante E., Mosca M., Baldini C.
Azienda Ospedaliera Universitaria Pisana (AOUP), Rheumatology Unit, Pisa, Italy

Background. Sjögren's syndrome-associated interstitial lung disease (SS-ILD) is among the most serious extra-glandular manifestations. Conflicting data have been reported regarding SS-ILD prevalence and clinical-serological risk factors, particularly considering that in a significant proportion of SS patients, ILD may precede sicca symptoms by many years.
Objectives. 1. To describe prevalence and phenotypes of SS-ILD in a single center cohort of patients, specifically comparing clinical, serological, and imaging features of patients developing ILD during disease course (SS-ILD-incident) with those of patients diagnosed with ILD before SS (SS-ILD-onset).
2. To examine predictive factors for the development of SS-ILD.
Methods. demographic, clinical, biological and imaging data of SS patients attending our center from Jan 2016 to Jan 2022 were retrospectively analyzed. According to chest HRCT findings, SS patients were divided into ILD (SS-ILD) and no ILD group (SS-N-ILD). The former group was subdivided in SS-ILD-incident and SS-ILD-onset based on the temporal relationship between ILD and SS diagnosis. For statistical analysis, we used the chi-square test for categorical data and the ANOVA t-test or Mann-Whitney test for continuous data. The association between ILD development and clinical characteristics was examined by Cox-proportional hazard models.
Results. We included 567 SS patients (533 F: 34 M), mean age (52 ±13 yrs), mean follow-up (7.5±6.7 yrs). Out of them 28 (4.9%) were defined as SS-ILD-onset, 16 (2.8%) as SS-ILD-incident and 523 (92.2%) as SS-N-ILD. Overall, prevalence of ILD in our cohort was 7.8% (44/567). Prevalence of ILD increased with disease duration with a median latency from SS diagnosis of 8 yrs (min 8-max 26). ILD pattern was defined as NSIP in 22 (40%), UIP in 10 (22.7%), OP in 3 (6.8%), LIP in 3 (6.8%), NSIP+OP in 2 (4.5%) and unclassifiable in 4 (9.1%) cases with no significant differences between SS-ILD-onset and SS-ILD-incident patients. However, UIP tended to be more frequent in the former group and LIP in the latter, while pulmonary function tests abnormalities were significantly more severe in SS-ILD-onset than in SS-ILD-incident group (p=0.03). Finally, SS-ILD-onset patients were more frequently male and presented higher prevalence of isolated anti-Ro52 with respect to the other two groups (p<0.05). When compared to SS-N-ILD, the 16 SS-ILD-incident cases were significantly older (61±8 vs 51±13 yrs, p<0.001), had higher ESSDAI at baseline (11±4 vs 5±5, p<0.001) and presented more frequently an increased ESR (80% vs 35.6%, p=0.006), low C4 (33% vs13.5%, p=0.05) and Raynaud's Phenomenon (71.4% vs 26.3%, v<0.0001). At the multivariate analysis the following predictors for ILD development were identified: age at diagnosis (HR1.30, 95%CI 1.11-1.52), ESSDAI at baseline (HR1.37, 95%CI 1.41-1.66), low C4 (HR 0.04, 95%CI 0.00-0.54) and ESR (HR 0.13, 95%CI 0.02-1.18).
Conclusions. ILD is relatively common in SS and quite heterogeneous in its presentation and outcome. Modifiable risk factors seem to be associated with ILD suggesting that decreasing systemic inflammation may delay SS-ILD development.

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NATURAL HISTORY OF SJÖGREN'S DISEASE FROM THE NATIONAL INSTITUTES OF HEALTH COHORT

Law B.*[1], Beach M.[2], Pelayo E.[2], Alevizos I.[2], Khavandgar Z.[2], Warner B.[2], Baer A.[1]
[1]Johns Hopkins, Baltimore, USA, [2]NIH, Bethesda, USA

Objectives. The objectives of this study were to assess the natural history of Sjögren's disease (SjD) over an interval reaching up to 32 years among participants of the U.S. National Institutes of Health (NIH) cohort.
Methods. Research participants consented and enrolled on salivary gland dysfunction-focused protocols at the NIH Sjögren's Disease Clinic between 1984 and 2020 were included in this analysis. Assessments varied according to protocol, but generally included baseline comprehensive serologic/

rheumatologic, oral, and ocular assessments including objective measures of salivary function (*e.g.*, sialometry), tear flow, minor salivary gland biopsy (MSGB), and laboratory testing. Sialometric measurements included unstimulated whole salivary (UWS) flow rate and total unstimulated salivary flow rate, which is the sum of parotid and submandibular/sublingual unstimulated salivary flow. The "percent unchanged" was defined as the percentage of participants with concordant test results at baseline and follow-up. For continuous variables, binary indicators using established cutoff values were used. Percentages were summarized with exact binomial 95% confidence intervals.

Results. Among 2,813 individuals evaluated, 1,198 had baseline evaluations that enabled classification into one of three subgroups: 1) 779 with SjD, 2) 127 with SjD coexistent with another systemic rheumatic disease, and 3) 292 with sufficient data to exclude SjD (non-SjD) with available baseline features. The majority of participants in the primary SjD subgroup were White (73%) with a mean age of 51 (SD=13) years. 73% had anti-SSA antibodies, 59% rheumatoid factor (RF), and 96% focus score ≥1 on MSGB. Follow up was available for 651 participants and stratified by follow up durations of ≤5 years, between 5-10 years, and ≥10 years. As summarized in Table I, the percent unchanged of follow up durations of ≤5 years ranged from 69% for Schirmer's test (n=270) to 97% for ANA (n=239). The percent unchanged remained high for participants with ≥10 years of follow up with 70% for Schirmer's test (n=79) and 94% for ANA (n=51). The percent unchanged for both UWS flow and MSGB for durations of >5 years were limited by small sample size. Among participants with a baseline Focus Score (FS) ≥1 with serial MSGB (n=52), 94% still had this at follow up and included 11 participants with a repeat positive FS at follow up durations of ≥5 years. Of the participants categorized as SjD at baseline, 94% again met criteria at follow up. Among participants who did not meet criteria for SjD at baseline, 7% (n=6) progressed to meet criteria at follow up. Conversely, 6% (n=7) of participants who met criteria for SjD at baseline did not meet criteria at follow up.

Conclusions. This appreciably large, single center cohort with longitudinal follow up provides rich detail from which to understand the natural history of SjD. A key takeaway of this study was the relative stability in the serologic, oral/sialometric, and ocular measurements over the follow-up interval. These data are critical to future clinical trials for designing appropriate endpoints.

Table I. Change in Sjögren's disease phenotypic features amoung 651 participants in the NIH cohort stratified by follow-up duration.

Sjögren's phenotypic feature	Follow up Duration (yrs)	Number of participants	+/+	-/-	-/+	+/-	Percent unchanged (95% CI)
SSA	≤5	310	169	138	7	6	96 (93-98)
+ is pos SSA	5-10	100	27	66	6	1	93 (98-97)
-is neg SSA	≥10	74	54	10	8	2	86 (77-93)
RF	≤5	469	139	277	27	26	89 (85-91)
+ is pos RF	5-10	185	58	85	27	15	77 (71-83)
. is neg RF	≥10	100	31	46	9	14	77 (68-85)
ANA	≤5	239	113	120	3	3	97 (95-99)
+ is pos ANA	5-10	107	62	35	6	4	91 (83-95)
- is neg ANA	≥10	51	41	7	2	1	94 (84-99)
MSGB	≤5	46	38	3	5	0	89 (76-96)
+ is FS ≥1	5-10	11	6	4	0	1	91 (59-99)
- is FS <1	≥10	8	5	0	1	2	63 (24-91)
UWS	≤5	51	29	15	4	3	86 (74-94)
+ is ≤0.1/min	5-10	18	4	7	3	4	61 (36-83)
- is >0.1/min	>10	3	3	3	3	1	67 (9-98)
TUS	≤5	214	123	41	29	21	77 (70-82)
+ is ≤0.1/min	5-10	105	64	9	17	15	70 (60-78)
-is >0.1/min	≥10	62	48	2	2	10	81 (69-90)
vBS	≤5	117	60	48	6	3	92 (86-96)
+ is ≥4	5-10	55	34	18	2	1	95 (85-99)
- is <4	≥10	28	17	10	1	0	96 (82-99)
Schirmer's test	<5	270	100	86	42	42	69 (63-74)
+ is ≤5	5-10	141	57	37	21	26	67 (58-74)
- is >5	≥10	79	38	17	11	13	70 (58-79)

RF: rheumatoid factor; ANA: antinuclear antibody; M5GB: minor salivary gland biopsy; FS: Focus Score; UW%: unstimulated whole salivary; TUS: total unstimulated; pos: positive; neg: negative; min: minute; vBS: van Bijsterveld Score; yrs: years.
+/+ indicates positive at baseline and follow-up; -/- indicates negative at baseline and follow-up; -/+ indicates negative at baseline and positive at follow-up; and +/- indicates positive at baseline and negative at follow-up. Percent unchanged is defined as the percentage of participants with concordant baseline and follow-up test results (ie. +/+ or -/-).

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COMPREHENSIVE ANALYSIS OF CLINICAL AND LABORATORY FEATURES OF 440 PUBLISHED CASES OF PRIMARY SJÖGREN'S SYNDROME AND RENAL TUBULAR ACIDOSIS

Sandhya P.*
St Stephens Hospital, Delhi, India

Objectives. To describe the clinical and laboratory features of primary Sjögren's syndrome (pSS) with renal tubular acidosis (RTA) from published literature.

Methods. A systematic search of PubMed, Google scholar, J-stage and koreamed was done to identify relevant publications, in all languages, published from inception till 31 December 2021 using a standard query (Sjögren's syndrome) AND (renal tubular acidosis OR hypokalemic paralysis OR interstitial nephritis OR osteomalacia). Non-English articles were translated using Google translate, DeepLTranslator or Google lens. Scanned documents were converted to text using i2ocr. Patients with a diagnosis of RTA and pSS were included only if either antibody [anti-SSA (anti-Ro) or anti-SSB (anti-La)] or salivary gland histopathology were positive.

Results. There were 440 cases of pSS-RTA (63.9% from Asia) curated from 360 publications. Non-English language publications (n=89) contributed 102 cases (Japanese-30, French-21, Korean-15, Chinese-14, Spanish-13, Turkish-2, Norwegian, Russian, Dutch, Serbian, Portuguese, Bulgarian and Hebrew- one each). The median (range) age was 37(6-78) years. Female:male ratio was 21:1. Approximately 6% each had juvenile and elderly-onset disease, respectively. Only 7.7% had a prior diagnosis of pSS. Oral or ocular sicca symptoms were present in 59%. Positive ocular tests, oral tests, anti-SSA, anti-SSB antibodies and salivary gland histopathology were reported in 256/331(77.3%), 123/128(96%), 382/407(93.9%), 298/379(78.6%) and 246/268(91.8%), respectively. ACR/EULAR 2016 classification criteria with modification (to include rose bengal stain and sialography/ scintigraphy to item 3 and 5 of the criteria, respectively) were fulfilled by 358(81.4%) patients. Hypokalemic paralysis (HP) was the presenting feature in 63.6%; 25% had multiple episodes of HP and 8.4% had respiratory paralysis. Type 1, type 2, combined type 1 & 2 and type 4 RTA was seen in 388, 8, 38 and 3 patients, respectively. Proximal dysfunction and RTA complications were infrequently evaluated. Fanconi's syndrome and nephrogenic diabetes insipidus were reported in 45 and 21 patients, respectively. Proteinuria and low eGFR were found 178/275(64.7%) and 157/346(45.4%), respectively. Nephrocalcinosis, renal stones, and osteomalacia were found in 92/255(36.1%), 79/237(33.3%) and 72/122(59%), respectively. Tubulointerstitial nephritis was found in 142 out of 152 renal biopsies. Other pSS features commonly reported were parotitis and purpura in 43 and 30 patients, respectively. History of renal tubular dysfunction was reported in blood relatives of four patients in this data set.

Conclusions. RTA is an early manifestation of pSS characterized by younger age and subclinical sicca symptoms. Majority of case reports were from Asia. Oral sicca signs and salivary gland biopsy were performed occasionally. HP was the most common presentation. RTA was mostly distal, proximal dysfunction and complications were infrequently evaluated.

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JUVENILE PRIMARY SJÖGREN SYNDROME - CLINICAL INSIGHTS

Rajão Martins F.*[1], Aguiar F.[2], Rodrigues M.[2], Brito I.[2]
[1]Centro Hospitalar do Algarve, Faro, Rheumatology Department, Faro, Portugal, [2]Centro Hospitalar Universitário de São João, Paediatric and Young Adult Rheumatology Unit, Porto, Portugal

Introduction. Juvenile primary Sjogren syndrome (pSS) is an extremely rare clinical entity, presenting in a pleiomorphic manner, complicating the diagnostic process. The aim of this study was to characterise the clinical and laboratorial aspects of these patients.

Methods. All patients under 18 years of age with a primary Sjogren disease diagnosis followed at a paediatric rheumatology unit of a Portuguese tertiary hospital were included in this analysis. Sociodemographic, clinical and analytical data were collected. Descriptive analysis was performed, and posterior comparison between groups included Fisher exact and Wilcoxon tests.

Results. A total of eight individuals were included, mainly females (6, 75%), with a median thirteen years of age at symptom onset, and a median delay of 1 year until diagnosis. The most frequent clinical finding at presentation was parotid gland swelling (5, 62.5%), followed by sicca symptoms - oral dryness (4, 50%) and eye dryness (3, 37.5%). Four patients had ophthalmologic alterations compatible with pSS. Six patients (80%), had extra glandular findings, skin dryness and polyarthralgia being the most frequent (3, 37,5%), followed by oral aphtosis (2, 25%). One patient was also diagnosed with juvenile systemic lupus erythematosus (jSLE) and another with autoimmune thyroiditis. Analytically, erythrocyte sedimentation rate (ESR) was only elevated in one patient, while C-reactive protein was elevated in six (80%) patients, averaging 11,50 (±3.69) mg/l. Four patients (50%) presented with hypergammaglobulinemia, averaging 2185 (±885,80) mg/dl. All patients had a positive antinuclear antibody (ANA) testing, frequently in titters ≥1:1000 (n=6, 75%), antiSSa and antiSSb (6, 75%), with two patients with isolated positivity (1 for antiSSa and 1 for antiSSb). Four patients had hypocomplementemia and three were rheumatoid factor positive. Most patients were treated with hydroxycloroquine (7, 87.5%), three in combination with low dose prednisolone, and one was under prednisolone in monotherapy. There was no statistical association between the serological markers and any of the overcited clinical findings, nor there was significant change in inflammatory markers between baseline and 6 or 12 months after treatment initiation. Histologically, two (25%) had findings compatible with Sjogren syndrome and one with chronic sialadenitis. Most patients fulfilled EULAR/ACR 2016 pSS criteria (5, 62.5%), with only one patient fulfilling AECG criteria.
Conclusions. There seems to be some similarities between juvenile pSS and adult patients: female predominance, parotiditis as the primary clinical finding, ANA, antiSSa and antiSSb positivity, hypergammaglobulinemia and rheumatoid factor positivity. One interesting difference in this cohort is the quite elevated frequency of hypocomplementemia, even though there was no statistical association with extra glandular disease as described in the literature, and the lower levels of ESR at presentation. The small size of this population may lead to biased conclusions, paving the way to bigger studies in the Portuguese paediatric population.

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CHARACTERIZATION OF SEROPOSITIVE AND SERONEGATIVE SJÖGREN'S SYNDROME ACCORDING TO THE 2016 ACR/EULAR CLASSIFICATION CRITERIA

Longhino S.*, Manfrè V., Rizzo M.T., De Vita S., Quartuccio L.
Rheumatology Clinic, ASUFC, Udine, Italy

Introduction. Sjögren's Syndrome (SS) is a systemic autoimmune and lymphoproliferative with high clinical and biological heterogeneity. The presence of anti-SSA and the minor salivary gland histopathology are the cornerstones of 2016 ACR/EULAR Classification Criteria for SS. The aim of this study is to compare the disease activity measured by ESSDAI at diagnosis and during the follow up, biological activity at diagnosis and lymphoma development between seronegative and seropositive SS patients classified according to the 2016 ACR/EULAR Criteria.
Patients and methods. 217 patients with SS were enrolled. For each patient we collected anti-SSA/SSB autoantibodies, demographic data, total ESSDAI and ESSDAI domains at diagnosis, C3, C4, RF, cryoglobulins at diagnosis, cumulative ESSDAI at last visit and the event 'lymphoma development' during the follow-up from diagnosis to the last visit. We compared data using chi-square test or Mann-Whitney test for non-parametric variables; differences were considered significant for p-value <0.05.
Results. Of 217 patients 192 were positive for anti-SSA/SSB (group 1, seropositive) and 25 were negative (group 2, seronegative). No differences were noted in the follow-up time between group 1 and 2 (12,4±0.52 vs 11.4±1.4 years p=0.26). Concerning demographic data, group 1 showed a statistically significant younger age at diagnosis than group 2 (51±2,2 vs 57±1 year; p=0.03), whereas no differences were found in gender (p=0.74). No differences were found also in C3, C4, RF and cryoglobulins (respectively p=0.08, p=0.76, p=0.53, p=0.55). Regarding ESSDAI domains at diagnosis, there were statistically differences between the 2 groups only in the hematological and biological domains (p=0.02 and p=0.006, respectively) but not in the remaining ones; of note, the hematological and biological domains were more associated with group 1 than group 2 (OR 4.74, CI 95% 1.1-20.7 and OR 3.59, CI 95% 1.4-9.4, respectively). Notably total ESSDAI at diagnosis and the cumulative ESSDAI at the last visit were similar between the two groups (p=0.80 and p=0.069 respectively). Finally, no differences between group 1 and group 2 were found in the lymphoma diagnosis (p=0.4).
Conclusions. Seronegative SS according to the 2016 ACR/EULAR classification criteria are not clinically different from seropositive SS, while they could be less biologically active. Since the biological ESSDAI domain is strictly linked to the B-cell hyperactivation, this feature should be considered in the trial design for new treatment options.

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TRANSITIONAL CD5+ B CELLS ARE ASSOCIATED WITH AUTOREACTIVITY IN PSS PATIENTS

Chatzis L.*[1], Hémon P.[2], Jamin C.[2], Le Dantec C.[2], Cornec D.[2], Pers J.O.[2]
[1]University of Athens, Athens, Greece, [2]Université de Brest, Inserm, Brest, France

The newly established role of CD5 in modulating different aspects of immune responses identifies this receptor as an immune checkpoint modulator. Using mass cytometry, we conducted an exhaustive analysis of CD5 expression in immune cells.
Whole blood from 30 healthy controls (HCs) and 39 primary Sjögren's syndrome (pSS) patients (PEPSS study) was analyzed using a cocktail of 38 antibodies on a CYTOF Helios system (Fluidigm). The percentage of CD5 for plasmablasts, B cell subsets, γδ T Cells, MAIT & NKT, early and late NK, classical, transitional and non-classical monocyte, pDC, mDC, neutrophils, basophils, eosinophils and CD66b- neutrophils was analyzed from the mass cytometry normalized files using Maxpar Pathsetter software v.2.0.45. The percentage of $CD5^+$ cells was increased in all T cell subsets analyzed (CD4 and CD8 TCM, TEM and TEMRA, Th1, Th2, Th17, TRegs, Tfh) from pSS patients compared to HCs. The percentage of $CD5^+$ cells was also increased in γδ T cells, MAIT/NKT cells and mDC from pSS patients compared to HCs. Regarding B cells, while no difference was observed for plasmablasts and switched memory B cells (SwM), the percentage of CD5+ cells was found increased in naïve, unswitched memory (UswM), double negative (DN) memory B cells and especially transitional B cells in pSS patients compared to HCs. This observation was confirmed by flow cytometry in the PRECISESADS cohort comprising of 74 pSS patients and 53 HCs. Finally, the distribution of, transitional, naïve, UswM, SwM, DN and plasmablasts was assessed for their association with clinical and biological parameters of the disease. Transitional $CD5^+$ B cells were strongly associated with anti-Ro/SSA (60 and 52 KDa), anti-La/SSB antibodies, circulating free light chains, and low C4 in the two independent cohorts. Interestingly, $CD5^+$ transitional B cells were also associated with anti-Ro60 antibodies in patients with systemic lupus erythematosus and with anti-Scl70 antibodies in patients with systemic sclerosis.

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WHAT DOES ISOLATED ANTI-RO52 ANTIBODY POSITIVITY MEAN IN SJÖGREN'S SYNDROME?

Bettacchioli E.*[1], Saraux A.[2], Tison A.[2], Cornec D.[2], Dueymes M.[1], Alarcón-Riquelme M.E.[3], Devauchelle-Pensec V.[2]
[1]Laboratory of Immunology and Immunotherapy, UMR1227, CHRU Morvan, Brest, France, [2]Rheumatology Department, UMR1227, CHRU Cavale Blanche, Brest, France, [3]Department of Medical Genomics, Center for Genomics and Oncological Research (GENYO), Granada, Spain

Background. Primary Sjögren's syndrome (pSS) is a systemic autoimmune disease characterized by a triad of dryness, pain and fatigue in affected patients. Its diagnosis is based on a combination of clinical, histological and biological findings. Anti-Ro autoantibodies comprise reactivity against two autoantigens (Ro52 and Ro60) encoded by separate genes and found in distinct cellular compartments. When expressed in pSS, a double positivity for anti-Ro 52 and anti-Ro 60 antibodies is usually observed (2/3 of the patients), and this presentation is often associated with more systemic involvement and severe evolution, as compared to patients with a negative serology. A small proportion of patients with isolated positivity for either anti-Ro52 or anti-Ro60 antibodies are also observed, but the impact of this partial biological profile remains unclear. The aim of this study was to characterize the clinical, serological and interferon profiles of Sjögren's patients with single anti-Ro52 or anti-Ro60 antibody positivity.

Methods. pSS patients were recruited from the European PRECISESADS cohort (NCT02890121 and NCT02890134). Anti-Ro52 and/or anti-Ro60 antibody levels were obtained by chemiluminescence. Clinical information, disease activity, and other autoantibodies including rheumatoid factor were also collected. Type I and type II interferon signatures were generated based on previously validated scores.
Results. Anti-Ro52 and/or anti-Ro60 antibody status was obtained for 378 pSS patients. Among the latter, 254/378 (67.2%) were double positive, 80/378 (21.2%) were double negative, 21/378 (5.5%) had only anti-Ro60 antibodies and 23 (6,1%) had only anti-Ro52 antibodies. Patients with isolated anti-Ro52 antibodies had a significantly higher proportion of positive rheumatoid factor and hypergammaglobulinemia than double-negative patients (p=0.02 and p=0.0006, respectively), as well as a trend toward a higher inflammatory index (p=0.08). Despite a similar trend, no significant difference was found for these parameters between isolated anti-Ro60 patients and double-negative patients. No statistical differences were found for disease activity (ESSDAI and PGA score), arthritis, sicca syndrome, glandular swelling or fatigue between the groups of single-positive patients, possibly due to the heterogeneity of patients included in terms of disease duration and drugs used. The interferon signatures according to two distinct modular scores were found to be significantly different in a graded manner with (i) the lowest interferon signature for double-negative patients, (ii) an intermediate interferon signature for patients with a single antibody positivity and (iii) a strong interferon signature for double-positive patients.
Conclusions. Taken together, these results suggest that pSS patients with single anti-Ro antibody positivity, especially anti-Ro52, adopt an intermediate phenotype between double-negative and double-positive patients, and should be considered at medium risk of disease progression.

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PALPABLE PURPURA ASSOCIATED RISK FACTORS IN PRIMARY SJÖGREN'S SYNDROME BY DATA DRIVEN ANALYSIS IN HARMONIZED PATIENTS.

Goules A.V.*[1], Pezoulas V.C.[2], Kalatzis F.[2], Chatzis L.[1], Kourou K.D.[2], Venetsanopoulou A.[3], Exarchos T.P.[2], Gandolfo S.[4], Votis K.[6], Zampeli E.[6], Burmeister J.[7], May T.[7], Pérez M.M.[8], Lishchuk I.[9], Chondrogiannis E.[10], Karanastasis E.[10], Andronikou V.[10], Varvarigou T.[10], Filipovic N.[11], Tsiknakis M.[12], Baldini C.[13], Bombardieri M.[14], Bootsma H.[15], Bowman S.J.[16], Shahnawaz Soyfoo M.[17], Parisis D.[18], Delporte C.[18], Devauchelle-Pensec V. [19], Pers J.O.[19], Dörner T.[20], Bartoloni Bocci E.[21], Gerli R.[21], Giacomelli R.[22], Jonsson R.[23], Ng W.F.[24], Colafrancesco S.[25], Priori R.[25], Ramos-Casals M.[26], Mavragani C.P.[1], Sivils K.[27], Skopouli F.[28], Torsten W.[29], Van Roon J.[30], Mariette X.[31], De Vita S.[4], Moutsopoulos H.M.[6], Fotiadis D.I.[32], Tzioufas A.G.[1]
[1]Dept. of Pathophysiology, School of Medicine, University of Athens, Athens, Greece, [2]Unit of Medical Technology and Intelligent Information Systems, Dept. of Materials Science and Engineering, University of Ioannina, Ioannina, Greece, [3]University Hospital of Ioannina, Ioannina, Greece, [4]Clinic of Rheumatology, Dept. of Medical and Biological Sciences, Udine University, Udine, Italy, [5]Centre for Research and Technology Hellas, Thermi, Thessaloniki, Greece, [6]Institute for Systemic Autoimmune and Neurological Diseases, Athens, Greece, [7]Fraunhofer Institute for Computer Graphics Research IGD, Darmstadt, Germany, [8]ATOS, Madrid, Spain, [9]Institute of Legal Informatics, Leibniz Universität Hannover, Hannover, Germany, [10]Institute of Communication and Computer Systems, School of Electrical and Computer Engineering, National and Technical University of Athens, Athens, Greece, [11]Bioengineering Research and Development Center, Faculty of Engineering, University of Kragujevac, Kragujevac, Serbia, Kragujevac, Greece, [12]Biomedical Informatics and eHealth Laboratory, Dept. of Electrical and Computer Engineering, Hellenic Mediterranean University, Heraklion, Greece, [13]Dept. of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy, [14]Centre for Experimental Medicine and Rheumatology, William Harvey Research Institute, Queen Mary University of London and Barts' Health NHS Trust, London, UK, [15]Dept. of Rheumatology and Clinical Immunology, University of Groningen, University Medical Center Groningen, Groningen, Netherlands, [16]Rheumatology Dept., University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK, [17]Dept. of Rheumatology, Erasme Hospital, Université Libre de Bruxelles, Brussels Belgium, [18]Laboratory of Pathophysiological Biochemistry and Nutrition, Université Libre de Bruxelles, Brussels, Belgium, [19]Univ Brest, Inserm, CHU de Brest, UMR1227, Lymphocytes B et Autoimmunité, Brest, France, [20]Dept. of Rheumatology and Clinical Immunology, Charité-Universitätsmedizin Berlin, Berlin, Germany, [21]Rheumatology Unit, Dept. of Medicine and Surgery, University of Perugia, Perugia, Italy, [22]Division of Rheumatology, Dept. of Biotechnological and Applied Clinical Sciences, University of L'Aquila, L'Aquila, Italy, [23]Dept. of Clinical Science, University of Bergen, Bergen, Norway, [24]Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, UK, [25]Dept. of Internal Medicine and Medical Specialties, Rheumatology Clinic, Sapienza University of Rome, Rome, Italy, [26]Laboratory of Autoimmune Diseases Josep Font, IDIBAPS-CELLEX, Barcelona, Spain, [27]Oklahoma Medical Research Foundation, Oklahoma, USA, [28]Dept. of Internal Medicine and Clinical Immunology, Euroclinic Hospital, Athens, Greece, [29]Dept. of Rheumatology and Immunology, Hanover Medical School, Hannover, Germany, [30]Dept. of Rheumatology and Clinical Immunology, University Medical Center Utrecht, Utrecht University, Utrecht, Netherlands, [31]Dept. of Rheumatology, Hôpital Bicêtre, Assistance Publique-Hôpitaux de Paris, Paris, France, [32]Dept. of Biomedical Research, FORTH-IMBB, Ioannina, Greece

Background. B cell mediated cryoglobulinemic manifestations constitute the systemic form of primary Sjögren's syndrome (pSS), which is clinically expressed as palpable purpura, glomerulonephritis and peripheral neuropathy. Palpable purpura is by the far the earliest and most common clinical manifestation of cryoglobulinemia. However, risk factors associated with palpable purpura per se have not been explored among pSS patients.
Methods. One thousand five hundred and eighteen fully characterized and harmonized pSS patients for 32 commonly used features were included in the working dataset to be analyzed for purpura associated risk factors in the context of the HarmonicSS project (Table I). No imputation method was applied, and therefore the working dataset contained only real data. All included patients fulfilled the 2016 ACR/EULAR criteria. Systemic manifestations were defined as described in the ESSDAI domains and for those not included in the ESSDAI system, either by tissue biopsy or by applying international consensus criteria. A Fast-Correlation based feature selection (FCBF)/logistic regression (LR) model with palpable purpura as an outcome was applied on the working dataset with down sampling strategy and triple matching according to age, gender and disease duration as described previously (1).
Results. Five prominent features in terms of magnitude of order were identified by the FCBF algorithm as potential risk factors including cryoglobulinemia, peripheral neuropathy, interstitial nephritis, anti-La antibodies and disease duration but only cryoglobulinemia was finally identified as an independent purpura associated risk factor (Table I). The overall performance of the FCBF/LR model after 10-fold cross validation was: sensitivity=63%, specificity=79%, AUC=68%.
Conclusions. Cryoglobulinemia is the only associated risk factor for palpable purpura in pSS.

Table I. FCBF-based multivariable logistic regression analysis for palpable purpura associated risk factors*.

Prominent feature*	Regression coefficient	Odds ratio	p-value	CI upper	CI low
Cryoglobulinemia**	1.896	6.947	**<0.001**	18.809	2.6
Peripheral neuropathy	0.93	2.689	0.138	8.236	0.895
Interstitial nephritis	0.771	2.272	0.369	11.888	0.455
Anti-La antibodies	0.425	1.547	0.122	2.427	0.987
Disease duration	0.022	1.022	0.123	1.047	0.998

*Features/Variables analysed by the FCBC algorithm: Gender, age at pSS diagnosis, disease duration, dry mouth, dry eyes, salivary gland swelling, Raynaud's phenomenon, arthritis, Renal disease, glomerulopathy, tubulointerstitial nephritis, pulmonary disease, small airways disease, interstitial lung disease, liver disease, autoimmune hepatitis, primary biliary cirrhosis, nervous system, peripheral nervous system disease, central nervous system disease, muscular disease, idiopathic inflammatory myopathy, inclusion body myositis, anti-La antibodies, anti-Ro antibodies, rheumatoid factors, ANA, low C4, lymphoma, MALT lymphoma, DLBCL lymphoma, and cryoglobulinemia
**<0.05 (95% confidence interval).

Poster 143 (withdrawn by authors - late withdrawal)

INCREASING THE NUMBER OF MINOR SALIVARY GLANDS IMPROVES THE DIAGNOSTIC AND MEASUREMENT PRECISION OF HISTOLOGICAL FOCUS SCORE

Tryposkiadis K.*[3], Nayar S.[1], Pucino V.[1], Bowman S.J.[2], Sitch A.[3], Price M.[3], Deeks J.[3], Barone F.[1], Fisher B.A.[1]
[1]Institute of Inflammation and Ageing, University of Birmingham, Birmingham, UK, [2]NIHR Birmingham Biomedical Research Centre, University Hospitals Birmingham NHS Foundation Trust and University of Birmingham, Birmingham, UK, [3]Test Evaluation Research Group, Institute of Applied Health Research, University of Birmingham, Birmingham, UK

Background. Minor salivary gland (MSG) biopsy with a focus score (FS) ≥1 has an important role in the diagnosis of Sjögren's (SjS). FS may also be associated with lymphoma risk or used as a clinical trial outcome measure. MSGs show within patient variation in number of foci per unit area. Previous recommendations for histopathology standardisation advised a minimum of 4 MSGs to achieve a representative result. This recommendation was not data driven and future work to establish the optimal number of MSGs to balance measurement error and clinical acceptability was advised.

Methods. Three Monte Carlo simulations were performed to investigate the impact of MSG number on (i) diagnosis based on FS≥1, (ii) measurement error, defined as the absolute difference between two consecutive FS measurements, made on the same patient, and (iii) the least sample size required to detect a clinically meaningful difference in the FS. 2500 data sets were simulated, with the generation of the FS based on a given number of patients, glands within each biopsy, and input values for the mean, between-patient variance, between-gland within-patient variance of foci number, and size of the glands. These values were informed by biopsies from 32 SjS patients meeting 2016 ACR/EULAR classification recruited in the Birmingham OASIS cohort with mean FS 1.75 (SD 1.07). The data simulation and analysis was repeated for different MSG numbers (range 2-7). The 2500 estimates produced from each simulated MSG number were summarised using appropriate statistics and compared across the six different MSG numbers.

Results. A decrease in the mean estimates for the median absolute difference was noted for every unit increase in MSG number, from a mean value of 1.05 (SD 0.25) for 2 glands, to 0.52 (SD 0.12) with 7 glands (Figure 1). A similar trend was observed for the interquartile range, with the mean value reducing from 1.60 (SD 0.48) for 2 glands, down to 0.71 (SD 0.18) with 7 glands.

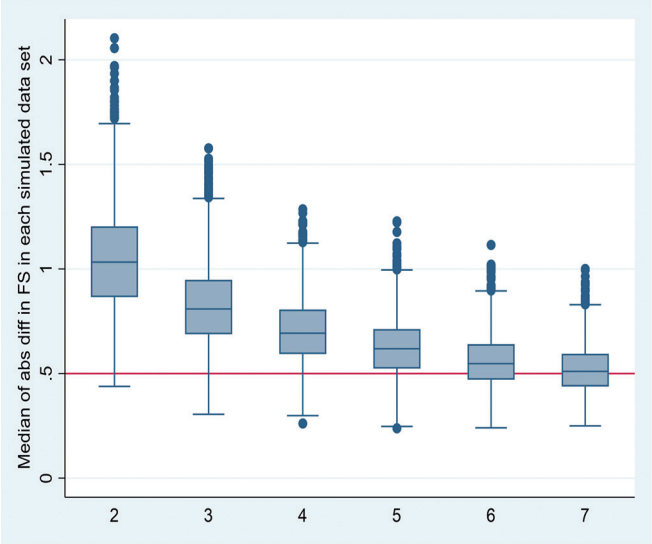
The number of glands also influenced the probability of a simulated patient receiving a FS ≥1, increasing from a median of 0.67 with 2 glands, 0.73 with 4 glands and 0.77 with 7 glands.

There was no increase in median probability between 5-7 glands.

The impact of MSG number on sample size calculations for a clinical trial with FS as an outcome measure was investigated across a range of effect sizes and statistical powers. For example, 80% statistical power to detect a 40% reduction in FS in the treatment group, required a sample size per group of 62 with 2 glands, 35 with 4 glands and 25 with 7 glands.

Conclusions. An increasing number of MSGs is associated with a decrease in measurement error. For a diagnostic threshold of FS≥1, a minimum of 5 glands should ideally be targeted. For continuous FS values as used in clinical trials, a larger number of MSGs (e.g. 6) will reduce measurement error further and reduce required sample sizes. Alternative tissue trial outcome measures should continue to be explored.

Fig. 1. Boxplot of median absolute difference in focus score for each simulated number of glands.



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CYTOKINE/CHEMOKINE EXPRESSION IN PRIMARY SJÖGREN'S SYNDROME PATIENTS

Chatzis L.*[1], Pochard P.[2], Le Dantec C.[2], Foulquier N.[2], Goules A.[1], Saraux A.[2], Devauchelle-Pensec V.[2], Cornec D.[2], Tzioufas A.G.[1], Pers J.O.[2]
[1]University of Athens, Athens, Greece, [2]Université de Brest, Inserm, Brest, France

Cytokines are important mediators in inflammation and immune reactions and over the past years the role of specific cytokines in SS has been extensively studied. In the context of the H2020 HarmonicSS project, we decided to run a Luminex dedicated assay to evaluate the quantification of the main cytokines previously described in primary Sjögren's syndrome (pSS). The choice of the different cytokines and chemokines has been established by the members of the consortium and will be applicable in the clinical cohort of the HarmonicSS project.

Twenty-three cytokines/chemokines have been analyzed (BAFF, FLT3-L, IFNα, IL-12p40, IL-13, IL-15, IL-17, IL-1RA, IL-6, IL-7, CXCL10/IP10, CCL2/MCP1, TNF-α, CXCL13/BCA, TSLP, IL-33, IL-21, IL-23, sIL-1RII, sTNFR2, sIL-2RA, CCL19, MMP8) in three different cohorts of pSS patients. The first cohort consisted of 66 pSS patients (32 seronegative and 34 seropositive for anti-Ro/SSA and anti-La/SSB) followed up at the Rheumatology outpatient clinic of the Department of Pathophysiolgy, at the University of Athens, the second PEPSS cohort consisted of 39 pSS patients (11 seronegative and 25 seropositive for anti-Ro/SSA and anti-La/SSB) and 38 healthy controls (HCs) followed at the Rheumatology Department, at the CHU Brest, and the third cohort consisted in 14 pSS patients included in the TEARS study (NCT00740948).

Among the cytokines/chemokines assessed, CXCL13/BCA, CCL19, IL-21, IL-33, IL-7, IL-12p40, CXCL10/IP10, CCL2/MCP1, sTNFR2, TSLP were increased, while IL-13, MMP8, sIL-1RII and sIL-2RA were decreased in pSS patients compared to HCs. In pSS patients, IFNα was positively associated with IL-12p40, IL-1Ra, IL-6, IL-7, TNF-α, CXCL13/BCA, IL-33, IL-21 and IL-23. While IL-13 and IL-15 were strongly positively associated together, both were negatively associated with IL-1RA, IL-6, IL-7, TNFα, TSLP, IL-33, IL-21, and sTNFR2. Interestingly, many cytokines including sTNFR2, CCL2/MCP1, CXCL10/IP10, IL-7, IL-1RA, IL-12p40, IL-33, IL-23, IL-21, IFNα and CXCL13/BCA were positively associated with the B cell subset abnormal distribution observed in pSS patients (i.e. increased of naïve B cells and decrease of memory B cells).

The median levels of CXCL10/IP10, CXCL13/BCA were found increased in seropositive patients with at least anti Ro/SSA positivity whereas MMP8 levels were decreased in seronegative patients.

In the context of the TEARS study machine learning approaches using Boruta algorithm are ongoing to establish whether some of these cytokines/chemokines could be associated with response to rituximab as defined by the CRESS and STAR scores.

Further studies with the use of bioinformatics and a larger group of patients will probably mirror the cytokine profile in different subgroups of SS patients, adding to the identification of new molecular biomarkers in this disease. As part of the HarmonicSS project, we have planned to analyze these cytokines/chemokines using the same Luminex batches in more than 1000 patients. Several analyzes are still in progress or awaiting standardization and will allow us to go much further in understanding the physiopathology of pSS.

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THE UNIVERSITY OF FLORIDA COHORT WITH CHILDHOOD SJÖGREN'S DISEASE CLASSIFIED BY THE LATENT CLASS ANALYSIS

Zeng W.*[1], Thatayatikom A.[2], Lieberman S.[3], Basiaga M.[4], Stern S.[5], Dizon B.[6], Shah A.[7], Beal C.J.[7], Winn N.[8], Schrepfer T.[7], Bhattacharyya I.[8], Benos P.V.[7], Cha S.[8]

[1]University of Florida College of Public Health and Health Professions and College of Medicine, Gainesville, USA, [2]AdventHealth Medical Group, Orlando, USA, [3]University of Iowa Carver College of Medicine, Iowa City, USA, [4]Mayo Clinic, Rochester, USA, [5]University of Utah School of Medicine, Salt Lake City, USA, [6]National Institute of Arthritis and Musculoskeletal Diseases, Bethesda, USA, [7]University of Florida College of Medicine, Gainesville, USA, [8]University of Florida College of Dentistry and Center for Orphaned Autoimmune Disorders (COAD), Gainesville, USA

Objectives. The study aims to propose a diagnostic criterion for Childhood Sjögren's Disease (cSjD) based on a data-driven, machine learning approach.

Methods. A total of 217 symptomatic individuals were enrolled for the University of Florida (UF) cSjD Cohort Study. To classify patient groups, latent class analysis (LCA) was performed based on 30 clinical and laboratory features, namely, hypergammaglobulinemia, cytopenia, autoimmune hemolytic anemia, low C3, low C4, anti-SSA, anti-SSB, ANA, RF, anti-dsDNA, anti-RNP, anti-TPO, anti-thyroglobulin, anti-mitochondrial, anti-centromere, and early SjD autoantibodies (CA6/SP1/PSP at least one positive, eSjA), unstimulated flow rate (USFR), focus score, Schirmer's test, salivary-gland-ultrasound (SGUS), recurrent parotitis/glandular swelling, dry mouth (subjective), dry eyes (subjective), candidiasis, and ESSPRI- and ESSDAI-related symptoms and signs. Random forest was used to rank the variable importance. The sensitivity and specificity of clinical, laboratory, and diagnostic tests in the LCA model were also calculated.

Results. The 2016 ACR/EULAR SjD criteria diagnosed 57 cSjD with 160 non-cSjD patients, whereas our LCA model classified the 217 patients into three distinct groups, which we defined as Class I (probable cSjD, n=27), Class II (symptom-dominant group, n=98) and Class III (likely non-cSjD, n=92). Class I was more likely to have high ESR and CRP, low C3 and C4, positive SGUS, and positive autoantibodies when compared to Class II and Class III. They also had higher rates of hypergammaglobulinemia, cytopenia, autoimmune hemolytic anemia, recurrent parotitis/glandular swelling, and renal and cutaneous symptoms. The Class II group had the highest ESSPRI scores as well as the highest rates of sicca symptoms along with articular, neurological, and gastrointestinal involvement. However, objective tests did not significantly differ between this symptom-dominant group and the likely non-cSjD group, although USFR appear to be higher in the former. The top five random forest classifier variables in the LCA model were ESS-fatigue, ESS-dryness, ESS-pain, dry eyes (subjective), and SGUS. ANA had the highest sensitivity (96.8%) in detecting the Class I (probable cSjD) from Class II and Class III, closely followed by SGUS (90.9%). Cytopenia had the highest specificity in differentiating Class I and Class II from Class III (98.9%) as well as Class I from Class II (99.0%), closely followed by anti-centromere autoantibody (98.3% and 97.0%), and hypergammaglobulinemia (96.7% and 99.0%).

Conclusions. LCA identified three distinct groups in the UF cSjD cohort, offering novel insights into the development of the cSjD criteria tailored to children.

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COLOR DOPPLER ASSESSMENT OF SALIVARY GLANDS IN PATIENTS WITH PRIMARY SJÖGREN'S SYNDROME

Giovannini I.*[1], Manfrè V.[1], Hocevar A.[2], Quartuccio L.[1], De Vita S.[1], Zabotti A.[1]

[1]Rheumatology Clinic, Azienda Sanitaria Universitaria Friuli Centrale c/o University of Udine, Udine, Italy, [2]Department of Rheumatology, University Medical Centre Ljubljana, Ljubljana, Slovenia

Background. The role of salivary gland ultrasonography (SGUS) of major salivary glands (SG) in primary Sjögren's Syndrome (pSS) is increasing due to its non-invasiveness, feasibility, and low cost. Even if SGUS is not included in the classification criteria for pSS (1), various grey-scale ultrasound scoring systems have been developed and tested over the years (2,3). Parenchymal color doppler (CD) signal is useful to assess the vascularization within SG as it may represent a marker of SG inflammation, and its utility is raising interest in the scientific community (4).

Objectives. To analyze the correlation between CD scoring system and clinical features, in particular to EULAR Sjögren's syndrome disease activity index (ESSDAI), and between SGUS scoring system (*i.e.*, OMERACT score) and clinical variables.

Methods. Consecutive pSS patients fulfilling 2016 ACR/EULAR classification criteria (1) evaluated between June 2021 and November 2021 were included in the study. Demographic and objective data such as sialometry were collected. SGUS score was assessed according to OMERACT scoring system, and CD value according to the score 0-3 proposed by Damjanov *et al*. (5).

Results. The study included 73 patients. Mean age was 49 (SD 12,4) years. 91.8% were anti-SSA positive, 58.9% anti-SSB, 67.1% rheumatoid factor (RF) positive. Mean ESSDAI was 5.08 (SD 4.99). Correlation between total ESSDAI and higher parotid CD SGUS score was found, as well as with specific domains of the ESSDAI (glandular, lymphadenopathy, hematological), as sshown in Table I. A correlation was reported between higher OMERACT scores in parotid and submandibular glands and the presence of anti-SSA and anti-SSB antibodies, as well as with RF and pathological sialometry.

Table I. Color doppler salivary gland ultrasonography assessment of the parotid glands.

	Color doppler grade 0 and 1	Color doppler grade 2 and 3	*p*-value
SSA positive, n (%)	52 (91.2%)	15 (93.8%)	1
SSB Positive, n (%)	34 (59.6%)	9 (56.3%9	0.807
RF Positive, n (%)	36 (63.2%)	13 (81.3%)	0.234
Pathological Sialometry, n (%)	40 (70.2%)	15 (93.8%9	*0.097*
Pathological Schinmer test, n (%)	45 (78.9%)	14 (87.5%)	0.721
VAS_oral, mean (SD)	6.49 (2.81)	7.58 (1.93)	0.288
VAS_ocular, mean (SD)	5.86 (2.70)	6.58 (2.61)	0.412
VAS_pain, mean (SD)	4.96 (3.42)	4.46 (2.03)	0.386
VAS_fatigue, mean (SD)	5.79 (3.23)	6.69 (2.21)	0.513
ESSDAL_ mean (SD)	**4.07 (4.26)**	**8.69 (5.83)**	**0.002**
ESSDAL_constitutional, mean (SD)	0 (0)	0 (0)	NA
ESSDAL_lymphoadenopathy, mean (SD)	**0.281 (1.03)**	**2.00 (3.58)**	**0.008**
ESSDAL_glandular, mean (SD)	0.211 (0.725)	1.88 (1.54)	<0.001
ESSDAL_articular, mean (SD)	0.632 (1.08)	0.750 (1.24)	0.774
ESSDAL_cutaneous, mean (SD)	0.386 (1.61)	0.375 (1.50)	0.927
ESSDAL_pulmonary, mean (SD)	0.526 (2.44)	0.313 (1.25)	0.919
ESSDAL_renal, mean (SD)	0.175 (0.928)	0 (0)	0.465
ESSDAL_muscular, mean (SD)	0.211 (1.59)	0 (0)	0.619
ESSDAL_PNS, mean (SD)	0.439 (1.171)	0.938 (2.72)	0.475
ESSDAL_haematological, mean (SD)	0.491 (0.947)	1.38 (1.59)	**0.019**
ESSDAL_biological, mean (SD)	0.754 (0.830)	1.19 (0.911)	*0.0854*

Conclusions. CD SGUS is feasible to assess the vascularization of major SG and may represent a tool to evaluate inflammatory activity in pSS, as it correlates with ESSDAI.

References

1. Shiboski CH *et al*.: *Arthritis Rheumatol* 2017; 69(1): 35-45.
2. De Vita S *et al*.: *Clin Exp Rheumatol* 1992 Aug; 10(4): 351-6.
3. Jousse-Joulin S *et al*.: *Ann Rheum Dis* 2019 Jul; 78(7): 967-73.
4. Hočevar A *et al*.: *Rheumatology* (Oxford) 2021 Nov 25; keab876.
5. Damjanov N *et al*.: *J Rheumatol* 2016 Oct; 43(10): 1858-63.

Poster 174

TOP LINE RESULTS FROM NOPRODNAP0017: A DIRECT-TO-PATIENT LONGITUDINAL STUDY FOR DIGITAL AND BIOMARKER DISEASE PROFILING OF PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) AND SJÖGREN'S SYNDROME (PSS)

Avey S.*[1], Reynoso E.[1], Hu X.[1], Ven K.[2], Pandis I.[3], Bonet D.[1], Lontoc T.[1], Patel C.[1], Mosca K.[1], Liu G.[1], Morris M.[1], Murphy P.[3], Franks C.[1], Leszczuk J.[1]
[1]Janssen R&D, Spring House, USA, [2]Janssen R&D, Beerse, Belgium, [3]Janssen R&D, London, UK

Introduction. Fatigue and poor sleep quality are prevalent in pSS and SLE but there has been limited progress in developing new therapies to treat these symptoms. Digital health technologies provide new opportunities to improve symptom assessment. The primary objective of the study was to identify differences in sleep and activity metrics using a wrist-worn actigraphy device in patients with SLE and pSS compared with demographic-matched healthy volunteers (HNV).
Methods. A decentralized direct-to-patient trial was conducted in the United States and 99 participants were enrolled (39 HNV, 30 SLE, 30 pSS). Digital health technologies were shipped to participants and worn (wrist-worn actigraphy device) or installed (touchless sensor) for 24 weeks. Daily electronic diary and weekly patient reported outcomes (eDiary/ePROs) were collected using a smartphone.
Analysis. Primary analysis focused on differentiating pSS and SLE patients vs. HNV with pre-specified actigraphy endpoints summarized as weekly averages. A mixed effect repeated measures model with actigraphy endpoints as the response variable and categorical variable of cohort, fixed variable of time, and group-by-time interaction was applied for the primary analysis. Correlations between actigraphy measures and eDiary/ePRO measures were investigated to understand the relationship between self-reported fatigue and actigraphy measures.
Results. At baseline pSS patients had significantly higher sleep efficiency than HNV (pSS: 0.93, HNV: 0.91; p=0.005) but this trend was not maintained over time and there were no significant differences in sleep metrics including sleep efficiency at week 24 (p=0.98). Physical activity was lower at baseline in both SLE and pSS patients compared to HNV when assessed by both pre-specified physical activity measures, namely, step count (SLE: 3170, pSS: 3343, HNV: 4616; $p\leq$0.001) and minutes spent in Moderate to Vigorous Physical Activity (SLE: 142, pSS: 145, HNV: 167; p<0.10). This difference in step count was maintained over 24 weeks. Within the pSS cohort steps were positively correlated with PROMIS physical function score (r=0.53, p<0.001) and inversely correlated to fatigue as assessed by FACIT-F (r=0.38, p<0.01) and weekly PROMIS total fatigue score (r= -0.34, p<0.001).
Conclusions. This study demonstrates that there are differences in pre-specified physical activity measures in both SLE and pSS patients compared to HNVs. The findings for sleep measures are generally consistent with a previous study published in pSS (Miyauchi *et al*. 2021) which did not demonstrate differences in wrist-actigraphy measures of sleep quality. Results can be used to define disease-specific normal ranges for actigraphy measures and to quantify variability over time to guide interpretation of changes in future clinical trials. Further analysis to extract new features from raw accelerometer data is planned to quantify with higher resolution the degree to which sleep and activity become dysregulated in SLE and pSS. In the future, these digital measures may be useful tools for patient stratification or efficacy endpoints in these heterogenous diseases.

Poster 187

DIAGNOSTIC VALUE OF MONOSPECIFIC ANTI-DFS70 ANTIBODIES IN PRIMARY SJÖGREN'S SYNDROME

Khvan Y.*, Torgashina A., Chaltsev B., Verizhnikova Z.
V.A. Nasonova Research Institute of Rheumatology, Moscow, Russian Federation

Background. Diagnosis of primary Sjögren's (pSS) syndrome is not difficult in most cases in the presence of anti-Ro antibodies in the patient. However, there is a subgroup of patients with an isolated increase of antinuclear antibodies (ANA) HEp-2 without increase other antibodies. In such cases, the diagnosis is not always confirmed by instrumental methods. The ability to detect of ANA HEp-2 that is not related to rheumatic pathology is of particular importance. The detection of anti-DFS70 antibodies can help in the differential diagnosis and be a marker for the exclusion of systemic rheumatic diseases.
Objectives. To explore the frequency of anti-DFS70 antibodies in patients with pSS and donors.
Methods. From 2021 to 2022, we examined 64 patients (49 women, 5 men) with the mean age 45.6±14.3 years (minimum 18, maximum 78) with ANA screen or HEp-2 positive and/or with clinical signs of salivary glands or lacrimal glands involvement. Patients underwent classical examination (stomatological, ophthalmological, immunological) according to the protocol for pSS diagnostics. All patients were divided into 2 groups: 29 patients (28 women, 1 man) with pSS diagnosed according to ACR/EULAR 2016 criteria and other 35 donors (31 women, 4 man). Antinuclear antibodies and anti-DFS70 antibodies were determined by indirect immunofluorescence reaction with kit ANA HEp-2/DFS Knock out (KO), IMMCO Diagnostics, USA. The results of fluorescence were processed by visual evaluation of the samples with microscope Cark Zeiss Axioskop 40, Germany. Positive ANA HEp-2 were >1:160.
Results. All patients with pSS had ANA HEp-2 >1:160. Only 28 (80%) in donor group had ANA HEp-2. Anti-DFS70 were not found in patients with pSS. At the same time, in the group of donors anti-DFS70 were detected in 18 (64,2%) donors: 16 did not have any signs of systemic rheumatic diseases and 2 donors were diagnosed with psoriatic arthritis and osteoarthritis.
Conclusions. Detection of anti-DFS70 may be useful in the differential diagnosis of patients with an isolated increase of ANA HEp-2 and may be a screening marker at the outpatient stage.

EVOLVING TOPICS IN pSS – RELATED LYMPHOPROLIFERATION

Poster 35

EARLY DETECTION OF MALT LYMPHOMA IN SJÖGREN'S SYNDROME PATIENTS THROUGH IMMUNOGENETICS

Kolijn P.M.*, Huijser E., Wahadat M.J., Van Helden-Meeuwsen C.G., Van Daele P.L., Versnel M.A., Langerak A.W.
Erasmus MC, Rotterdam, Netherlands

Activated B cells have a pivotal role in the pathogenesis of primary Sjögren's syndrome (SjS), both through the production of autoantibodies and the development of ectopic germinal centers. Furthermore, up to 10% of SjS patients develop B-cell lymphoma, typically lymphomas of the mucosa-associated lymphoid tissue (MALT). Strikingly, parotid MALT lymphomas in SjS frequently produce antibodies with rheumatoid factor activity, suggesting autoreactivity is an early driver during lymphoma development. By screening peripheral≠≠ blood mononuclear cell (PBMC) samples from SjS patients collected prior to MALT lymphoma diagnosis, we aimed to investigate if the immunoglobulin heavy chain (IGH) of the BCR can be used as a marker for minimally invasive early detection of MALT lymphoma in SjS patients, expanding on previous biopsy-based evidence.
We studied 5 SjS patients who were diagnosed with MALT lymphoma, alongside 5 matched controls. All PBMC samples were drawn after SjS diagnosis and a median of 3 years before MALT lymphoma diagnosis (interquartile range 2 years). For 4 out of 5 cases, a matched diagnostic biopsy of the affected lymph node was available. A leader-based PCR was utilized to amplify the immunoglobulin heavy chain (IGH) of the PBMC samples before sequencing on an Illumina Miseq. In 3 out of 5 (60%) MALT lymphoma patients we identified clonotypes in PBMC samples taken three months to two years prior to diagnosis. These clonotypes were present at an abnormal frequency compared to the healthy background clonotypes.
Notably, skewing of the IGH gene repertoire was absent in controls. While the abundance ratio of cases was increased compared to controls, the absolute frequency of these skewed clonotypes remained relatively low, at <1% of the total IGH gene repertoire. Thus, the anomaly in the PB repertoire of SjS patients developing lymphoma appears to not be characterized by the absolute frequency of the clonotype of interest, as previously observed for CLL, but instead a notable elevation above the normal B-cell background. Both abnormal pre-diagnostic clonotypes identified in parotid MALT lymphoma patients utilized the IGHV1-69/IGHJ4 or IGHV4-59/IGHJ5 rearrangements stereotypic for rheumatoid factors. Our preliminary results reveal context- dependent abnormalities in the IGH gene repertoire with potential value for early minimally-invasive detection of MALT lymphoma in SjS patients up to 2 years before diagnosis.

Poster 43

CHARACTERISTICS, PREDICTIVE AND PROGNOSIS FACTORS OF RELAPSE OR DEATH FOR NON-HODGKIN LYMPHOMAS IN PRIMARY SJÖGREN SYNDROME

Rocca J.[1], Beydon M.[1], Le Guern V.[2], Hachulla E.[3], Dubost J.J.[4], Jousse-Joulin S.[5], Devauchelle-Pensec V.[5], Gottenberg J.E.[6], Vittecoq O.[7], Lavigne C.[8], Schmidt J.[9], Marcelli C.[10], Larroche C.[11], Mariette X.[1], Nocturne G.*[1], Seror R.[1]
[1]Department of Rheumatology, Assistance Publique - Hôpitaux de Paris, Hôpital Le Kremlin-Bicêtre, Le Kremlin Bicêtre, France, [2]Department of Internal Medicine, Hopital Cochin, Paris, France, [3]Department of Internal Medicine CHRU Lille, Lille, France, [4]Department of Rheumatology, Clermont Ferrand, France, [5]Department of Rheumatology, Brest, France, [6]Department of Rheumatology, Strasbourg, France, [7]Department of Rheumatology, Rouen, France, [8]Department of Internal Medicine, Angers, France, [9]Department of Internal Medicine, Amiens, France, [10]Department of Rheumatology, Caen, Finland, [11]Department of Internal Medicine, Bobigny, France

Background. Primary Sjögren syndrome (pSS) patients present an increased risk of Non-Hodgkin lymphoma (NHL). There is no consensus on the therapeutic management of low-grade NHL. Two strategies can be proposed; either a ''wait and see'' strategy or active therapeutic strategy. The objective of our study was to describe characteristics of NHL in pSS and identify predictive and prognosis factors of relapse or death.

Materials and methods. This multicentric retrospective cohort study, included all lymphoma patients of the ASSESS cohort, enriched with patients recruited in Internal Medicine and Rheumatology departments in 13 French hospitals. For each patient, we have collected biological and clinical manifestations of pSS, NHL type, staging, and treatment strategy. During follow-up, response to treatment and overall survival (OS) were analyzed.
Results. A total of 105 pSS patients who presented a B cell-NHL between 1985 and 2019 were included. Among them, 18 (17%) did not have low-grade B cell lymphoma, including 14 (13%) large B cell lymphoma (DLBCL). Among the 87 pSS patients with a low-grade B cell NHL, the most frequent histologic subtype was mucosa-associated lymphoid tissue (MALT) lymphomas (n=67, 77%). Location was extra-nodal in 46% of the cases including isolated salivary glands involvement in 28% of the cases. 37% of patients had a MALT-IPI score of 2 (high risk) and 86% had an Ann Arbor staging of 4. Median follow-up was 8 years [IQR 4.2-14] and OS was 86%. Overall, 68/87 (78%) patients received a specific treatment for lymphoma; 11/65 (17%) of them further received rituximab maintenance therapy. Compared with treated patients, untreated patients tended to be older (mean 63.6 vs 56.1, p=0.053). There was no difference in clinical and biological characteristics of pSS and MALT IPI score. No significant difference in OS was observed between treated and untreated patients (p=0.4). In univariate analyses, older age (HR 1.13 [1.05-1.22], p=0.007), pulmonary lymphoma location (HR 5.80 [1.53-22.0], p=0.01), MALT IPI score of 2 (p=0,007) and use of Bendamustine (p=0.003) were associated with an increased risk of death. In multivariate analysis, only age (HR=1.16 [1.06–1.26], p=0.007) and pulmonary location (HR=8.6 [1.79-41.7]; p=0.009) were associated with death, suggesting a potential indication bias for the risk associated with bendamustine.
In univariate analyses, risk of relapse in treated patients was lower if first line chemotherapy included anti-CD20 (HR 0.39 [0.16-0.95], p=0.04) and decreased with calendar year of LNH diagnosis (p=0.007). Since these 2 data are very related, we did not perform multivariate analysis. Interestingly no relapse occurred in patients who received maintenance therapy with RTX (0/11 events in maintenance therapy group vs 20/54, p=0.01).
Conclusions. This study based on a large number of pSS patients with lymphoma shows that age and pulmonary location are the main factors associated with the risk of death. Among treated patients, it appears that maintenance therapy with RTX may be associated with a lower risk of relapse.

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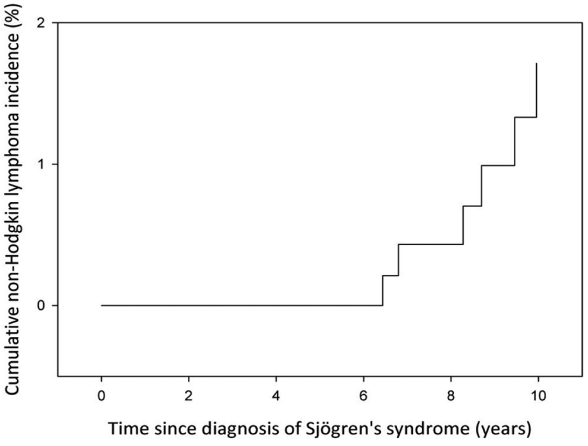
HIGHER LYMPHOMA RISK IN SJÖGREN'S SYNDROME IN THE NORTH EAST OF ITALY OVER 15 YEARS OF FOLLOW-UP: THE FIRST ITALIAN STUDY MATCHING THE CANCER REGISTRY AND THE ADMINISTRATIVE DATABASE

Treppo E.*[1], Toffolutti F.[2], Manfrè V.[1], Taborelli M.[2], De Vita S.[1], Serraino D.[2], Quartuccio L.[1]
[1]ASUFC Rheumatology Clinic, Udine, Italy, [2]Unit of Cancer Epidemiology, Aviano, Italy

Background. Connective tissue diseases (CTD) include systemic lupus erythematosus (SLE), Sjögren's syndrome (SS), systemic sclerosis (SSc), polymyositis (PM), and dermatomyositis (DM). Shared genetics, environmental factors, medical treatment of autoimmune diseases and dysregulated immune function have led to speculation of an elevated cancer incidence in patients with autoimmune diseases (1, 2).
Objectives. The present study aimed to evaluate the cancer risk associated with the most relevant CTD in the northern Italian region of Friuli Venezia Giulia (FVG) over the years 2002-2017. The primary objective was to determine whether the risk of malignancy was higher among these rheumatic conditions than the age- and sex-corresponding general population.
Methods. A retrospective population-based cohort study was conducted using data from healthcare databases of the FVG region, north-east of Italy (1,206,000 inhabitants). Information on demographic characteristics, hospital discharges, exemption from medical charges, drug prescriptions, were individually matched with data from the population-based cancer registry. The cancer risk was assessed in people diagnosed with the following diseases: SLE, SS, SSc, PM, and DM. To compare the cancer incidence in the cohort with the general population, Standardized Incidence Ratios (SIRs) were calculated as the ratio between the observed and the expected number of cancer cases. The cohort included subjects resident in the FVG region,

diagnosed with at least one of the following diseases: SLE, SSc, SS, DM, and PM. To guarantee the highest homogeneity and comparability of the exemption codes, the analysis was restricted to the years 2002-2017.
Results. 2504 patients were followed-up for a total of 18,006 person-years (median follow-up: 6.8 years). After 5 and 10 years of follow-up, the cumulative cancer incidence was 2.6% and 8.5%, respectively. The most common cancers were breast (n=34), lung (n=24), colon-rectum-anus (n=20), and non-Hodgkin lymphomas (NHL) (n=20). Overall, no excess cancer risk was noted (SIR=0.87, 95% CI: 0.75-1.00), whereas the number of observed NHL cases was more than two-fold significantly higher than expected (SIR=2.52, 95% CI: 1.54-3.89). The subgroup analysis showed a higher risk of NHL among SS patients (SIR=3.84, 95% CI: 1.92-6.87) and SLE patients (SIR=2.69, 95% CI: 0.99-5.84). Conversely, the study population showed a decreased risk for cancers of breast (SIR=0.61, 95% CI: 0.42-0.85) and corpus uteri (SIR=0.21, 95% CI: 0.03-0.77).
Conclusions. The incidence of NHL was higher among patients with SS and SLE. A careful surveillance for haematological malignancies in these patients is recommended. The lower risk of cancer for breast and corpus uteri in CTD indirectly supports cancer screening programs.



Poster 62

THE COURSE OF PRIMARY SJÖGREN'S SYNDROME PRIOR TO THE DEVELOPMENT OF LYMPHOMA: SHOULD SYSTEMIC THERAPY BE USED IN THE TREATMENT OF GLANDULAR FORMS OF THE DISEASE?

Chaltsev B.[1], Vasiliev V.[2], Torgashina A.[1], Khvan Y.[1], Sokol E.*[1]
[1]V.A. Nasonova Research Institute of Rheumatology, Moscow, Russian Federation, [2]MEDSI, Moscow, Russian Federation

Background. According to the latest EULAR recommendations for the management of Sjögren's syndrome, systemic therapy in the absence of extraglandular manifestations is not recommended, and only symptomatic drugs are recommended in the treatment of glandular forms of the disease. Purpose: to evaluate the course of pSS prior to the development of lymphoma, to evaluate the frequency of extraglandular manifestations in pSS+lymphoma pts.
Methods. We evaluated 37 pSS+lymphoma pts. pSS was diagnosed based on ACR/EULAR2016 criteria. Lymphomas were diagnosed according to morphology of affected organs biopsies. The median duration of pSS before the development of lymphoma was 7 years, in 23/37 cases (62%) the diagnoses of pSS and lymphoma were made simultaneously. Among the 37 lymphomas, there were: 34 marginal zone lymphomas (33 MALT-lymphomas [transformed into DLBCL in 2 cases], 1 splenic lymphoma), 1 primary DLBCL, 1 follicular lymphoma, 1 T-cell large granular lymphocyte leukemia.
Results. Clinical and laboratory signs in pSS+lymphoma pts are shown in Table 1. In the present study, only 16/37 pts (43%) with pSS+lymphoma had extraglandular manifestations. The course of pSS prior to the development of lymphoma in most cases was characterized by the predominant progression of glandular manifestations in the absence of extraglandular manifestations, the gradual development of severe lesions of the salivary glands with their significant infiltration and severe functional insufficiency, and then the development of parotidomegaly and / or lymphadenopathy (in some cases, combined with hypocomplementemia, monoclonal gammopathy and decrease of the peripheral blood CD19+lymphocyte count) and the diagnosis of lymphoma. 58% of pts with pSS+lymphoma received systemic therapy before the development of lymphoma (of which 100% received glucocorticoids, 33% methotrexate, 20% azathioprine, 6% hydroxychloroquine and leflunomide), 42% of patients with pSS+lymphoma did not receive systemic therapy before the development of lymphoma (only symptomatic treatment).
Conclusions. In the present study, the development of lymphomas in pSS was predominantly associated with the progression of glandular manifestations of the disease; therefore, in pSS, early administration of systemic therapy, regardless of the presence of extraglandular manifestations, may be rational. In our study, treatment with glucocorticoids, methotrexate, azathioprine, hydroxychloroquine, and leflunomide did not prevent the development of lymphoma.

Table I. Clinical and laboratory sign in pSS+lymphoma pts.

Sign	pSS+lymphoma (n = 37)
ANF	100 %
RF-IgM	49 %
Anti-Ro	59 %
Anti-La	30 %
Hypergammaglobulinemia	35 %
High IgG	32 %
High IgM	22 %
High CRP	17 %
High ESR	35 %
Low C4	46 %
Cryoglobulinemia	16 %
Monoclonal gammopathy	29 %
Low peripheral blood CD19+cells	80 %
Reccurent parotitis	38 %
Severe xerostomia	94 %
Focus score >3	82 %
Parotidomegaly	89 %
Keratoconjunctivitis sicca	81 %
Severe xeroophthalmia	76 %
Extraglandular manifestations	43 %
Lymphadenopathy	27 %
Arthralgias	35 %
Neuropathy	11 %
ILD	8 %
Hypergammaglobulinemic purpura	8 %
Cryoglobulinemic vasculitis	11 %
Raynaud's phenomenon	22 %

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MARGINAL ZONE LYMPHOMAS IN PRIMARY AND SECONDARY SJÖGREN'S SYNDROME

Vasiliev V.[1], Palshina S.[1], Gaiduk I.[2], Probatova N.[3], Gorodetskiy V.[4], Kokosadze N.[3], Shornikova N.[1], Rodionova E.[1], Safonova T.[1], Aleksandrova E.[1], Chaltsev B.[4], Torgashina A.[4], Sokol E.*[4], Novikov A.[1]
[1]Rheumacentr, Moscow, Russian Federation, [2].I. Yevdokimov Moscow State University of Medicine and Dentistry, Moscow, Russian Federation, [3]FGBU "N.N. Blokhin National Medical Research Center of Oncology" of the Ministry of Health of Russia, Moscow, Russian Federation, [4]V.A. Nasonova Research Institute of Rheumatology, Moscow, Russian Federation

Background. Marginal zone lymphomas (MZL) most commonly develop in pts with Sjögren's syndrome (SS).
Objective. to provide clinical and morphological characteristics of MZL developed during a long-term prospective observation of SS pts.
Methods. From 1975 to 2021 MZL were diagnosed in 217 pts with pSS, 11 - SSc+SS, 13 - RA+SS. To diagnose extranodal MZL (ENMZL), we performed resections of parotid salivary glands [PSG] (20), lungs (6), removal of submandibular salivary glands [SSG] (3), thymus (2), spleen (2),

biopsies of PSG (340), SSG (8), lymph nodes (55), labial salivary glands [LSG] (205), lacrimal glands [LG] (12), stomach (5), bone marrow biopsy (40). PET-CT or scintigraphy with Ga-67, detection of mIg and light chains in blood and urine, morphological study of biopsy specimens, detection of B-cell clonality were performed in all pts. Lymphomas were classified according to the WHO and Musshoff stage classification.

Results. The following types of MZL were encountered in this study: ENMZL - 237 cases, nodal MZL - 2, splenic MZL - 2. Median duration of SS before developing MZL was 6, 11.1, and 11 yrs, respectively. Localized type of MALT-lymphomas occurred in 154 (65%) pts, locally disseminated - 18 (7.6%), disseminated - 65 (27.4%). A transformed DLBCL developed in 30 (14%), 1 (9%) and 1 (7.7%) pts, respectively, with a median age of 58.5 yrs (37-79) and a median duration of 20.5 yrs from the onset of SS and 8 yrs after ENMZL diagnosis. Plasma cell differentiation occurred in 19 (8.0%) pts. The most common locations for ENMZL were PSG (97%), lymph nodes (27.2%), SSG (12.8%), LG (12.8), lungs (10.2%), LSG (6 %), bone marrow (5.1%), with disseminated type there were also rarer lesions: stomach, bones, tonsils, soft tissues, thymus, tongue. Debut of lymphoma with unilateral lesion of PSG was observed in 13%. The main immunological disorders were: ANF (100%), Ro (80%), La (48%), RF (74%), ACA (8.3%), AMA (2.1%), RNP (2 .1%), mIg (27%), low C3 (27.5%), C4 (37.5%), cryoglobulinemia (24%), monoclonal cryoglobulinemia (13%). The mIg frequency increased to 32% with the development of DLBCL. The main immunophenotypes of SS in ENMZL pts were: ANF+Ro/La+-RF (82.8%), ANF+ACA+-Ro/La+-RF+-AMA (6.5%), ANF+RF (4.6%), ANF (2.8%), ANF+AMA (0.9%). Dynamics was assessed in 154 (71%) of 217 pSS pts. 5-year relapse-free survival of localized ENMZL was 91%, 10-year - 87% in the presence of histological (90%) and molecular (75%) remission according to the results of restaging after 2 years of monotherapy with RTX, or RTX+cyclophosphamide/bendamustine or R-CHOP. 20 pts who underwent surgery and 3 who received radiation therapy rapidly developed relapses of MALT-lymphoma.

Conclusions. In SS during the first 10 yrs 25% pts develop ENMZL with localized involvement of salivary/lacrimal glands (64.3%) and disseminated type (28.6%) of MALT-lymphoma with peripheral lymph node involvement, regardless of the SS immunophenotype. With late diagnosis and the absence of antilymphoproliferative therapy for SS, 13.6% develop a transformed type of DLBCL with a fatal outcome in 75% of cases.

Oral communication 69

THE VALUE OF FDG-PET/CT IN THE DETECTION OF LYMPHOMAS ASSOCIATED WITH PRIMARY SJÖGREN'S SYNDROME

Van Ginkel M.S.*[1], Glaudemans A.W.[2], Van Der Vegt B.[3], Vissink A.[4], Kroese F.G.[1], Bootsma H.[1]

[1]Department of Rheumatology and Clinical Immunology, University Medical Center Groningen, University of Groningen, Groningen, Netherlands, [2]Department of Nuclear Medicine and Molecular Imaging, University Medical Center Groningen, University of Groningen, Groningen, Netherlands, [3]Department of Pathology and Medical Biology, University Medical Center Groningen, University of Groningen, Groningen, Netherlands, [4]Department of Oral and Maxillofacial Surgery, University Medical Center Groningen, University of Groningen, Groningen, Netherlands

Introduction. Primary Sjögren's syndrome (pSS) patients have an increased risk of developing a lymphoma. PSS-associated lymphomas are mostly of the mucosa associated lymphoid tissue (MALT) type and most commonly arise within the parotid glands. Although fluorine-18-fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET/CT) is widely used in oncology and inflammatory diseases, the usefulness of FDG-PET/CT in detecting pSS-associated lymphomas is not yet clear. Therefore, we aimed to assess the usefulness of FDG-PET/CT for the diagnosis of pSS associated lymphomas in a large retrospective cohort of pSS patients.

Methods. PSS patients fulfilling the ACR-EULAR criteria for pSS, who underwent FDG-PET/CT between 2010 and 2021, were recruited from the electronic patient file system of the University Medical Center Groningen. Patients were excluded if FDG-PET/CT was performed due to an intercurrent malignancy not related to pSS. All FDG-PET/CT scans were performed on integrated PET/CT camera systems (Siemens Biograph mCT or Vision) and were reconstructed according to standardized European guidelines. FDG-PET/CT scans were visually and semi-quantitatively analysed by two investigators, focusing on the uptake in salivary and lacrimal glands and lymph nodes. Furthermore, systemic disease activity was assessed in the organs that can be visualized by FDG-PET/CT.

Results. Of the 71 included pSS patients, 26 (37%) were histologically diagnosed with a lymphoma. 23 (88%) of the pSS-associated lymphomas were of the MALT type; biopsy location: parotid (n=17), lacrimal gland (n=2), lungs (n=2) and lymph node (n=2). The maximum standardized uptake value (SUVmax) and the SUVpeak were significantly higher in both the parotid and the submandibular glands of pSS patients with lymphoma (p<0.001 for both parameters in both glands). Furthermore, patients with lymphoma more often showed presence of nodular lung lesions, compared to non-lymphoma patients (31% vs 7%, p=0.014). There was no significant difference in the presence of abnormal FDG-uptake in lymph nodes (81% for lymphoma vs 70% for non-lymphoma). Furthermore, no differences were found in the presence of arthritis, myositis, enthesopathy, vasculitis, nephritis or interstitial lung disease, and lymphoma patients did not more frequently show abnormal uptake in the thyroid gland, liver, spleen or pancreas, compared to non-lymphoma patients.

Conclusions. PSS patients with lymphoma have significantly higher SUV-values in both the parotid and submandibular glands, and more often show nodular lung lesions. Standardized FDG-PET/CT can be useful in the diagnostic work-up of pSS-associated lymphomas, since (1) it can assist in the decision if, and subsequently at which location, a biopsy is needed, and (2) it could reduce the number of biopsies in patients who do not have salivary gland FDG-PET/CT abnormalities nor presence of nodular lung lesions. Importantly, abnormal uptake in lymph node regions is frequent in pSS and does not discriminate between lymphoma and non-lymphoma.

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VALUE OF UHFUS IN THE DIAGNOSTIC WORK UP AND GUIDED BIOPSY OF SUSPECTED LABIAL SALIVARY GLAND LYMPHOPROLIFERATIVE LESIONS IN SJÖGREN'S SYNDROME

Fulvio G.*[1], Izzetti R.[3], Ferro F.[1], La Rocca G.[1], Fonzetti S.[1], Navarro Garcia I.C.[1], Mosca M.[1], Donati V.[2], Baldini C.[1]

[1]Rheumatology Unit, University of Pisa, Pisa, Italy, [2]Unit of Pathological Anatomy, University of Pisa, Pisa, Italy, [3]Unit of Dentistry and Oral Surgery, University of Pisa, Pisa, Italy

Background. Labial MALT lymphomas are extremely rare localization of lymphoproliferative complications in patients with Sjögren's syndrome (SS). However, performing labial salivary gland (LSG) biopsies as a routine part of screening for SS, may lead in some instances to early diagnosis of labial MALT lymphomas in asymptomatic patients. Recently, a growing interest has arisen in last generation ultra-high frequency ultrasonography (UHFUS) that can achieve tissue resolution up to 30 μm, opening up new possibilities for the study of LSGs.

Objectives. to describe, in SS, UHFUS features of LSGs lymphoproliferative lesions and to differentiate the UHFUS pattern of lymphoma from the "typical" inflammatory infiltrate pattern.

Methods. At our department, in the work-up of SS for research purposes, UHFUS imaging is currently used to locate the LSG for the US-guided biopsy. UHFUS of LSGs was performed with a 70 MHz probe, scanning

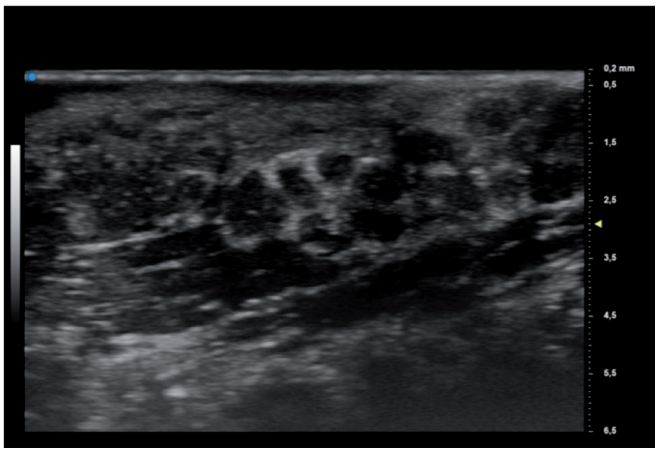

Fig. 1. Lymphoma of labial salivary glands, diffuse pattern, grey scale

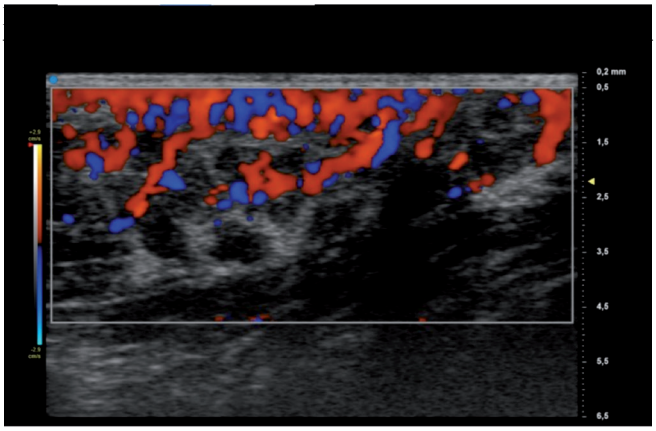

Fig. 2. Lymphoma of Fig. 1, color Doppler.

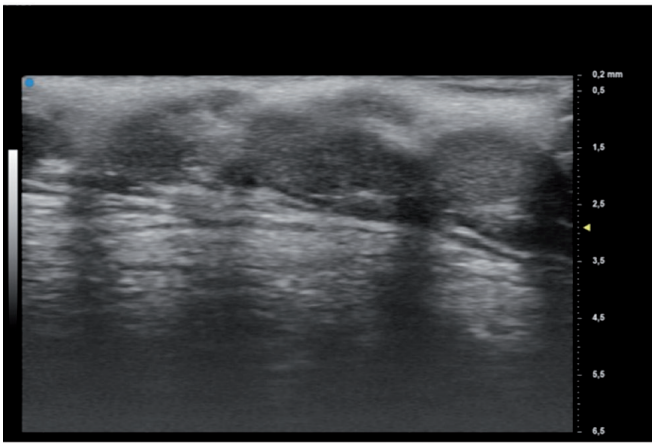

Fig. 3. Normal labial salivary glands, grey scale.

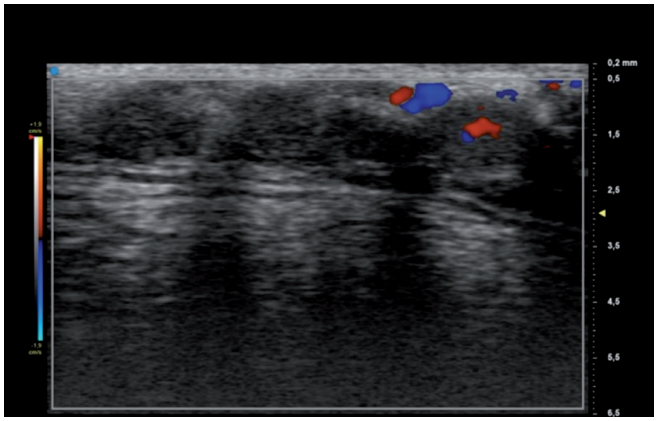

Fig.4. Labial salivary glands of Fig. 3, color Doppler..

first the central compartment of the inferior lip, and then both peripheral compartments. Prospectively, from Apr 2021 to Apr 2022, we identified all the cases of incidental MALT lymphoma or atypical severe inflammatory infiltrate of the LSG (L-pSS group). During the same period, we enrolled patients that underwent a UHFUS-guided biopsy of the LSGs and were diagnosed with SS without LSG lymphoma (NL-pSS group). For each patient, we assessed the OMERACT score, on a scale of 0 (normal) to 3 (evident inhomogeneity), and we compared ultrasonographic features between L-pSS and NL-pSS groups. For suspected lesions, echogenicity, and vascularization were also assessed and compared between the two groups. For statistical analysis, we used the Fisher test for categorical data and the ANOVA t-test or Mann-Whitney test for continuous data.

Results. We included in this study 3 incidental cases of LSG-MALT lymphoma and 2 SS patients with atypical severe inflammatory infiltrate (L-pSS). During the same period, 29 patients undergoing a UHFUS-guided biopsy of the LSGs were diagnosed with pSS (NL-pSS). No differences between the two groups were observed regarding demographic features, serology, ocular tests and unstimulated salivary flow rate. Regarding UHFUS features the OMERACT score 3 was detected in all the 5 L-pSS patients and only in 10/29 NL-pSS patients (p=0.05). In the latter group a score 2 was detected in 12/29 patients, a score 1 in 2/29 and a score 0 in 5/29 patients. Independently from the diagnosis of lymphoma, pSS patients with an OMERACT score 3 presented a higher number of foci, focus score and ectopic lymphoid structures (p<0.05). In 4/5 L-pSS patients a diffuse echo structure change was present, while 1/5 patient presented a focal lesion that was successfully sampled under UHFUS guidance. Notably, lymphoproliferative lesions, compared to "typical" inflammatory infiltrate, were all very hypoechoic and presented high perilesional Doppler signal.

Conclusions. UHFUS findings suggestive for MALT lymphoma in LSGs closely resemble those detected by SGUS in major salivary glands. UHFUS may identify labial lymphoproliferative lesions in asymptomatic pSS patients, guaranteeing the accuracy, success, and safety of the lymphoma biopsy.

Poster 105 (withdrawn by authors - late withdrawal)

NON-HODGKIN MARGINAL CELL LYMPHOMA IN PATIENTS WITH RHEUMATOID ARTHRITIS AND SJÖGREN'S SYNDROME

Vasiliev V.*[1], Gorodetskiy V.[2], Palshina S.[1], Gaiduk I.[3], Shornikova N.[1], Novikov A.[1], Chaltsev B.[2]

[1]Revmocenter, Moscow, Russian Federation, [2]V.A. Nasonova Research Institute of Rheumatology, Moscow, Russian Federation, [3]Moscow State University of Medicine and Dentistry, Moscow, Russian Federation

Objectives. To characterize clinical, laboratory manifestations, immunohistochemical (IHC) parameters of Non-Hodgkin's lymphoma (NHL) developing in patients with rheumatoid arthritis (RA) and Sjögren's s syndrome or disease in a long-term prospective study. To assess disease activity and therapy on the risk of developing NHL in RA.

Methods. 48 patients (38 females, 10 male) with RA who had NHL predictors underwent hematological examination to confirm or exclude lymphoma. For this purpose, biopsies of 9 parotid (PG) and 9 submandibular gland (SMG), 2 lacrimal glands and 4 lymph nodes were performed, 2 partial resections of PSG and 1 lung, 2 total resections of SMG and 1 splenectomy and 29 bone marrow biopsies followed by B-cell clonality analysis in fresh tissue (30) and paraffin embedded blocks (3), T-cell clonality assessment. Histological and IHC phenotype of NHL was evaluated according to WHO classification of tumors of hematopoetic and lymphoid tissues (revised 4th edition, 2016).

Results. 48 patients with RA, 31 (64.5%) of whom (group 1) had Sjögren's syndrome (n=24) or 7 RA with Sjogren's disease (primary SS) and the rest 17 (13 female, 4 male) did not (group 2). Non-Hodgkin lymphomas (NHL) were detected in 19/31 (61.3%) patients in group 1 and in 70.6% (12/17, 10 female, 2 male) in the second group. The IHC characteristics of NHL in both groups see in the table. In the first group prevailed extranodal marginal zone lymphoma (ENMZL) (63.1%, 12 from 19) of parotid and submandibular salivary glands (n=11) and of the lung (n=1) (63%), in the second group - T-cell large granular lymphocyte leukemia (T-LGL) (75%, 9 from 12). ENMZL were diagnosed in 12 patients (10 female, 2 male) at the age of 44-64 and the mean disease duration of 11+2.1 years. Only in 2 cases, NHL was confirmed after 1 and 3 years of RA. In 1 case simultaneous identification in the parotid gland of MALT lymphoma and DLBCL associated with EBV infection was observed. Immunological parameters in group 1 (RA with ENMZL +/- DLBCL): 100% positive anti-CCP, anti-MCV, ANA (ANF), rheumatoid factor; 50% had increased CRP, 31% had aRo/SS-A and 10.5% anti-Mig2, hypocomplementemia C3 (20%) and C4 (20%) and decreased levels of CD19+B cells in 78%. Before NHL diagnostics, 25% patients had no therapy, 33% were treated by NSAIDs, 50% by corticosteroids, 50% by methotrexate (MTX), by infliximab (n=1), adalimumab (n=1), and olokizumab (n=1) (TNF inhibitors in 25% cases). Patients in group 1 had erosive arthritis of IIB stage (n=7, 58.3%) and stage III (n=5, 41.7%) with low, moderate and high RA activity by DAS28 in 50%, 41.5% and 8.5%. 6 patients received a high cumulative dose of MTX (1.9-7.2 gramm) at the time when ENMZL was established. ENMZL were presented by isolated involvement of parotid gland (n=6), submandibular gland (n=2) with simultaneous bilateral (n=8) and unilateral (n=3) process. 10 patients had localized ENMZL, whereas 2 patients had disseminated one with bone marrow involvement and in IHC with plasma cell differentiation.

Table.

NHL variants	Group 1 (n=31) RA + Sjögren's syndrome (n=24) RA + Sjögren's disease (n=7)	Group 2 (n=17, RA)
All NI-IL	19 (61,3%)	12 (70,6%)
Extranodal marginal zone lymphoma (ENMZL)	12	0
Multiple myeloma (MM)	3	1
T-cell large granular lymphocyte leukemyia (T-LGL)	3	9
Follicular lymphoma (FL)	1	1
Chronic lymphocytic leukemia (CLL)	1	0
Diffuse large B.-cell lymphoma (DLBCL)	1	0

Conclusions. ENMZL is exclusively associated with SS/SD, but not RA, whereas T-LGL develops in seropositive RA.

Poster 110

SALIVARY GLAND ULTRASONOGRAPHY IN MALT LYMPHOMA COMPLICATING SJÖGREN'S SYNDROME: DYNAMIC CHANGES AFTER IMMUNOSUPPRESSIVE TREATMENT

Torgashina A.*, Chaltsev B., Khvan Y.
V.A. Nasonova Research Institute of Rheumatology, Moscow, Russian Federation

Background. There is no data on reliable ultrasonography signs that distinguish sialadenitis from lymphoma. According to some researches, large hypoechogenic lesions in Sjögren's syndrome (SjS) may indicate the presence of lymphoproliferative changes in the salivary glands (SG).
Objectives. To describe ultrasound features of SG in SjS complicated by lymphoma. To assess the dynamics of these changes after immunosuppressive therapy.
Methods. The study included 38 SjS patients with MALT lymphoma. In all cases lymphoma involved the parotid SG. At the time of inclusion none of the patients was on immunosuppressive therapy. SjS was diagnosed based on the ACR-EULAR 2016 criteria. Lymphoma was diagnosed on the basis of histological examination of salivary gland biopsies, immunohistochemical examination and determination of B-cell clonality in SG tissue. Patients were treated with rituximab (RTX) or RTX+ Cyclophosphamide (CyC). Patients received 2 1g intravenous infusions of RTX 2 weeks apart, then 375 mg every 3 months for 2 years. CyC 1000 mg was administered every two weeks for a period of 12 weeks. We evaluated the following ultrasonic parameters: size of parotid salivary glands, size of hypoechogenic or anechogenic lesions (HAL), vascularization, lymph nodes without differentiation into cortical and medulla layers. Ultrasonography was performed in all patients at baseline at diagnosis of lymphoma and then annually for 2 years.
Results. All patients were women with a mean age at diagnosis of lymphoma 48±14,5 years. The duration of the disease between Sjs and lymphoma did not exceed a year in all cases. Twelve patients received RTX monotherapy, 26 – combination therapy with RTX and cyclophosphamide. Parotidomegaly in 60% of cases was bilateral at baseline. Before the start of therapy, all patients had HAL in large numbers, their size varied from 2,5 to 10 mm and averaged 4.5 mm. Vascularization was increased in 72% of patients, pathological lymph nodes were found in 67% cases.
Ultrasound examination in dynamics was performed in 15 patients. The size of the glands returned to normal in 13 patients one year after the start of therapy. A year after the start of treatment, the number of formations significantly decreased in all but one patient. After 2 years, the formations disappeared completely in 5 patients. Interestingly, they all received combination therapy. In 2 patients in whom the size of the glands did not normalize, HAL up to 2 mm in diameter were also preserved. In the rest of the patients, single HAL no more than 1.5 mm in diameter remained.
Conclusions. In our study, lymphomas were characterized by the presence of HAL size more than 2.5 mm in great numbers, lymph nodes without differentiation into layers and increased vascularization in addition to the enlarged SG. During therapy, there was a disappearance or a significant decrease in the size of formations in patients with the effect of therapy. RTX therapy for uncomplicated sialadenitis in the SjS led to less significant changes.

Poster 114

UNCERTAIN DIAGNOSIS OF MALT LYMPHOMA IN SJÖGREN'S SYNDROME: THE POSSIBLE ROLE OF CENTROCYTE-LIKE CELL CONFLUENCE AND B-CELL CLONALITY FOR A BETTER STRATIFICATION

Longhino S.*[1], Scott C.A.[2], Fabro C.[1], Quartuccio L.[1], De Vita S.[1]
[1]Rheumatology Clinic, ASUFC, Udine, Italy, [2]Institute of Anatomic Pathology, ASUFC, Udine, Italy

Background. Primary Sjögren's Syndrome (pSS) is a systemic autoimmune disease associated with chronic inflammation of major salivary glands (MSG) from which neoplastic clones can gradually emerge according to a continuous process in which from a totally benign lymphoproliferative form (MESA), a clearly malignant (MALT lymphoma) can develop. Among pSS subjects at high lymphoproliferative risk who undergo MSG biopsy, there may be situations in which even an expert pathologist is unable to make a definite diagnosis of MALT lymphoma (MALT-NHL) or MESA. The aim of our study is to define histopathological and molecular characteristics of pSS patients with uncertain MESA/MALT-NHL diagnosis and, based on the follow-up, to identify predictive factors for stratifying the risk of evolution to an overt lymphoma.
Materials and methods. We enrolled 24 pSS patients with persistent salivary glands swelling who underwent MSG biopsy. Based on the evaluation of a team of experienced pathologists in the diagnosis of salivary MALT-NHL we defined 3 patients' groups: 6 MESA, 10 MALT-NHL and 8 MESA/MALT-NHL uncertain cases. We revised pathological and molecular data of all the patients at baseline to find items which characterized the 3 groups and then we reassessed uncertain cases in the light of their evolution or not to MALT-NHL during the follow-up. The screened pathological items were: lymphoepithelial lesions (LELs), lymphatic follicles (LFs) and semiquantitative centrocyte-like cell confluence (CCLC) degree (+, ++, +++). The molecular items were: polyclonality, oligoclonality and monoclonality.
Results. Among investigated pathological items, we found that both LELs and LFs are present in all the patients of the 3 groups. The CCLC was: + and ++ in 83% and 17%, respectively in MESA group; +, ++ and +++ respectively in 25%, 63% and 12%, in uncertain group; ++ and +++ in 20% and 80%, respectively in MALT-NHL group (Table I). Regarding molecular items we found that, when performed, molecular biology resulted 100% polyclonal in MESA, oligoclonal in 57% and monoclonal in 43% of uncertain cases, and finally monoclonal in 100% MALT-NHL cases (Table II). Focusing on follow-up of uncertain cases 1/8 patients was lost at follow-up, ++ CCLC degree was present in 3/4 and 2/3 patients who developed and did not develop MALT-NHL, whereas + and +++ CCLC degree was present only in patients who developed (1/4) and did not develop MALT-NHL (1/3), respectively (Table III). Regarding molecular data, monoclonality was present specifically in uncertain cases who developed MALT-NHL (3/4), conversely oligoclonality was seen in all cases who did not develop MALT-NHL (3/3) and in 1/4 who developed it (Table IV).

Table I. CCLC degree in MESA, MESA/MALT-NHL uncertain diagnosis and MALT-NHL groups.

	CCLC degree +	CCLC degree ++	CCLC degree +++
MESA	5/6 (83%)	1/6 (17%)	0/6 (0%)
MESA/MALT-NHL uncertain	2/8 (25%)	5/8 (63%)	1/8 (12%)
MALT-NHL	0/10 (0%)	2/10 (20%)	8/10 (80%)

Table II. Molecular biology in MESA, MESA/MALT-NHL uncertain diagnosis and MALT-NHL groups.

	Molecular biology performed in	Polyclonal	Oligoclonal	Monoclonal
MESA	2/6 (33%)	2/2 (100%)	0/2 (0%)	0/2 (0%)
MESA/MALT-NHL uncertain	7/8 (88%)	0/7 (25%)	4/7 (57%)	3/7 (43%)
MALT-NHL	8/10 (80%)	0/8 (0%)	0/8 (20%)	8/8 (100%)

Table III. CCLC degree in MESA/MALT-NHL uncertain patients who developed and did not develop overt MALT-NHL.

	MALT-NHL development (4)	No MALT-NHL development (3)
CCLC degree +	0/4 (0%)	1/3 (34%)
CCLC degree ++	3/4 (75%)	2/3 (66%)
CCLC degree +++	1/4 (25%)	0/3 (0%)

Table IV. Molecular biology in MESA/MALT-NHL uncertain patients who developed and did not develop overt MALT-NHL.

	MALT-NHL development (4)	No MALT-NHL development (3)
Polyclonal	0/4 (0%)	0/3 (34%)
Oligoclonal	1/4 (75%)	3/3 (66%)
Monoclonal	3/4 (75%)	0/3 (0%)

Conclusions. CCLC degree and molecular biology may provide a better stratification of pSS patients with high lymphoproliferative risk. Uncertain cases with higher CCLC degree and monoclonality at baseline seem to be most at risk of evolution in clear lymphoma. These features might justify treatment interventions targeting pre-lymphomatous proliferation.

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MULTI-MODAL ANALYSIS SUPPORTS IL-7/IL-7 RECEPTOR AXIS AS A RELEVANT TARGET IN SJÖGREN'S SYNDROME

Desvaux E.*[1], Soret P.[2], Hemon P.[3], Le Dantec C.[3], Chatzis L.[4], Duguet F.[2], Laigle L.[2], Poirier N.[5], Moingeon P.[2], Bretin S.[2], Pers J.O.[3]

[1]Institut De Recherches Internationales Servier (I.R.I.S), LBAI, Inserm UMR1227, University of Brest, Paris, France, [2]Institut De Recherches Internationales Servier (I.R.I.S), Paris, France, [3]LBAI, Inserm UMR1227, University of Brest, Brest, France, [4]University of Athens, Athens, Greece, [5]OSE Immunotherapeutics, Nantes, France

The major components underlying primary Sjögren's syndrome (pSS) pathophysiology relates to massive infiltration of exocrine glands by T and B lymphocytes. Autoreactive effector and memory T cells have been described to play a key pathogenic role by inducing direct tissue lesions and promoting B cell hyperactivity. IL-7 is known to regulate T cell homeostatic proliferation and survival for both memory and naïve T cell populations. Considering these findings, we deeper characterized the IL-7 receptor (IL-7R) expressing cells and the involvement of IL-7R pathway in blood and salivary glands of pSS patients.

We first investigated IL-7 molecular signature and IL-7R expression on RNA-Seq data from whole blood and sorted cells (T cells, B cells, PMN and monocytes) of pSS patients recruited in the PRECISESADS project and a meta-analysis based on three different RNA-Seq datasets from parotid and minor salivary glands (MSG) biopsies were used for in silico characterization of the IL-7 pathway. Second, IL-7R expression was characterized on peripheral immune cells using flow cytometry and mass cytometry (CyTof) from adaptive and innate-related panels investigating 35 leukocyte subsets. Third, high-content spatial immunophenotyping using imaging mass cytometry (IMC) with a dedicated panel of 25 markers was developed to characterize in situ IL-7R expression.

In blood and tissues, transcriptomic IL-7 signature was highly and consistently enriched in pSS patients and was able to effectively discriminate them from Sicca patients. Pathway analysis showed a significant upregulation of the IL-7 signaling pathway and the later was predicted to be activated in pSS tissues. In blood, IL-7R was shown to be highly expressed on $CD4^+$ and $CD8^+$ T cells, especially naive, memory, central memory and effector memory T cells, followed by terminally differentiated effector memory T cells. Among helper $CD4^+$ T cells, Tfh, Th1, Th17 and Th17.1 expressed highest levels of IL-7R. Interestingly, IL7-R was shown to be significantly upregulated on double-negative B cells from pSS patients, compared to healthy volunteers (HV). From the innate compartment, Innate Lymphoïd cells (ILCs) expressed highest levels of IL-7R followed by MAIT cells, γδ T cells, and NKT cells. Interestingly, IL-7R expression was significantly expanded on classical monocytes in pSS relative to HV.

IMC showed that IL-7R expression was observed in 9.2±11.2% of the total cells analyzed. IL-7R expression was increased in pSS compared to sicca patients and variations were seen according to the degree of infiltration. IL-7R was mainly expressed by epithelial cells (striated ducts), plasma cells and to a lower extend by B cells, T cells and strongly interacting B and T cells. We went deeper in the analysis of the different T cell, B cell and macrophage subsets and observed that, when expressed, IL-7R was mainly found on $CD4^+$ and $CD8^+$ T cells, switched memory and IgD-CD27- double negative B cells and M1.

These investigations revealed new findings on IL-7R expression patterns and highlighted the strong involvement of the IL-7/IL-7R axis in pSS, supporting IL-7R targeting as a promising therapeutic strategy in pSS.

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LYMPHOMA ASSOCIATED RISK FACTORS IN PRIMARY SJÖGREN'S SYNDROME BY DATA DRIVEN ANALYSIS IN HARMONIZED PATIENTS.

Goules A.V.*[1], Pezoulas V.C.[2], Kalatzis F.[2], Chatzis L.[1], Kourou K.[2], Venetsano-poulou A.[1], Exarchos T.P.[2], Gandolfo S.[3], Votis K.[4], Zampeli E.[5], Burmeister J.[6], May T.[6], Pérez M.M.[7], Lishchuk I.[8], Chondrogiannis E.[9], Karanastasis E.[9], Andronikou V.[9], Varvarigou T.[9], Filipovic N.[10], Tsiknakis M.[11], Baldini C.[12], Bombardieri M.[13], Bootsma H.[14], Bowman S.J.[15], Soyfoo M.S.[16], Parisis D.[17], Delporte C.[17], Devauchelle-Pensec V.[18], Pers J.O.[18], Dörner T.[19], Bartoloni Bocci E.[20], Gerli R.[20], Giacomelli R.[21], Jonsson R.[22], Ng W.F.[23], Serena C.[24], Priori R.[24], Ramos-Casals M.[25], Mavragani C.P.[1], Sivils K.[26], Skopouli F.[27], Torsten W.[28], Van Roon J.[29], Mariette X.[33], De Vita S.[3], Moutsopoulos H.M.[31], Fotiadis D.I.[32], Tzioufas A.G.[1]

[1]Dept. of Pathophysiology, School of Medicine, University of Athens, Athens, Greece, [2]Unit of Medical Technology and Intelligent Information Systems, Dept. of Materials Science and Engineering, University of Ioannina, Ioannina, Greece, [3]Clinic of Rheumatology, Dept. of Medical and Biological Sciences, Udine University, Udine, Italy, [4]Centre for Research and Technology Hellas, Thermi, Thessaloniki, Greece, [5]Institute for Systemic Autoimmune and Neurological Diseases, Athens, Greece, [6]Fraunhofer Institute for Computer Graphics Research IGD, Darmstadt, Germany, [7]ATOS, Madrid, Spain, [8]Institute of Legal Informatics, Leibniz Universität Hannover, Hannover, Germany, [9]Institute of Communication and Computer Systems, School of Electrical and Computer Engineering, National and Technical University of Athens, Athens, Greece, [10]Bioengineering Research and Development Center, Faculty of Engineering, University of Kragujevac, Kragujevac, Serbia, [11]Biomedical Informatics and eHealth Laboratory, Dept. of Electrical and Computer Engineering, Hellenic Mediterranean University, Heraklion, Greece, [12]Dept. of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy, [13]Centre for Experimental Medicine and Rheumatology, William Harvey Research Institute, Queen Mary University of London and Barts' Health NHS Trust, London, UK, [14]Dept. of Rheumatology and Clinical Immunology, University of Groningen, University Medical Center Groningen, Groningen, Netherlands, [15]Rheumatology Dept., University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK, [16]Dept. of Rheumatology, Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium, [17]Laboratory of Pathophysiological Biochemistry and Nutrition, Université Libre de Bruxelles, Brussels, Belgium, [18]Univ Brest, Inserm, CHU de Brest, UMR1227, Lymphocytes B et Autoimmunité, Brest, France, [19]Dept. of Rheumatology and Clinical Immunology, Charité-Universitätsmedizin Berlin, Berlin, Germany, [20]Rheumatology Unit, Dept. of Medicine and Surgery, University of Perugia, Perugia, Italy, [21]Division of Rheumatology, Dept. of Biotechnological and Applied Clinical Sciences, University of L'Aquila, L'Aquila, Italy, [22]Dept. of Clinical Science, University of Bergen, Bergen, Norway, [23]Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, UK, [24]Dept. of Internal Medicine and Medical Specialties, Rheumatology Clinic, Sapienza University of Rome, Rome, Italy, [25]Laboratory of Autoimmune Diseases Josep Font, IDIBAPS-CELLEX, Barcelona, Spain, [26]Oklahoma Medical Research Foundation, Oklahoma, USA, [27]Dept. of Internal Medicine and Clinical Immunology, Euroclinic Hospital, Athens Greece, [28]Dept. of Rheumatology and Immunology, Hanover Medical School, Hanover, Germany, [29]Dept. of Rheumatology and Clinical Immunology, University Medical Center Utrecht, Utrecht University, Utrecht, Netherlands, [30]Dept. of Rheumatology, Hôpital Bicêtre, Assistance Publique-Hôpitaux de Paris, Paris, France, [31]Institute for Systemic Autoimmune and Neurological Diseases, Athens, Greece, [32]Dept. of Biomedical Research, FORTH-IMBB, Ioannina, Greece

Background. Lymphoma development is the most serious complication of primary Sjögren's syndrome (pSS), with MALT lymphoma being the most frequent histologic type covering almost 75% of lymphoma cases. Although many risk factors for lymphoma development have been described so far from our laboratory and others, large scale data driven analysis on totally harmonized pSS patients is missing and potential differences between overall lymphoma and MALT lymphoma have not been studied adequately.

Methods. Two distinct datasets with fully characterized and harmonized pSS patients for 30 commonly used features were constructed to be analyzed for lymphoma and MALT lymphoma associated risk factors in the

context of the HarmonicSS project (Tables I, II). The first dataset (n=1519) included 124 lymphoma patients and non-lymphoma controls (n=1395) and the second (n=1490) 95 MALT lymphoma patients after excluding from the first dataset those patients with other or unknown lymphoma histologic types. No imputation method was applied and therefore the working datasets contained only real data. All included patients fulfilled the 2016 ACR/EULAR criteria. Systemic manifestations were defined as described in the ESSDAI domains and for those not included in the ESSDAI system, either by tissue biopsy or by applying international consensus criteria. A Fast-Correlation based feature selection (FCBF)/logistic regression (LR) model with lymphoma and MALT lymphoma as outcomes, was applied on both datasets with down sampling strategy and triple matching according to age, gender and disease duration as described previously (1).

Results. Regarding lymphoma, 5 prominent features in terms of magnitude of order were identified by the FCBF algorithm as potential risk factors including cryoglobulinemia, salivary gland swelling, disease duration, rheumatoid factor (RF) and antinuclear antibodies (ANA) of which only cryoglobulinemia and salivary gland swelling were finally identified as independent lymphoma associated risk factors (Table I). For MALT lymphomas, a similar set of prominent features was found by the FCBF algorithm with the exception of RF which was replaced by low C4 complement levels, but still cryoglobulinemia and salivary glands swelling were the only independent lymphoma associated risk factors (Table II). Both FCBF/LR models had very good overall performance after 10-fold cross validation approach (lymphoma: accuracy=74%, sensitivity=74%, specificity=72%, AUC=79% and MALT lymphoma: accuracy=76%, sensitivity=76%, specificity=72%, AUC=80%).

Conclusions. Cryoglobulinemia and salivary gland swelling are strong associated risk factors for MALT lymphoma, overshadowing additional risk factors for non-MALT lymphoma related to pSS. Further studies on diffuse large B cell lymphomas will disclose associated risk factors for aggressive lymphomas in pSS.

Reference

1. Chatzis *et al.*: *J Clin Med* 2020 Aug 12; 9(8): 2620.

Table I. FCBF-based multivariable logistic regression analysis for lymphoma associated risk factors*.

Prominent feature*	Regression coefficient	Odds ratio	p-value	CI upper	CI low
Cryoglobulinemia**	1.791	6.248	**0.002**	18.753	2.108
Salivary gland swelling**	1.693	5.582	**<0.001**	10.164	3.067
Disease duration	0.011	1.011	0.557	1.051	0.973
Rheumatoid Factor (RF)	0.611	1.877	0.094	3.428	1.027
Antinuclear antibodies (ANA)	0.531	1.776	0.218	3.466	0.911

*Features/Variables analysed by the FCBC algorithm: Gender, age at pSS diagnosis, disease duration, dry mouth, dry eyes, salivary gland swelling, Raynaud's phenomenon, arthritis, renal disease, glomerulopathy, tubulointerstitial nephritis, pulmonary disease, small airways disease, interstitial lung disease, liver disease, autoimmune hepatitis, primary biliary cirrhosis, nervous system, peripheral nervous system disease, central nervous system disease, palpable purpura, muscular disease, idiopathic inflammatory myopathy, inclusion body myositis, anti-La antibodies, anti-Ro antibodies, rheumatoid factors, ANA, low C4, and cryoglobulinemia
**<0.05 (95% confidence interval).

Table II. FCBF-based multivariable logistic regression analysis for MALT lymphoma associated risk factors*.

Prominent feature*	Regression coefficient	Odds ratio	p-value	CI upper	CI low
Cryoglobulinemia**	1.557	4.994	**0.017**	17.315	1.467
Salivary gland swelling**	1.892	6.822	**<0.001**	13.785	3.379
Antinuclear antibodies (ANA)	0.706	2.134	0.173	4.746	0.961
Disease duration	0.01	1.01	0.612	1.057	0.965
Low C4 complement levels	0.521	1.736	0.231	3.545	0.851

*Features/Variables analysed by the FCBC algorithm: Gender, age at pSS diagnosis, disease duration, dry mouth, dry eyes, salivary gland swelling, Raynaud's phenomenon, arthritis, renal disease, glomerulopathy, tubulointerstitial nephritis, pulmonary disease, small airways disease, interstitial lung disease, liver disease, autoimmune hepatitis, primary biliary cirrhosis, nervous system, peripheral nervous system disease, central nervous system disease, palpable purpura, muscular disease, idiopathic inflammatory myopathy, inclusion body myositis, anti-La antibodies, anti-Ro antibodies, rheumatoid factors, ANA, low C4, and cryoglobulinemia
**<0.05 (95% confidence interval).

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LYMPHADENOPATHY IN SJÖGREN'S SYNDROME

Chatzis L.*[1], Pezoulas V.C.[2], Stergiou I.E.[1], Paraskevi V.[3], Baldini C.[4], Exarchos T.P.[2], Fotiadis D.I.[2], Skopouli F.[5], Goules A.V.[1], Voulgarelis M.[1], Moutsopoulos H.M.[6], Tzioufas A.G.[1]

[1]Department of Pathophysiology, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece, [2]Unit of Medical Technology and Intelligent Information Systems, University of Ioannina, Ioannina, Greece, [3]Rheumatology Clinic, Department of Internal Medicine, Medical School, University of Ioannina, Ioannina, Greece, [4]Rheumatology Unit, Department of Clinical and Experimental Medicine, Pisa, Italy, [5]Department of Nutrition and Clinical Dietetics, Harokopio University of Athens, Athens, Greece, [6]Academy of Athens, Athens, Greece

Introduction. Primary Sjögren's syndrome (pSS) is a chronic systemic autoimmune disease with a diverse clinical picture, extending from a mild, benign exocrinopathy to a systemic disease. The involvement of B cells in the pathogenesis of the disease is well known as attested by the prolific autoantibody profile, hypergammaglobulinemia and the increased risk for the development of B cell lymphomas. On this prism, lymphadenopathy that may shield the hidden link between autoimmunity and lymphoproliferation, even though a common manifestation of SS, has never been extensively studied.

Methods. From a total population of 1643 consecutive patients fulfilling the 2016 ACR-EULAR criteria for SS who were followed-up in 3 Rheumatology centers from Greece (Universities of Athens, Harokopio, and Ioannina) and Italy (University of Pisa), those with a history of persistent lymphadenopathy were identified and selected. All remaining patients with a documented negative history of lymphadenopathy served as the control group. Persistent lymphadenopathy was defined as lymphadenopathy in any region for at least 6 months on the basis of clinical assessment or imaging. Glandular (dry mouth, dry eyes, parotid gland enlargement) and extra-glandular manifestations (Raynaud's phenomenon, lymphadenopathy, arthralgias/arthritis, palpable purpura, liver involvement, kidney involvement, lymphoma) as well as serology (anti Ro/SSA, anti La/SSB, rheumatoid factor, cryoglobulinemia, low C4 complement levels) and histologic features (focus score, presence) were recorded and compared. Statistical analysis for categorical data was performed by Fisher exact test or χ^2 square test accordingly and numerical data with Man Whitney test.

Results. Two hundred and four patients with persistent lymphadenopathy (study group) and 1162 without (control group) were identified and compared. The median disease duration of the study group was 6 years (range, 0-28) while of the control group 5 (range, 0-36) whereas the median age of SS diagnosis was 47 (range, 10-81) and 53 (range, 11-85) (p<0.0001),

DEMOGRAPHICS	Lymphadenopathy n= 224	Controls n= 1162	P VALUE
Median age at disease diagnosis, (range)	47, (10-81)	(11-85)	**<0.0001**
Median disease duration from SS diagnosis to last follow up, (range)	6, (0-28)	5, (0-36)	0.12
GLANDULAR AND NON SPECIFIC MANIFESTATIONS			
Dry mouth	92.8 (208/224)	93.5 (1082/1156)	0.79
Dry eyes	93.3, (209/224)	93.3 (1084/1161)	0.91
Salivary gland enlargement	45.5% (101/222)	24.5% (283/1153)	**<0.0001**
Raynaud's phenomenon	22.5% (49/218)	24.8% (278/1120)	0.51
Arthralgias	62,5% (140/224)	63.5% (735/1156)	0.82
EXTRAEPITHELIAL MANIFESTATIONS			
Glomerulonephritis	4.9% (11/223)	0.7% (8/1157)	**<0.0001**
Interstitial Lung Disease	3.5% (8/224)	4.2% (49/1161)	0.79
Autoimmune hepatitis	0.5% (1/215)	1.0% (9/886)	0.69
Peripheral nervous disease	5.9% (13/222)	2.0% (24/1157)	**0.003**
Palpable purpura	21.4% (48/224)	6.9% (81/1162)	**<0.0001**
Splenomegaly	5.1% (5/97)	0.2% (2/789)	**0.0002**
PERIEPITHELIAL MANIFESTATIONS			
Tubulointerstitial nephritis	3.6% (8/224)	4.2% (49/1161)	0.79
Small Airway disease	7.5% (17/224)	3.2% (38/1160)	**0.004**
Primary biliary cholangitis	2.2% (5/224)	1.9% (22/1162)	0.94
FOCUS SCORE	2	1,5	0.56
SEROLOGY			
Rheumatoid Factor	64.3% (139/216)	54.2% (590/1087)	**0.008**
Anti-Ro	87.9% (197/224)	76.1% (867/1139)	**0.0001**
Anti-La	49.1% (10/224)	33.6% (379/1126)	**<0.0001**
LOW C4	38.8% (84/216)	29.9% (329/1098)	**0.01**
ANA antibodies	95.0% (211/222)	89.8% (1021/1136)	**0.02**
Cryoglobulinemia	16.3% (32/196)	7.9% (54/677)	**0.0009**
HEMATOLOGIC			
Leukopenia	19.6% (44/224)	8.3% (96/1157)	**<0.0001**
Neutropenia	12.1% (25/206)	7.0% (69/976)	**0.02**
Lymphopenia	23.3% (48/206)	10.1% (98/970)	**<0.0001**
LYMPHOMA	26.3% (59/224)	7,9% (92/1161)	**<0.0001**

respectively. SS patients with lymphadenopathy had statistically significant higher frequency of salivary gland enlargement (45.6% vs 24.5%, $p<0.0001$), glomerulonephritis (4.9% vs 0.7%, $p<0.0001$), peripheral nervous disease (5.9% vs 2.0%, $p=0.003$), palpable purpura (21.4% vs 6.9%, $p<0.0001$), splenomegaly (5.1% vs 0.2%, $p=0.0002$), rheumatoid factor (64.3% vs 54.2%, $p=0.008$), anti SSA/Ro antibodies (87.9% vs 76.1%, $p=0.0001$), anti SSB/La antibodies (54.9% vs 33.6%, $p<0.0001$), low C4 serum levels (38.8% vs 29.9%, $p=0.01$), ANA antibodies (95.0% vs 89.8%, $p=0.02$), cryoglobulinemia (16.3% vs 7.9%, $p=0.0009$), leukopenia (19.6% vs 8.3%, $p<0.0001$), neutropenia (12.1% vs 7.0%, $p=0.02$), lymphopenia (23.3% vs 10.1%, $p<0.0001$) and lymphoma (26.3% vs 7.9%, $p<0.0001$).
Conclusions. SS patients with lymphadenopathy constitute a specific high-risk disease subgroup with distinct clinical phenotypes associated with increased B cell activation and prevalence of lymphoma.

Oral communication 125

THE ANALYSIS OF MACROPHAGE TISSUE HETEROGENEITY IN THE SALIVARY GLANDS OF PATIENTS WITH PRIMARY SJÖGREN'S SYNDROME REVEALS NOVEL PLAYERS IN THE LYMPHOMAGENESIS OF THE DISORDER

Tsirogianni A.K., Vakrakou A.G., Stergiou I.E., Voulgarelis M., Tzioufas A.G., Manoussakis M.N.*
Department of Pathophysiology, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece

Objectives. We comparatively assessed salivary gland (SG) specimens derived from Sjögren's Syndrome (SS) patients stratified in various groups based on the extent of lymphocytic lesions and the disease severity for the presence and tissue distribution of differently polarized macrophages. To this end we assesed the expression of defined cellular markers, including CD68 (pan-macrophage marker), IL-18 cytokine (marker of classically activated pro-inflammatory M1 macrophages) and CD163 (marker of alternatively activated anti-inflammatory M2 macrophages).
Methods. The immunohistochemical expression of CD68, CD163 and IL18-expressing cells was determined in paraffin-embedded SG biopsy specimens (parotid glands or minor salivary glands) derived from 49 patients with primary SS and 5 non-SS disease control individuals. The medical records of patients were retrospectively evaluated for various clinical and laboratory parameters, including the presence of known high-risk prognostic factors for lymphoma development. Accordingly, SS patients were classified in patients with low risk and high risk for lymphoma development (SS-LR, n=17, and SS-HR, n=17 respectively) and 15 patients with established SS-associated extranodal MALT-type marginal zone B-cell lymphoma (SS-MALT-L).
Results. In line with our previous report, significant infiltrates of $CD68^+$/$IL\text{-}18^+$ macrophages were observed in SS patients studied that correlated significantly with the severity of the histopathologic lesions (biopsy focus score, r=0.429, $p<0.011$), the presence of known risk factors for lymphoma development and increased progressively from SS-LR to SS-HR and to SS-MALT-L ($p<0.0001$). The SG lymphomatous tissue of SS-MALT patients displayed the highest number of IL-18+ macrophages compared to the lymphocytic infiltrates of non-lymphoma patients ($p<0.001$). $CD163^+$ macrophages, known to be implicated in resolution of inflammation, displayed two discrete distribution patterns. CD163+ macrophages were either found to be diffusely dispersed among the mononuclear cell infiltrates and their numbers and distributions were similar to that of $CD68^+$ macrophages (diffuse pattern), or to be restricted at the periphery of infiltrations, with completely negative staining in the core ("rim" $CD163^+$ pattern). Importantly, the presence of such rim CD163+ pattern was markedly present in all lymphomatous tissues of SS-MALT patients studied, whereas it was significantly more pronounced in the SG specimens of SS-HL patients, compared to SS-LR ($p<0.0001$). In addition, the CD163/CD68 ratios were found to be reduced progressively from SS-LR to SS-HL and to SS-MALT-L SG specimens ($p<0.0001$).
Conclusions The analysis of distribution of the various macrophage types in the inflammed SG tissues of SS patients reveals that the infiltrates of SS-HL and SS-MALT-L patients manifest diffuse expression of highly inflammatory IL-18 expressing macrophages and a rim expression pattern of regenerative $CD163^+$ macrophages. These findings likely emphasize the role of IL-18 expressing macrophages in the lymphomagenesis of SS and may introduce novel immunopathology aspects for the disease stratification of SS subgroups.

Poster 127

EXPRESSION OF MIR-155 IN SALIVARY GLANDS TISSUE OF PRIMARY SJÖGREN'S SYNDROME: CORRELATION WITH DISEASE CHARACTERISTICS AND LYMPHOPROLIFERATIVE EVOLUTION

Bruno D.*[1], Di Mario C.[2], Paglionico A.[1], Varriano V.[3], Ferraccioli G.[3], Tolusso B.[2], Alivernini S.[3], Gremese E.[3]
[1]Division of Clinical Immunology, IRCCS Fondazione Policlinico Universitario A.Gemelli, Rome, Italy, [2]Immunology Research Core Facility - Gemelli Science and Technology Park (GSTeP) - Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy, [3]Università Cattolica del Sacro Cuore, Rome, Italy

Background. Primary Sjögren's syndrome (pSS) is primarily driven by B-cell activation and associated with a high risk of developing non-Hodgkin's lymphoma (NHL). Despite MicroRNA-155 (miR-155) arose over the last decades as a key regulator of B-cells in autoimmune and lymphoproliferative disorders, its role in the pSS remains still debated.
Objectives. (i) to explore the miR-155 expression in the labial salivary glands (LSG) of patients with pSS and its correlation with clinical parameters at disease onset;(ii) to identify LSG and serum biomarkers associated with the risk of NHL development in pSS.
Methods. 24 patients fulfilling the 2016 ACR-EULAR Classification Criteria for pSS were enrolled in the study. As comparison group, 20 age/gender matched patients with sicca syndrome (SS) were included. At study entry, clinical and laboratory parameters were recorded and the enrolled cohorts underwent LSG biopsy to assess Focus Score (FS), immunohistochemistry (IHC) for $CD20^+$cells and CD138+cells as well as miR-155 and BAFFR local expression (fold-change). Patients were followed in an outpatient setting and treated based on EULAR recommendations.
Results: Among the pSS cohort, 4(16.7%) patients developed NHL, showing a higher mean age than pSS patients not experiencing NHL (72.50±15.02 vs 53.65±11.63 years, $p=0.04$) as well as SS patients ($p=0,02$). Stratifying the pSS cohort according to the NHL development, there were no significant differences in terms of FS at baseline, though pSS patients who developed NHL had higher IgA plasma levels than ones not developing NHL ($p=0.05$) as well as SS patients ($p=0.05$).Considering serological status, no significant association was found between IgA/IgM-RF positivity and NHL development in pSS cohort, as well as no differences were detected in terms of inflammatory markers serum levels nor ESSDAI score. Regarding IHC, pSS patients showed higher IHC score of $CD20^+$ cells and $CD138^+$ cells compared to SS patients ($p<0.0001$ and $p=0.02$, respectively) irrespective to neoplastic evolution. Moreover, a direct correlation was observed between IHC score for CD20+ cells and CD138+ cells in pSS cohort (R=0.57, $p=0.004$). MicroRNAs analysis showed that miR-155 was upregulated in pSS patients compared to SS patients ($p=0.002$) regardless of NHL development. Interestingly, stratifying the pSS cohort based on NHL development, the expression of miR-155 was significantly higher in pSS patients who experienced NHL than ones not experiencing NHL ($p=0.02$). Moreover, considering pSS cohort, miR-155 expression in LSG positively correlated with the FS (R=0.77, $p<0.0001$) as well as the IHC $CD20^+$ score (R=0.44, $p=0.003$) and hypergammaglobulinemia (R=0.70, $p=0.001$). Finally, miR-155 levels positively correlated with BAFFR expression (R=0.66, $p=0.01$). Moreover, BAFFR expression in LSG was increased in PSS patients than SS cohort ($p=0.04$) and its expression was higher in pSS patients who experienced NHL compared to ones not developing NHL ($p=0.04$).
Conclusions: Epigenetic modulation by induction of miR-155 may play a crucial role in the aberrant activation of B cells in pSS, profoundly impacting on the risk of NHL development throughout the disease course.

Poster 150

PREDICTING LYMPHOMA IN PRIMARY SJÖGREN'S SYNDROME: THE ROLE OF PRECISE PAROTID SWELLING RECORDING

Rizzo M.T.*[1], Isola M.[2], Baldini C.[3], Goules A.V.[4], Chatzis L.[4], Quartuccio L.[1], Zabotti A.[1], Giovannini I.[1], Donati V.[3], Ferro F.[3], Pegolo E.[5], Manfrè V.[1], Voulgarelis M.[4], Zaja F.[6], Fanin R.[7], Masaoutis C.[8], Rontogianni D.[8], Fotiadis D.I.[9], Ponzoni M.[10], Tzioufas A.G.[4], De Vita S.[1]
[1]Clinic of Rheumatology, ASUFC, Udine, Italy, [2]Institute of Statistics, Department of Medical Area, Udine, Italy, [3]Rheumatology Unit, Department of Clinical and Experimental Medicine, Pisa, Italy, [4]Department of Pathophysiology and Institute for Autoimmune Systemic and Neurological Diseases, Athens, Greece, [5]Institute of Anatomic Pathology, Udine, Italy, [6]Department of Hematology, Trieste, Italy, [7]Hematology and SCT Unit, Udine, Italy, [8]Department of Pathology, Athens, Greece, [9]Department of Biomedical Research, Institute of Molecular Biology and Biotechnology, Ioannina, Greece, [10]Pathology Unit, San Raffaele Scientific Institute, Milan, Italy

Objectives. Parotid swelling (PSW) is a major predictor of non-Hodgkin lymphoma (NHL) in primary Sjögren's syndrome (pSS). However, since detailed information on the time of onset and duration of PSW is scarce, aim of our study was to investigate whether precise parotid gland swelling may further improve lymphoma prediction in pSS. Secondly, NHL localization was concomitantly studied to evaluate the role of the parotid gland microenvironment in pSS-related lymphomagenesis.
Methods. A multicentre study was conducted among patients with pSS who developed B-cell NHL (cases) during follow-up (n=144) and matched controls that did not develop NHL. The study focused on the history of salivary gland and lachrymal gland swelling, evaluated in detail at different times and for different durations.
For the glandular swelling, we studied if the onset occurs at pSS symptom onset, at pSS diagnosis, at any time during the follow-up or, among cases, only late, after NHL diagnosis. PSW was then categorized as episodic of short duration (<2 months), episodic of prolonged duration (≥2 months but <12 months) or chronic (lasting ≥12 months). The localization, histotype and stage of NHL at the onset was also identified and described.
Results. The study included 144 patients affected by pSS who developed B-cell NHL (cases) and 222 matched controls who did not develop NHL in the follow up. PSW was significantly more frequent among the cases: both at the time of first referred pSS symptoms before diagnosis, at diagnosis, and from pSS diagnosis to NHL. The duration of PSW was evaluated starting from pSS diagnosis: it was shown that the risk of NHL increased from PSW of 2–12 months to >12 months. An extranodal localisation of NHL at onset was observed in most cases, and among the different extranodal NHL localisations, the most frequent was in the parotid glands.
Conclusions. A more precise clinical evaluation of the parotid glands is needed in pSS, since PSW proved to be a risk factor at all points in the history of pSS, from the first symptoms before diagnosis to lymphoma. Importantly, the duration of PSW is relevant above all for duration >2-12 months, with the highest risk for chronic PSW (>12 months). Furthermore, since lymphoma usually localizes in the parotid glands, and not in the other salivary or lachrymal glands, it seemed the parotid microenvironment might be involved in the whole history of pSS and related lymphomagenesis. Clinical and research implications are relevant.

Poster 182 (withdrawn by authors - late withdrawal)

LYMPHADENOPATHY TRANSFORMATION IN PRIMARY SJÖGREN'S SYNDROME

Haji F.*
Salmaniya Hospital, Manama, Bahrain

A 46-year-old Bahraini lady with previous diagnosis of Primary Sjögren's syndrome based on complaining of severe dry eyes and dry mouth with peripheral arthritis. Her ANA was 1:640 speckled pattern with both SSA SAB positive. She had labial biopsy confirming the diagnosis of PSS.
She was kept on HCQ 400 mg. Her background history is positive for Hypertension, IHD and bronchial asthma. In 2019 she started to complain of worsening of her cough and exertional SOB.
HRCT was performed which showed multiple large hilar lymphadenopathy with cervical lymphadenopathy and mild splenomegaly and LIP ILD changes suggestive of active lung PSS involvement.
Investigation with bronchoscope EBUS of the lymph nodes was done which was reported as reactive lymphadenopathy. She had at same time excisional biopsy of the largest cervical lymph nodes 1.8 cm x 0.5 cm which showed mixed T and B cell with negative immunostaining CD 5 CD 10 and BCL-2 reported as reactive lymphadenopathy with paracortical expansion. Then she was started on prednisone and MMF 1000 bd and her symptoms settled dramatically and became asymptomatic. She was kept under surveillance for her lymadenopathy every 6 months.
In April 2021 she presented with history of on and off fever, fatigue and myalgia. Severe lower back pain. She had also a weight loss of 3 kg last two months. She was admitted for further work up.
Her CBC was normal except Hemoglobin of 9.4 with low indices. ESR 27. SPEP showed low gamma globulins 3 (6-17) and immunoelectrophoresis was negative.
1 day post admission she started to complain of left lower leg pain.
Clinical examination showed swelling of left leg. D diner was high 3.9. Left lower limb Doppler arranged was negative for DVT but multiple enlarged left inguinal lymph nodes largest 2.1x1 cm.
She had CT TAP the day after which showed significant reduction of the mosaic pattern and cystic lesions of LIP ILD with significant enlargement of mediastinal Axillary abdominal and pelvic and inguinal lymph nodes with filling defect in the left internal iliac vein.
She was diagnosed with left iliac DVT LMWH therapeutic dose continued and arranged for inguinal lymph node biopsy.
The report confirmed large B cell non-Hodgkin lymphoma. She was referred to an oncology centre where diagnosis was confirmed and treatment started. She responded well to treatment till September. In October 2021 she had recurrence of her lymphoma and passed away in the oncology centre.

Poster 193

EFFICACY OF RITUXIMAB ON CLINICAL, HISTOLOGICAL, IMMUNOHISTOCHEMICAL AND MOLECULAR CHARACTERISTICS OF MALT-LYMPHOMA IN PATIENTS WITH PRIMARY SJÖGREN'S SYNDROME

Chaltsev B.*, Torgashina A., Khvan Y.
V.A. Nasonova Research Institute of Rheumatology, Moscow, Russian Federation

Objectives. To evaluate the efficacy of rituximab (RTX) on clinical, histological and molecular characteristics of MALT-lymphomas (MALT-L) in primary Sjögren's syndrome (pSS).
Methods. We assessed the efficacy of RTX therapy in 14 pSS+MALT-L pts. pSS was diagnosed based on ACR/EULAR2016 criteria. The diagnosis and dynamic assessment of MALT-L was based on a biopsy of the affected salivary glands. The median duration of pSS before the development of MALT-L was 7,5 yrs (min. 1, max. 25), in 8/14 cases (57%) the diagnoses of pSS and MALT-L were made simultaneously. Among the 14 MALT-L, there were: 10 localized salivary gland lymphomas (9 parotid, 1 submandibular), 1 locally disseminated salivary gland lymphoma (parotid and submandibular), 3 disseminated lymphomas (salivary glands + lymph nodes + thymus – 1, salivary glands + lymph nodes + lungs – 1, salivary glands + lymph nodes + bone marrow – 1). All pts received RTX: monotherapy – 4, combination therapy – 10 (with cyclophosphamide – 7, bendamustine – 2, chlorambucil, R-CHOP, RCVP – 1). Median follow-up duration was 5 yrs (min. 2, max. 8).
Results: Clinical remission (defined as normalization of the salivary glands size, as well as lymph nodes and thymus in case of their involvement) was achieved in 13/14 pts (93%). Repeat biopsy of the salivary glands was performed in 9/14 pts: histological and immunohistochemical remission (defined as the disappearance of the tumor according to biopsy data) was observed in 8 pts (89%), molecular remission (defined as the disappearance of B-cell clonality in the tissue) was achieved only in 2 pts (22%). Lymphoma relapse was noted in 2 pts: in the first patient with localized parotid lymphoma, clinical, histological and molecular signs of lymphoma persisted during combined treatment first with RTX and cyclophosphamide, and then with RTX and chlorambucil; in the second patient with disseminated lymphoma with salivary glands, lymph nodes and bone marrow involvement, after a course of R-CHOP clinical, histological and immunohistochemical remission was noted, however, parotid gland B-cell clonality persisted, so 2 years after stopping treatment the patient developed a relapse, the development of diffuse B-cell large cell lymphoma was stated. Thus, the 5-year relapse-free survival was 86%.
Conclusions. The present study noted the high efficacy of RTX in pSS+MALT-L with achievement of clinical, histological and immunohistochemical remission in most patients and a high level of 5-year relapse-free survival, but the absence of molecular remission in most pts. Given chronic sialadenitis in pSS, after completion of lymphoma therapy in pts with persistent tissue B-cell clonality, it seems reasonable to continue maintenance RTX therapy to prevent lymphoma relapse.

EVOLVING TOPICS IN THE EVALUATION OF pSS

Oral communication 3

NOVEL AUTOANTIBODIES IDENTIFIED IN SERONEGATIVE SJÖGREN'S USING INNOVATIVE WHOLE PEPTIDOME ARRAY TECHNOLOGY

Parker M., Zheng Z., Parker Q., Vande Loo A., Newton M., Shelef M., McCoy S.*
University of Wisconsin, Madison, USA

Objectives. Sjögren's Disease (Sjögren's) is typically diagnosed by the presence of an anti-SSA antibody or focal lymphocytic sialadenitis in salivary gland tissue. Among Sjögren's patients who are anti-SSA antibody negative (SSA), a salivary gland biopsy is required for diagnosis. Our objective was to identify novel autoantibodies as a non-invasive means to diagnose SSA- Sjögren's.

Methods. Using sera from SSA- Sjögren's (n=8; Table 1) and age- sex-matched healthy controls (n=8), IgG binding to a high density whole human peptidome array was quantified. The highest bound peptides from the array, as defined by MixTwice method, were internally validated by ELISA using sera from the same subjects (Figure 1 & 2). Based on results from internal validation, 12 peptides were selected for ELISA external validation using sera from the following age-, sex-, and race-matched groups from the SICCA biorepository: SSA- Sjögren's subjects (meet 2016 ACR/EULAR criteria for Sjögren's; n=76), sicca controls (sicca with negative ANA, rheumatoid factor, SSA, and focus score <1; n=75), and autoimmune controls (positive ANA (≥1:320), rheumatoid factor, or SSA, but fail to meet 2016 ACR/EULAR criteria for Sjögren's; n=38). ELISA results were compared using parametric testing for sample sizes >15 and likelihood ratio chi-square for categorical variables. We performed adaptive shrinkage with Lasso regression to select peptides for a random forest model to predict SSA- Sjögren's.

Results. IgG against a peptide from Q8NEN9 (PDZ domain-containing protein 8) was greater in SSA- Sjögren's and sicca controls than autoimmune controls (p<0.001 and 0.02, respectively; Figure 3). IgG against Q9NSI6 (Bromodomain and WD repeat-containing protein 1) and Q9H2G2 (STE-like serine/threonine-protein kinase) was higher in SSA- Sjögren's than sicca controls among White/Hispanic subjects (p=0.02 and p=0.03, respectively; Figure 4). After defining positive cutoffs, Q9NSI6 and Q9H2G2 were positive more in SSA- Sjögren's than sicca controls (16% vs. 0 [p=0.0002] and 20% vs. 5% [p=0.03], respectively) in White/Hispanic subjects. We also found IgG bound Q8NG31 (Kinetochore scaffold 1) less in SSA- Sjögren's than sicca controls (60% vs. 89% positive, respectively; p=0.02). IgG from Sjögren's and sicca control subjects binds a Q8NEN9 peptide more than autoimmune controls. We included eight peptides in our random forest model and achieved an area under the receiver operator curve of 0.97 to predict SSA- Sjögren's among White/Hispanic subjects. Among Asian/African American subjects, IgG binding to peptides from Q9NSI6 and Q12756 (Kinesin-like protein KIF1A) differed between SSA- Sjögren's, autoimmune, and sicca controls (Figure 7).

Conclusions. We present novel autoantibodies unique to SSA- Sjögren's compared to autoimmune- and sicca-controls. These antibodies have good predictive value amongst Whites/Hispanic subjects for Sjögren's. Future directions include performing further modeling in validation cohorts and discerning associations between autoantibodies and Sjögren's characteristics.

Table I. Demographics of the array and the SICCA registry subjects.

Peptidome Array			
	SSA- Sjögren's (n=8)	Healthy Control (n=8)	
Age mean (SD)	58 (12)	59 (10)	
Female n (%)	8 (100)	8 (100)	
White n (%)	8 (100)	8 (100)	
Hispanic n (%)	0	0	
External Validation			
	SSA- Sjögren's (n=76)	Autoimmune Control (n=38)	Sicca Control (n=75)
Age mean (SD)	55 (12)	55 (12)	55 (12)
Female Sex n (%)	65 (86)	33 (87)	64 (85)
White/Hispanic n (%)	45 (59)	24 (63)	41 (55)
Other race n (%)	31 (41)	14 (37)	34 (45)

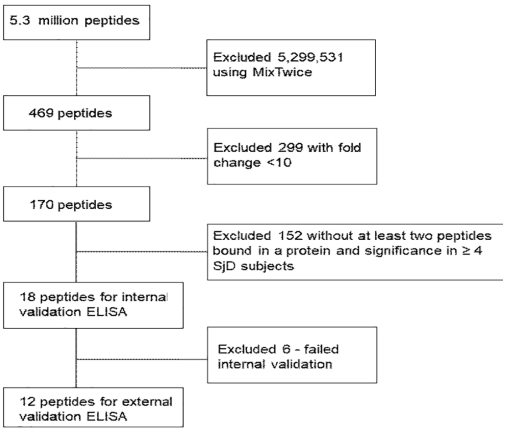

Fig. 1. Consort flow diagram demonstrating peptide selection for external validation.

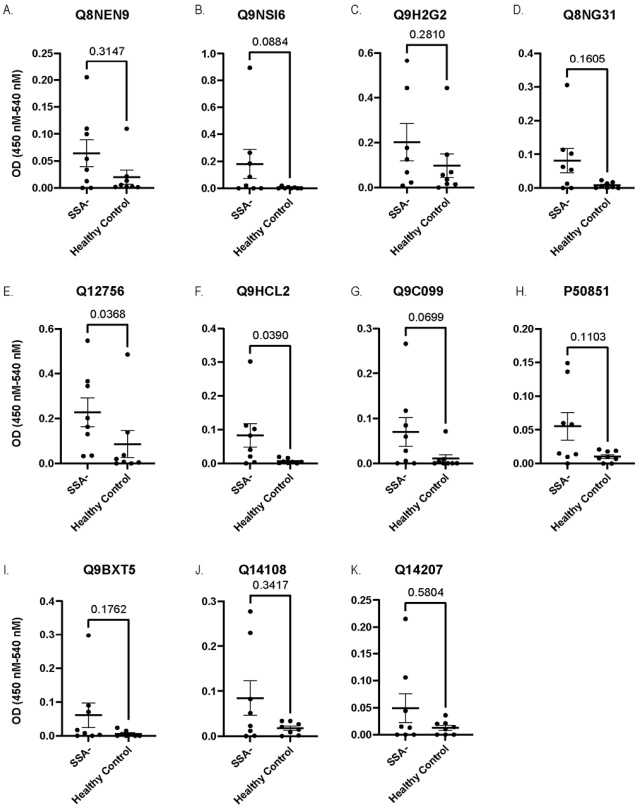

Fig. 2. Internal validation of select peptides identified from the whole peptidome array. ELISA for each peptide was performed using sera from SSA-Sjögrens (n=8) and healthy control (n=8) subject.

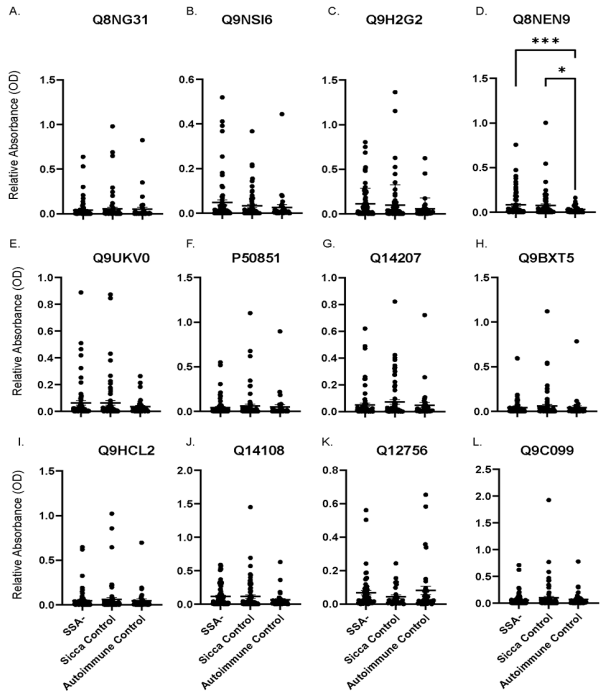

Fig. 3. External validation of novel autoantibody binding to peptides among SSA- Sjögrens disease, autoimmune- and sicca-control subject from the SICCA registry. Sera from 76 SSA- Sjögrens. 75 sicca control, and 38 autoimmune control subjects were used in ELISA to evaluate IgG binding to four different peptides. IgG from SSA- Sjögrens and sicca controls bound a peptide from Q8NEN9 more than autoimmune controls. *=p<0.05. ***=p<0.001.

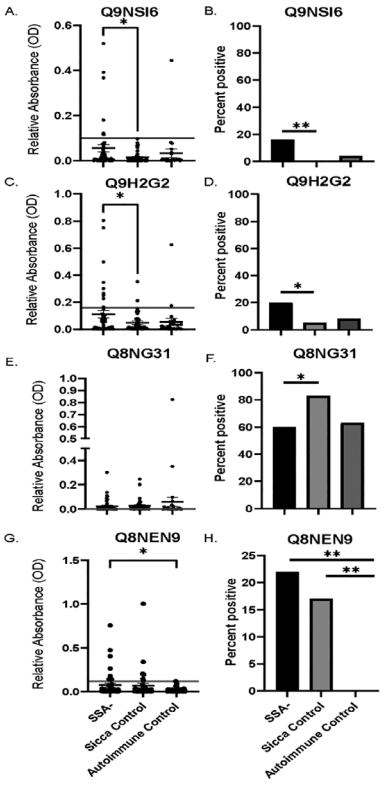

Fig. 4. Novel IgG binding to peptides by ELISA among SSA- Sjögrens, autoimmune- and sicca-controls by Hispanic/White race (n=45 SSA- Sjögrens subject, n=41 sicca controls, and n=24 autoimmune controls).A-D) SSA- Sjögrens subjects bind peptides from Q9NSI6 and Q9H2G2 more than sicca controls. E-F) SSA- Sjögrens subjects bind a peptide from Q8NG31 less than sicca controls. G-H) SSA- Sjögrens and sicca control subject IgG binds a peptide from Q8NEN9 more than autoimmune controls. The light gray line represents the positive cut-off. *=p<0.05. **=p<0.01. ***=p<0.001.

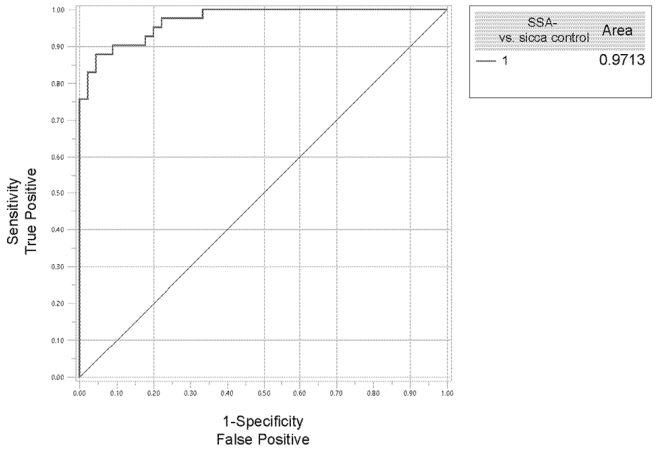

Fig. 5. Receiver operator characteristics curve of a random forest model showing an area under the curve of 0.97 for a panel of eight peptides predicting SSA- Sjögrens among Caucasian/Hispanics.

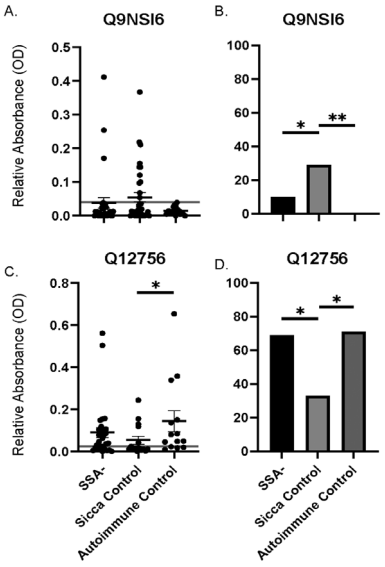

Fig. 6. Novel IgG binding to peptides by ELISA among SSA- Sjögrens, autoimmune- and sicca controls by Asian/African American race (n=31 SSA- Sjögrens subjects, n=35 sicca controls, and n=14 autoimmune controls). A-B) SSA- Sjögrens and autoimmune control subject bind peptides from Q9NSI6 less than sicca controls. C-D) SSA- Sjögrens and autoimmune control subjects bind a peptide from Q12756 more than sicca controls. *=p<0.05. **=p<0.01.

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IDENTIFICATION OF A SALIVA EXOSOMAL-RNA SIGNATURE FOR SJÖGREN'S SYNDROME

Papas A.*[1], Sawicki B.[2], Chakrabortty S.[2], Singh M.[1], Cole J.[2], Lang S.[2], Khodor Y.[2], Rauscher M.[2], Yu S.[2], Skog J.[2]
[1]Tufts School of Dental Medicine, Boston, USA, [2]R&D Exosome Dx, Waltham, MA, USA

Introduction. Sjögren's syndrome (SS) is an autoimmune disorder in which immune cells attack and destroy moisture producing glands of the body. Sjögren's syndrome is particularly difficult to diagnose due to overlapping symptoms with associated autoimmune disorders leading to an average diagnosis time of 3 years. A non-invasive saliva exosomal-RNA (exoRNA) based test capable of diagnosis for SS would be highly desirable. Here we present a Sjögren's-specific gene signature, obtained from non-invasively collected saliva exoRNA, to facilitate this diagnosis.

Methods. We began by first developing a novel, long RNA-Seq workflow incorporating a targeted hybrid-capture to selectively enrich and profile hu-

man exosomal mRNAs and long non-coding RNAs (lncRNAs) from saliva. We then profiled salivary exoRNA from 45 disease samples (including SS, systemic lupus erythematosus, and Rheumatoid arthritis) and 40 healthy, matched controls. Differential gene expression analysis, followed by feature selection using machine learning algorithms was performed to identify a SS-specific exoRNA signature.
This signature was further validated on a second cohort of samples.
Results: RNA-Seq data analysis demonstrated highly efficient enrichment, with over 75% of sequencing reads mapping to the human transcriptome. Further RNA biotype analysis revealed over 60% of transcriptome reads mapping to protein coding genes and lncRNA. At a conservative threshold of 1 read per million (RPM), we detected over 12,000 mRNAs and approximately 500 lncRNAs. Differential gene expression analysis of SS vs. healthy controls identified 70 differentially expressed genes; 63 upregulated genes in Sjögren's and 7 downregulated genes ($p<0.05$). Moreover, gene ontology analysis revealed enrichment of interferon-α and β signaling pathways, among other immune system functions. Most importantly, principal component analysis (PCA) resulted in clear separation of SS patients from healthy controls. Finally, using a machine learning algorithm, we identified a 4 gene signature, which was validated on a separate cohort with an AUC of 0.86.
Conclusions: Saliva exosomal RNA profiling has been primarily focused on small RNAs and has been limited due to the large contribution of sequencing reads from the oral microbiome. Our novel workflow overcomes this limitation and enables the potential of saliva exosomal mRNAs and lncRNAs for biomarker discovery. The gene signature identified in this currently ongoing study could potentially provide a non-invasive molecular means of diagnosing Sjögren's Syndrome.

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HOW TO EVALUATE ULTRASOUND ABNORMALITIES OF SALIVARY GLANDS IN SJÖGREN SYNDROME USING WEB TRAINING SESSION DURING COVID 19 PERIOD? AN INTERNATIONAL RELIABILITY EXERCISE

Quéré B.*[1], Saraux A.[1], Carvajal Alegria G.[2], Guellec D.[1], Mouterde G.[3], Lamotte C.[4], Hammenfors D.[5], Jonsson M.[5], Sung-Eun C.[6], Hong-Ki M.[7], Stel A.[8], Fisher B.A.[9], Hofauer B.[10], Ferro F.[12], Milic V.[11], Direnzo D.[13], Devauchelle-Pensec V.[1], Jousse-Joulin S.[1]
[1]Hospital Cavale Blanche, Brest, France, [2]Hospital Trousseau, Tours, France, [3]Hospital Lapeyronie, Montpellier, France, [4]Hospital Huriez, Lille, France, [5]Hospital Haukeland, Bergen, Norway, [6]Chonnam National University, Gwangju, Republic of Korea, [7]Konkuk University Medical Center, Seoul, Republic of Korea, [8]University Medical Center, Groningen, Netherlands, [9]University Hospitals, Birmingham, UK, [10]University Medical, Freiburg, Germany, [11]Hospital Belgrade, Belgrade, Serbia, [12]Hospital of Pisa, Pisa, Italy, [13]Penn Medicine University City, Philadelphia, USA

Background. Salivary glands ultrasonography (SGUS) is an emerging tool to evaluate damages in primary sjögren patients (pSS). Up to date, SGUS has demonstrated its metric properties as an outcome measure for diagnosing pSS. As New therapeutics protocols are in developing it seems mandatory to use validated SGUS scoring systems.
Objectives. The goal of our study was to evaluate international SGUS reliability exercise before beginning an international SGUS study to evaluate Modification Abnormalities of Salivary glands in pSS According to disease duration (MASAI study).
Methods. Fourteen sonographers with different levels of SGUS participated in the exercise, evaluating 60 grey scale static images (30 parotid and 30 submandibular glands). Before the exercise, training was done by videoconferencing showing the different pathological SGUS findings and explaining the new OMERACT scoring system. We evaluated homogeneity (yes/no), location of hypoechogenity (0 to 3), hyperechoic band (0-3), comprehensive OMERACT scoring system (0-3), binary comprehensive OMERACT (0-1 versus 2-3) and diagnosis appreciation (No/yes). Intra-reader and inter-reader reliability were estimated by computing Cohen's ϰ coefficients using SPSS 25.0 (SPSS Inc., Chicago, IL), and was interpreted as follows: slight, 0-0.20; fair, 0.21-0.40; moderate, 0.41-0.60; substantial, 0.61-0.80; and almost perfect, 0.81-1. The most experienced sonographer (P4) was considered as the gold standard.
Results. Intra-reader reliability of the most experienced was perfect and substantial for the OMERACT scoring system. Intra-reader reliability of the other sonographers was fair to almost perfect for homogeneity and diagnosis whereas the reliability was fair to substantial for other items. Inter-reader reliability between the two most experienced sonographers (P4 and P12) was almost perfect for homogeneity, substantial for diagnosis and moderate for OMERACT scoring system. Changing OMERACT scoring system in binary items, the reliability of the most experienced sonographer was good 0.65 (9 images with homogeneity and low OMERACT, 42 had heterogeneity and high OMERACT, 9 had no homogeneity but low OMERACT and none had homogeneity with high OMERACT), clearly lower that of homogeneity. Compared to the most experienced sonographer, reliabilities of other sonographers were moderate to almost perfect for both homogeneity and diagnosis but only fair to moderate for OMERACT (Table I, II).
Conclusions. According to the updated literature, we confirmed that homogeneity is the most reliable item, very close to diagnosis appreciation. Structural damages evaluations by the OMERACT scoring systems gave lower kappa values but remain still useful for diagnosing and particularly following parenchymal modifications.

Table I. Intra reader reliability.

	Participants (p)	Homogeneity	Nodules location	Hyperechoic bands	Comprehensive OMERACT	Diagnosis appreciation
Lowest experienced sonographers	P1	0,467	0,504	0,497	0,41	0,502
	P2	0,603	0,559	0,45	0,236	0,762
	P3	0,401	0,615	0,55	0,48	0,664
	P5	0,857	0,668	0,316	0,637	0,823
	P6	0,812	0,662	0,283	0,712	0,931
	P7	0,838	0,302	0,306	0,802	0,791
	P8	0,535	0,635	0,226	0,518	0,826
	P9	0,609	0,705	0,629	0,549	0,708
	P10	0,495	0,602	0,379	0,501	0,753
	P11	0,76	0,481	0,385	0,479	0,734
	P13	0,667	0,462	0,437	0,306	0,706
	P14	0,827	0,372	0,326	0,338	0,672
Most experienced sonographers	P4	0,88	0,884	0,886	0,731	0,921
	P12	0,857	0,747	0,788	0,81	0,918

Table II. Inter reader reliability between 14 participants. P4 is taking as a gold standard.

		Homogeneity	Comprehensive OMERACT	Diagnosis appreciation
Concordance between the 2 most experienced	P4/P12	0,828	0,493	0,718
Concordance between the most experienced sonographer and other sonographers	P4/P1	0,554	0,463	0,669
	P4/P2	0,812	0,377	0,792
	P4/P3	0,521	0,4	0,527
	P4/P5	0,828	0,489	0,811
	P4/P6	0,617	0,519	0,679
	P4/P7	0,712	0,42	0,718
	P4/P8	0,76	0,492	0,627
	P4/P9	0,563	0,539	0,672
	P4/P10	0,68	0,408	0,615
	P4/P11	0,76	0,352	0,661
	P4/P12	0,828	0,493	0,718
	P4/P13	0,59	0,408	0,576
	P4/P14	0,76	0,231	0,556

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ULTRASOUND SCORING SYSTEMS AFFECT THE DISTRIBUTION OF SIALADENITIS SCORES IN SJÖGREN'S SYNDROME: AN INTER-SYSTEM REPRODUCIBILITY STUDY

Cafaro G.*, Perricone C., Bursi R., Riccucci I., Calvacchi S., Gerli R., Bartoloni Bocci E.
Rheumatology Unit. Department of Medicine and Surgery, Perugia, Italy

Background. Although not included in any set of classification criteria, salivary gland ultrasonography (SGUS) is commonly employed in the diagnosis and follow-up of patients with Sjögren's syndrome (SS) and has been employed to non-invasively detect active inflammation and chronic damage. Multiple scoring systems have been developed in order to quantify the grade of sialadenitis of major salivary glands (SG). Sensitivity and specificity of the different sialadenitis scoring systems seem overall comparable. However, the parameters evaluated by the various systems are different. The objective of this study was to compare how four different scoring systems affect the distribution of sialadenitis grades.
Methods. SGUS images of primary SS patients classified according to 2016 ACR/EULAR criteria obtained with Esaote MyLabSeven (Esaote, Genoa, Italy) were reviewed. One representative longitudinal scan was selected for each major SG. Salivary gland images were blindly scored by two inves-

tigators according to the De Vita, Salaffi, Milic and OMERACT scoring systems in independent sessions.
Results. One hundred and three US images were collected from 26 SS patients The distribution of SGUS images according to De Vita, Salaffi, Milic and OMERACT systems was significantly different. At post-hoc analysis, Milic system performed differently compared to De Vita (p<0.0001), OMERACT (p<0.0001), Salaffi (p<0.0001) systems, showing a relative overestimation of sialadenitis grade. No other significant differences were found among the scoring systems analyzed (Table I).
Conclusions. Milic scoring system showed to relatively overestimate the grade of sialadenitis in comparison to De Vita, Salaffi and OMERACT systems. Although all scoring systems seem to be comparable in terms of diagnostic accuracy, in the prospect of selecting one system to be potentially included in future versions of SS classification criteria, it is important to compare their ability to classify SGUS images among the various degrees of sialadenitis.

Table.

	Z	P
Salaffi vs De Vita	-0.015	1.000
Salaffi vs OMERACT	-0.340	0.353
Salaffi vs Milic	-1.238	<0.0001
De Vita vs OMERACT	-0.325	0.424
De Vita vs Milic	-1.223	<0.0001
OMERACT vs Milic	-0.898	<0.0001

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PATIENT ACCEPTABLE SYMPTOM STATE (PASS) IN PATIENTS WITH PRIMARY SJÖGREN'S SYNDROME IN DAILY CLINICAL PRACTICE

De Wolff L.*, Vissink A., Mossel E., Van Zuiden G., Van Nimwegen J., Olie L., Stel A., Delli K., Verstappen G., Kroese FGM., Bootsma H., Arends S.
University of Groningen, University Medical Centre Groningen, Groningen, Netherlands

Background. Primary Sjögren's syndrome (pSS) has great impact on all aspects of patients' lives, not only physically, but also mentally, socially and financially (1). Sicca symptoms are mainly treated with local treatment, but no systemic immunosuppressive treatment is registered yet for pSS, which may have significant consequences on whether patients find their symptom state acceptable (PASS). In a previous study, a cut-off for acceptable symptom state based on the EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI, score <5) was developed for inclusion of patients with an unacceptable symptom state in clinical trials (2).
Objectives. To explore the presence of PASS in a standard of care cohort of pSS patients and to compare patient characteristics and disease activity including ESSPRI between patients with and without PASS.
Methods. Consecutive outpatients with pSS from the REgistry of Sjögren Syndrome LongiTudinal (RESULT) cohort, who fulfilled the ACR/EULAR classification criteria and had available PASS data at baseline were included. Patient-reported outcomes included the PASS ("Considering all the different ways your disease is affecting you, if you were to stay in this state for the next few months, do you consider your current state satisfactory?"; yes/no) and ESSPRI ("How severe has your dryness, fatigue and pain been during the last two weeks?"; scale 0-10; acceptable symptom state: score<52). Systemic disease activity was assessed with EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI). Mann-Whitney U test or Chi Square test were used to analyse differences between groups. ROC analysis was performed for determining the optimal ESSPRI cut-off point for presence of PASS. Results: Of 278 included pSS patients, 248 (89%) were female, median age was 54 years (IQR 44-64) and disease duration 5 years (2-11). 199 (72%) patients scored the PASS question as acceptable. Patients with PASS were significantly older and had a longer disease duration compared to patients without PASS. Furthermore, patients with PASS had more often a low disease activity according to ESSDAI (Table I). The difference in ESSDAI was mainly observed in the articular and constitutional domains. ESSPRI was significantly lower in patients with PASS (median 5 vs. 7). No differences were seen in functional or laboratory parameters (Table I). Of all included patients, only 87 (31%) patients had an acceptable symptom state according to ESSPRI (score<5). The ESSPRI cut-off point for presence of PASS with the highest combined sensitivity and specificity was 7.2 (85% and 56%, resp.), followed by 5.2 (48% and 90%, resp.).

Table I. Baseline characteristics of pSS patients with and without PASS.

	PASS (n=199)	Without PASS (n=79)
Gender (female)	177 (89)	71 (90)
Age (years)	57 (44-65)*	48 (41-60)*
Disease duration (years)	6 (2.12)*	5 (2-8)*
ESSDAI (total)	4.0 (2.0-6.0)	4.5 (2.0-9.0)
<5	130 (66)*	39 (50)*
5-14	54 (28)*	34 (44)*
<14	12 (6)	5 (7)
ESSPRI (total)	5 (4-7)**	7 /6-()**
<5	81 (41)**	6 (()**
Schrmer's test (mm)	4 (1-10) (n=182)	4 (1.10) (n=72)
Ocular staining score	2 (1-4) (n=191)	2 (0-4) (n=77)
Unstimulated whole salivary flow (ml/min)	0.04 (0.01-0.14) (n=188)	0.07 (0.01-0.19) (n=77)
Stimulated whole salivary flow (ml/min)	0.54 (0.15-0.98) (n=189)	0.57 (0.20-0.96) (n=74)
SSA positive	172/198 (87)	66/79 (84)
IgG (g/L)	14 (11-19) (n=197)	14 (10-19) (n=79)
Rheumatoid factors (IU/ml)	11 (3-39) (n=197)	16 (2-47) (n=78)

Data presented as median (IQR) 0f n (%)
*Significant difference p<0.05.
**Significant difference p<0.001.

Conclusions. The majority (72%) of pSS patients reported being in an acceptable symptom state according to the PASS question in our standard of care cohort, despite high ESSPRI scores (59% with score ≥5). In our cohort, the optimal cut-off point of ESSPRI to predict PASS is different when focusing on sensitivity (±7) or specificity (±5).

References
1. Vieira *et al.*: *Clin Exp Rheum* 2021; 39(Suppl. 133): S14-16.
2. Seror *et al.*: *Ann Rheum Dis* 2016; 75: 382-89.

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ASSOCIATION BETWEEN SALIVARY SCINTIGRAPHIC AND HISTOPATHOLOGIC DATA OF MINOR SALIVARY GLANDS IN PRIMARY SJOGREN'S SYNDROME

Han J.H.*[1], Kim J.[2], Roh J.[1], Kim H.[2]
[1]Department of Pathology, Ajou University School of Medicine, Suwon, Republic of Korea, [2]Department of Rheumatology, Ajou University School of Medicine, Suwon, Republic of Korea

Objectives. Sjögren's syndrome (SS) is a chronic autoimmune disease characterized by xerophthalmia and xerostomia which are caused by lymphocytic infiltrates of the lachrymal and salivary glands. Minor salivary gland (MSG) biopsy is an invasive procedure that carries mild complications. It may be necessary to replace biopsy and it has been suggested that a non-invasive and more easily accessible imaging technique be used. This study was to evaluate the association of salivary scintigraphic and clinical parameters with histological characteristics of salivary glands in patients with Sjögren's syndrome (SS).
Methods. In 41 patients with suspected SS, salivary scintigraphy and salivary gland biopsy were performed. Salivary scintigraphy was interpreted as semi-quantitative methods obtained by calculating peak uptake and washout of each gland using region of interests. All specimens were examined by pathologists for focus scores and positivity for leukocyte common antigen (LCA) explaining the degree of inflammatory infiltration. The correlations between histological data of salivary gland and salivary scintigraphic and clinical parameters were analyzed.
Results. The mean age of SS patients was 46.4 years, 82.9% of them were female, and the mean symptom duration was 2.5 years. The focus score was negatively correlated to the mean peak uptake (r= -0.396, p=0.019) and mean washout (r = -0.391, p=0.02). In addition, the focus score and number of LCA positive cell per mm^2 were correlated with the clinical parameters including ESR (r=0.582, p<0.001 and r=0.591, p 0.001, respectively), globulin (r=0.521, p=0.001 and r=0.501, p=0.001), and RF (r = 0.533, p<0.001 and r=0.608, p<0.001, respectively), unstimulated (UWS) (r= -0.512, p=0.006 and r= -0.471, p=0.013, respectively) and stimulated whole saliva flow (SWS) (r= -0.491, p=0.009 r= -0.519, p=0.006) and only number of LCA positive cell per mm^2 was negatively correlated to leukocyte (r= -0.37, p=0.019), and hemoglobin (r= -0.367, p=0.02).

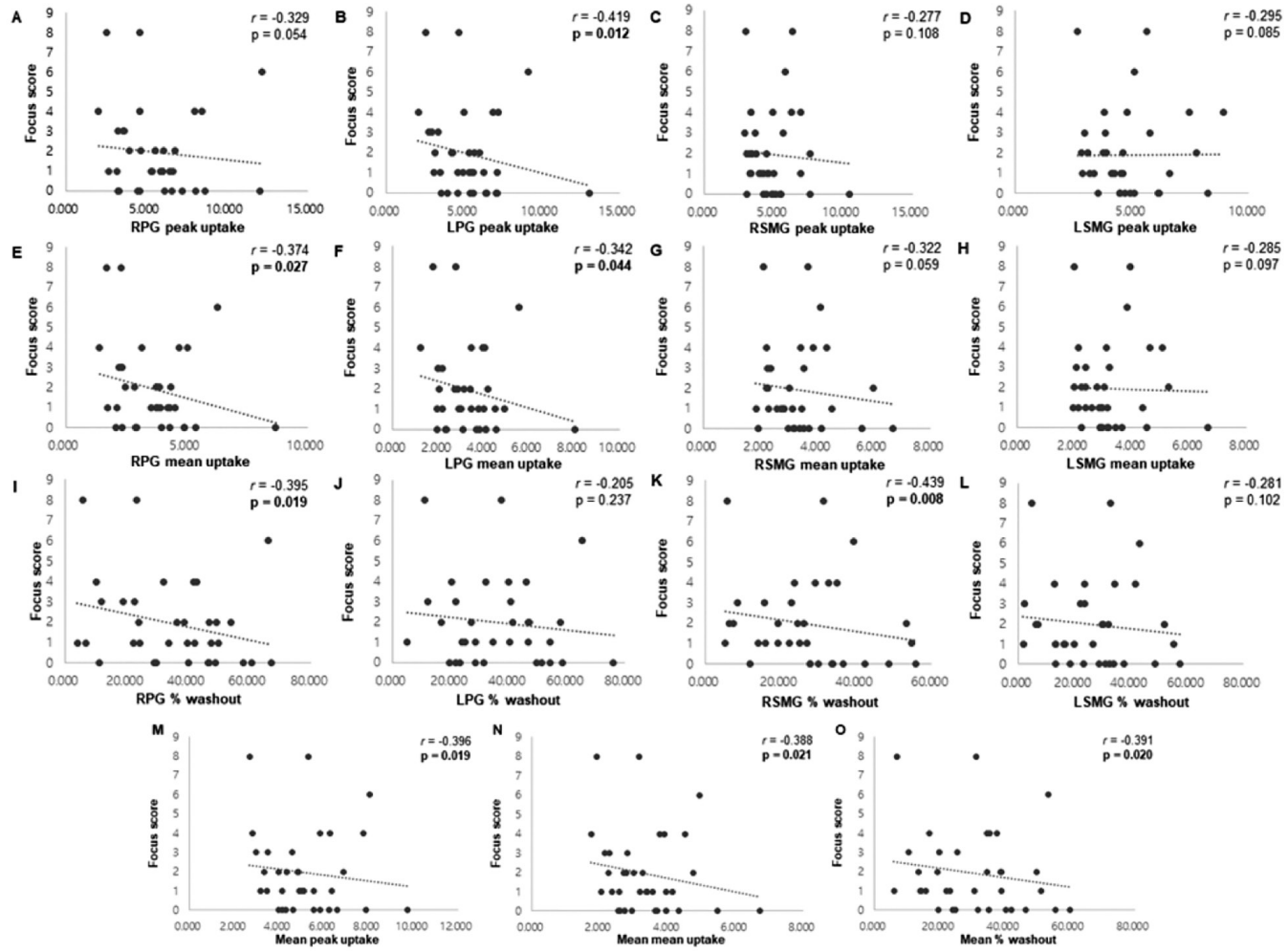

Fig. 1. Correlation between focus score 2 and salivary scintigraphic parameters in patients with pSS.

Conclusions. Although the diagnostic role of salivary gland biopsy is widely accepted and features in the classification criteria of Sjogren's syndrome, salivary gland scintigraphy may be an acceptable alternative method especially if a non-invasive test is required.

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CELL TYPE-SPECIFIC DYSREGULATION FOUND TO DIFFERENTIATE PATIENT SUBSETS OF SJÖGREN'S DISEASE

Li C.[1], Khatri B.[1], Stolarczyk A.[1], Tessneer K.[1], Rasmussen A.[1], Guthridge J.[1], James J.A.[1], Scofield R.H.[1], Li H.[2], Farris A.D.[1], Sivils K.[2], Lessard C.J.*[1]
[1]Oklahoma Medical Research Foundation, Oklahoma City, USA, [2]The Janssen Pharmaceutical Companies of Johnson & Johnson, Spring House, USA

Background. Sjögren's disease (SjD) is a heterogenous autoimmune disorder with inflammatory destruction of exocrine glands. Transcriptional and cell type differences between SjD subphenotypes have been reported.
Objectives. Evaluate the role of cell type-specific dysregulation in subpopulations of SjD cases having focal lymphocytic sialadenitis and/or anti-Ro/SSA and/or ANA positivity using single cell RNA-seq (scRNA-seq).
Methods. Peripheral blood mononuclear cells (PBMCs) were captured from 30 SjD cases based on ACR/EULAR 2016 criteria and 10 healthy controls (HCs). Libraries were processed using 10X Genomics Chromium v3.1 and sequenced (~45,000 reads/cell). Reads were aligned to the GRCh38 human genome using 10X Genomics Cell Ranger (v 6.1.2) cell multiplexing pipeline, then data separated to per-sample output files. Seurat R package was used for quality control (QC), integration, clustering, and cell type assignment. Differential expression (DE) analysis was done using Seurat for genes expressed in >10% of cells. DE transcripts (padj<0.05) were evaluated using Ingenuity Pathway Analysis (IPA).
Results. After QC, 331,981 cells were captured. After mapping, cell types were predicted using marker genes from an in-house reference panel of publicly available scRNA-seq datasets. Analyses condensed 28 observed cell clusters to 19 cell type-specific clusters. CD14 monocytes were decreased in Ro-/ANA- vs. Ro+ or Ro-/ANA+ cases (p<0.05) and trended downward compared to HCs (p=0.057). CD8 central memory T cells (TCM) were decreased in Ro+ vs. Ro- or Ro-/ANA- cases (p<0.02) and trended downward compared to HCs (p=0.076). Conventional dendric cells (DCs) were increased in Ro+ vs. Ro-/ANA- cases (p=0.036) and trended upward in Ro+ vs. Ro- cases (p=0.08) but were not significantly different from HCs. Natural killer (NK) cells were increased in both Ro-/ANA- and Ro- vs. Ro+ (p<0.05). IPA analysis of DE transcripts revealed interferon signaling upregulation in CD14 monocytes, naïve B, and CD4 central memory (TCM) cells from Ro+ cases. Ro+ cases also showed T cell receptor signaling upregulation in CD4 cytotoxic T (CTL), CD4 TCM, and CD4 effector memory T (TEM) cells, but downregulation in CD8 TCM cells. Ro+ cases also had increased B cell receptor signaling in naïve and memory B cells. Ro+ cases had downregulation of autophagy in naïve B, CD4 CTL, CD4 TCM, and CD4 TEM cells. Several cell types in Ro+ and Ro-(ANA±) cases had decreased DE of genes involved in nitric oxide production and NRF2 oxidative stress pathways. Ro-(ANA±) cases had increased IL6 and TREM1 signaling pathways in CD14 and CD16 monocytes, and dysregulation of osteoarthritis and neuroinflammatory pathways. Interestingly, among the DE long intergenic non-coding RNAs, LINC01871, which we identified as DE in SjD in whole blood, was overexpressed in CD4 CTL and NK cells in both Ro+ and Ro- (ANA-) cases.
Conclusions. Immune cell subsets from our Ro+ and Ro- (ANA±) SjD cases exhibit similarities and differences in the dysregulation of genes and pathways, potentially allowing for future tailored diagnostics and interventions.

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COMPARISON BETWEEN PRIMARY SJÖGREN'S SYNDROME PATIENTS WITH AND WITHOUT DRYNESS

Kachaner A.*[1], Mariette X.[2], Desmoulins F.[2], Nocturne G.[2], Seror R.[2]
[1]*Université de Paris, Paris, France,* [2]*Hôpital Kremlin Bicêtre, Kremlin Bicêtre, France*

Background. To date, no study has clinically focused on primary Sjögren's syndrome (pSS) patients presenting without or with low level of dryness features.
Objectives. To describe pSS patients presenting no dryness or with low level of dryness and to compare them with pSS patients with dryness features to determine whether a specific clinical presentation can be identified in these patients.
Methods. All patients diagnosed with pSS according to AECG or ACR/EULAR criteria in our tertiary reference center were included. All patients were recruited between 1999 and 2020. Patient were considered without subjective dryness if the VAS for dry eyes or dry mouth was ≤ 30/100 and/or without objective dryness if having both normal Schirmer and salivary flow rate.
Results. Overall, 509 patients were included in the subjective dryness comparison group and 472 in the objective one (Table). Compared to patients with subjective dryness (n=456), patients without subjective dryness (n=53) were significantly younger (p=0.0025), were diagnosed earlier (p=0.0056), were more frequently anti-SSA positive (p=0.008), had lower levels of fatigue (p=0.0005). But no difference was observed regarding the level of disease activity or frequency of organ involvement. By contrast, patients reporting subjective dryness had more frequently chronic cough (p=0.022), with no more frequent objective lung involvement. Thus, the higher prevalence of chronic cough might be explained by dryness of the upper airways.
The patients without objective dryness (n=113) were also younger (p=0.0016) and had more frequently anti-SSA positive (p=0.0033). They also had a higher disease activity (ESSDAI median (IQR): 2 (1-6) versus 2 (0-4), p=0.0035). In this group of patients, the higher frequency of anti-SSA might be explained by the need of other criteria to fulfil diagnostic criteria, in the absence of abnormal Schirmer and salivary flow.
Patients with objective dryness had more frequently arthralgia (p=0,03), a higher level of pain VAS (p=0.02) and subjective dryness VAS (p=0.019 for ocular and p=0.001 for oral) than patients without objective dryness.
Among the 113 patients with no objective dryness, only 17 had also had no subjective dryness (VAS <30mm).
Conclusions. Among the patients with pSS, those without subjective or objective dryness features had a younger profile, shorter diagnosis delay which may result from a more acute onset, were more frequently anti-SSA positive. Those having no objective dryness also had more systemic disease, arthralgias and pain than patients with dryness features. Subjective dryness was associated with higher level of fatigue.

Table I. Comparison of pSS patients with or without dryness.

	No Subjective dryness n=53	Subjective dryness n=456	P value
Age, median (IQR)	49 (39-62)	58 (47-67)	0,0025**
Time from first symptoms to diagnosis, median (IQR), years	2 (0.5-4.5)	4 (1-9.25)	0,0056**
ESSDAI, median (IQR), years	3 (1-4.5)	2 (1-4)	0.53
MSGB# focus score ≥1, n (%)	36 (68)	370 (81)	0.01*
Anti Ro/SSA, n (%)	44 (83)	282 (64)	0.008**
Chronic cough, n (%)	5 (9)	110 (24)	0,022*
VAS pain, median (IQR)	4 (0.4-7)	5.3 (2.3-7.7)	0,06
VAS fatigue, median (IQR)	4.7 (1.3-7.1)	6.5 (4.4-8.2)	0.0005***
	No Objective dryness n=113	Objective dryness n=359	
Age, median (IQR)	51 (41-60)	59 (47-67)	0,0016**
Time from first symptoms to diagnosis, median (IQR), years	3 (1-7)	4 (1-9)	0,55
ESSDAI, median (IQR), years	2 (1-6)	2 (0-4)	0,035
MSGB# focus score ≥1, n (%)	87 (77)	282 (79)	0,57
Anti Ro/SSA, n (%)	89 (79)	225 (63)	0,0033**
Arthralgia, n (%)	83 (74)	226 (63)	0.03*
VAS pain, median (IQR)	6 (3.3-8.0)	5.0 (2.0-7.3)	0.02*
VAS fatigue, median (IQR)	6.6 (4.4-8.3)	6.1 (3.9-8.0)	0.23
VAS eye dryness, median (IQR)	4.9 (1.7-7.1)	5.7 (2.5-8.0)	0.019*
VAS mouth dryness, median (IQR)	5.8 (3.4-7,5)	7.0 (4.8-8.8)	0.0012**

MSGB: minor salivary gland biopsy.
P value corresponds to the comparison of the two strata with Student's t or Mann Whitney-U test.

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THE COURSE OF JUVENILE ONSET SJÖGREN'S SYNDROME

Vasiliev V.[1], Palshina S.[1], Shornikova L.*[1], Rodionova E.[2], Novikov A.[1]
[1]*Revmocenter, Moscow, Russian Federation,* [2]*Treatment Center, Moscow, Russian Federation*

Objectives. Primary Sjögren's syndrome (pSS) is considered to be a rare disease in children according to 2016 ACR/EULAR classification criteria. The aim of this study is to characterize the prevalence, presentation, course and outcome of juvenile onset pSS diagnosed by 2001 Russian criteria.
Methods. Out of 412 adult patients with pSS 62 patients with juvenile onset of disease were examined in 1975-2006, 135 were diagnosed with pSS at the age of 1-20 during 2006-2020. All 197 patients fulfilled 2001 Russian criteria for pSS. The patients were divided into groups: (I) 60 patients (57 female, 3 male) with prolonged undiagnosed period (median=12 years) and (II) 137 patients (133 female, 4 male) diagnosed with pSS in childhood (52 at the age 1-16 (IIa), 85 at age 17-20 (IIb)). 153 patients had been followed up for 2-40 years (median=14 years).
Results. Juvenile onset pSS involved 15% of patients with pSS. The disease developed in 8, 38, 66, 25, and 60 patients at age 1-5, 6-10, 11-16, 17-18, and 19-20 years old, respectively.
Initial presenting symptoms included recurrent parotitis (76%), xerostomia and cervical caries (8%), parotid gland enlargement (4.5%), ophthalmological manifestations (11.6%), arthralgia (9%), fatigue (3.6%), fever (4.5%), hypergammaglobulinemic purpura (7%), Raynaud syndrome (3.6%). There were sialectasia on sialography in 100% patients, abnormal salivary gland ultrasound in 85% and positive minor salivary gland biopsy in 75%. Serologic tests revealed hyperproteinemia with hypergammaglobulinemia (87.5%) due to elevated levels of IgG (80%), IgA (60%); positive ANA (100%), RF (90%), anti-Ro/SSA (92%), anti-La/SSB (64%), and increased ESR (80%), anti-DNA (ELISA) (14%) and anti-RNP (3%) antibodies, whereas ACPA, anti-Sm, and anti-DNA (Crithidia luciliae IFT) were negative. Long-term follow-up of 153 patients revealed improvement in 47% and deterioration in 35.5%, including death in 13 (11%) patients at the age of 31-62 (median=41.5). Among those patients 44 left untreated, 66 received corticosteroids (CS), methotrexate, mycophenolate mofetil, or hydroxychloroquine (DMARDs), 43 received rituximab (RTX). Long-term RTX treatment for 2-10 years demonstrated the best result with no progression or deaths.
Untreated patients developed sicca syndrome along with interstitial lung disease (ILD), tubulointerstitial nephritis, peripheral neuropathy and non-Hodgkin lymphoma (p<0.001).
ILD (5), myelo- and lymphoproliferation (1 and 3), autoimmune cytopenia (2), transverse myelitis (1) and cryoglobulinemic glomerulonephritis (1) were the main cause of death in the group IIa (10) and IIb (3). Parotid gland MALT-lymphoma was diagnosed in 3-10 years after pSS onset in 3 patients at the age of 16, 17 and 19.
Conclusions. pSS in children prevails in 15% and is manifested with recurrent parotitis, high immunologic activity along with minimal functional tests abnormalities and systemic manifestations. Sialography and immunological tests confirm juvenile onset pSS in 100% cases. CS and DMARDs do not prevent deterioration. Rituximab should be considered as a first-line treatment option in children with pSS.

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AUTOMATIC QUANTIFICATION OF DRY EYE BY ARTIFICIAL INTELLIGENCE IN THE CONTEXT OF SJÖGREN'S SYNDROME

Brahim I.*[1,2], Lamard M.[1], Benyoussef A.[4], Conze P.[3,4], Cochner-Lamard B.[4], Quellec G.[1], Cornec D.[2]
[1]*Inserm, UMR 1101, Brest, France,* [2]*Inserm, UMR 1227, Univ Bretagne Occidentale, Brest, France,* [3]*IMT Atlantique, Inserm UMR 1101, Brest, France,* [4]*Service d'Ophtalmologie CHRU, Inserm UMR 1101, Univ Bretagne Occidentale, Brest, France*

Backgrounsd. Primary Sjögren syndrome-related dry eye disease (DED) is a common condition and a primary reason for visits to the ophthalmologist worldwide. Several clinical tests exist for both DED diagnosis and progression measurement. Unfortunately, these tests are sometimes invasive, non-reproducible, lacking in accuracy and constantly subjective. There are many

grading scales that estimate the number of punctate dots using a slit-lamp, yet a major flaw is that it is impossible to visualise all the parts of the eye simultaneously.
Objectives. The main goal is to help provide a better quantification of the subjective DED and help evaluate the extent of the damage using deep learning. We could build a complete 3-D view of the eye's anterior segment to help refine DED quantification.
Methods. To overcome this problem, we could predict the camera motion and build a mosaic of the eye using methods that have been previously deployed for autonomous driving (1, 2). Two CNN (Convolutional neural networks) are trained simultaneously to estimate the camera motion and the depth maps. Methods that were created for autonomous driving have various assumptions that do not align with our objective. We made modifications and altered these CNNs given our circumstances. We first calibrated the camera on the slit-lamp to obtain the intrinsic parameters. We included semantic segmentation as input to help the models differentiate between the eyelid, cornea, and sclera. We also include prior knowledge of the shape of the eye. We approximate the cornea and the sclera by a spherical cap. By including this penalisation we help guide the depth maps for both structures to be spherical.
Results. Our new method has shown promising results with tracking errors that outperform the state-of-the-art. We obtain a Euclidean distance as low as 0.48% of the image width (7.7 px out of 1600 px).
Conclusions. To the best of our knowledge, this paper is the first to address DED diagnosis with self-supervised methods and monocular videos.

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References
1. Casser V, Pirk S. Mahjourian R, Angelova A: Unsupervised monocular depth and ego-motion learning with structure and semantics. In: Proceedings of the IEEE/CVF Conference on Computer Vision and Pattern Recognition Workshops. pp. 0–0 (2019).
2. Gordon A, Li H, Jonschkowski R, Angelova A: Depth from videos in the wild: unsupervised monocular depth learning from unknown cameras. In: Proceedings of the IEEE/CVF International Conference on Computer Vision. pp. 8977-86 (2019).

Poster 71

SALIVARY GLAND ULTRASONOGRAPHY (SGUS) IN PRIMARY SJÖGREN'S SYNDROME AS MARKER OF DISEASE SEVERITY AND ITS ASSOCIATIONS WITH CLINICAL CHARACTERISTICS, ESSDAI AND ESSPRI AND SALIVARY PROTEOMICS.

Bisaralli R.*[1], Rath P.D.[1], Nanda R.[2], Sahu A.K.[1], Chouhan S.[1]
[1]Max Super Speciality Hospital, New Delhi, India, [2]ICGEB New Delhi, New Delhi, India

Background. Primary Sjögren's syndrome is a disease with predominantly Glandular manifestation like sicca syndrome and extra glandular manifestations. There are validated disease activity indices ESSDAI and ESSPRI. Salivary gland ultrasonography (SGUS) has emerged as a promising non-invasive tool for both diagnosis and prognostic implications in pSS, the focus over recent decades in the study of Sjögren's syndrome has been on determining disease specific biomarkers in biological fluids such as saliva, Liquid chromatography-mass spectrometry (LC-MS) has been applied in order to discover biomarkers and therapeutic targets by studying the salivary proteome. In the present study we aimed to study the associations between SGUS of major salivary glands, salivary proteomics and clinical characteristics, disease activity (ESSDAI & ESSPRI) in patients with pSS.
Methods. In this single centre observational study, 30 patients with pSS satisfying ACR/EULAR 2016 criteria for Sjögren's syndrome were included and ESSDAI and ESSPRI was calculated for all, SGUS was performed on all the patients, for analysis, patients were stratified into three groups based on SGUS findings as Normal, mild-moderate changes (Grade I & II) and severe changes (Grade III & IV). The saliva samples were collected from the patients using 50 ml Falcon tubes by drooling or spitting method. The data was then statistically analysed to find the correlations between SGUS, clinical characteristics, ESSDAI, ESSPRI and salivary proteomics with SGUS severity. Data analysis was done using Univariate analysis and independent t-test/ Mann-Whitney test was used to compare the continuous variable. The study was approved by institutional ethical committee (TS/MSSH/MHIL/SKT-1/MHEC/RHEUMA/20-04).
Results. 30 pSS patients were included in the study, with mean age of 48.9±10.44 years, with female comprising 96.7% of the study population. In parotid SGUS 16.7% had normal SGUS and 83.3% had abnormal SGUS, similarly in submandibular 23.3% had normal SGUS and 76.7% had abnormal SGUS findings. Mean ESSDAI in the study was 5.86±6.8 and mean ESSPRI was 6.02±0.83. The study showed that patients with abnormal SGUS had higher ESSDAI, however SGUS determined severity did not statistically correlate with ESSDAI (p=0.105 for parotid and p=0.863 for submandibular) There was no correlation observed between SGUS severity and ESSPRI in the study (p=0.982 for parotid and 0.407 for submandibular). The study also showed that patients with any abnormality seen on SGUS in both submandibular and parotid glands had higher extra glandular manifestations like musculoskeletal, peripheral neuropathy (NLD), ILD, renal and haematological manifestations. Salivary Proteomics study was carried out in 10 patients representative of the whole cohort.
Conclusions. SGUS abnormalities in pSS may help in assessing disease activity and recognizing Extra glandular manifestations (ILD, renal and haematological). Proteins S-100 A12, A8, A9 in the salivary proteome may be a marker of severe glandular and extra glandular manifestations, down regulation of Nucleobindin-2 in salivary proteome could be potential biomarker for pSS.

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AUTONOMIC DYSFUNCTION IN SJÖGREN'S DISEASE

Fenando A.[1], Estes J.[1], Shah S.[2], Lee J.[2], Jabari D.[1], Baker J.[3], Noaiseh G.*[1]
[1]University of Kansas Health System, Kansas City, Kansas, USA, [2]University of Missouri-Kansas City, Kansas, USA, [3]University of Pennsylvania, Philadelphia, USA

Background/Purpose. Sjögren's Disease (SjD) is a heterogenous autoimmune disease associated with debilitating symptoms. Autonomic dysfunction (AD) is common in SjD and may contribute to symptom burden. We sought to compare AD symptom severity in SjD patient to those with FMS and healthy controls and implemented a patient-based stratification method to assess if AD is more prominent in certain subsets.
Methods. This is a cross-sectional study of SjD and FMS patients recruited in our Sjögren's center between December 2021 and March 2022. Patients fulfilled 2016 ACR-EULAR criteria and FMS Survey Diagnostic Criteria and Severity Scale, respectively. Demographic, clinical and laboratory variables were collected.
A symptom-based stratification method was used1 to categorize SjD patients into 4 subgroups, based on severity of pain, fatigue, dryness, anxiety, and depression, using Newcastle Sjögren's Stratification software (available online at https://github.com/SJOGRENS/Symptom-Based-Subgroups), in which fatigue, dryness, and sicca symptoms were evaluated using EULAR's Sjögren's Syndrome Patient Reported Index (ESSPRI), while Hospital Anxiety and Depression Scoring (HADS) was used to assess anxiety and depression. Mean COMPASS-31 scores were compared between SjD, fibromyalgia groups and historical controls (n=30) using a previously published data2. We also assessed COMPASS-31 scores in SjD subgroups and studied the association with clinical and laboratory variables, particularly in relation to the anti-SSA and SSB status.
Results. Sixty-two consecutive SjD and 20 FMS patients were recruited. Mean age for SjD patients was 55 years, with mean disease duration of 8.3 year. Fifty-two (84%) were female. The mean COMPASS-31 score was significantly higher in SjD patients, compared to healthy controls (30.8±16.7 vs 8.9±8.7, p<0.0001), but lower compared to FMS patients (30.8±16.7 vs 41.9±20.3, p=0.0169). Of 62 SjD patients, Eight were classified as high

Table I. COMPASS-31 scores in SjD patients according to Anti-SSA and Anti-SSB status. Data are presented as mean (standard deviation).

	Anti-SSA *and* SSB positive	Anti-SSA - only positive	Anti-SSA *and* SSB negative	*P*-value
Mean COMPASS-31 score (SD)	23 (13.7)	28.9 (16.8)	40.7 (15.8)	0.0057

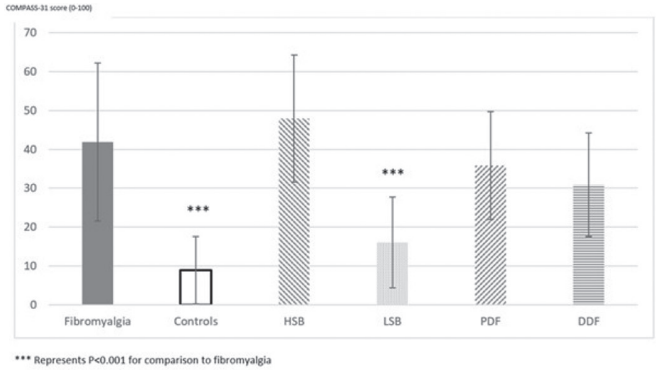

Figure 1. Total COMPASS-31 scores in FMS, healthy controls, and SjD Subgroups.

symptom burden (HSB), 16 as low symptom burden (LSB), 20 as pain dominant with fatigue (PDF), and 18 as dryness dominant with fatigue (DDF). COMPASS-31 score inversely correlated with Sjogren's serotype and was the highest in the seronegative group (Table I). COMPASS-31 score was highest in the high symptom burden subgroup (Figure 1).

Conclusions. To our knowledge, this is the first study that assesses AD in SjD using COMPASS-31 in comparison to FMS patients and a healthy population. Higher COMPASS-31 were observed in seronegative patients and those with the highest symptom burden, highlighting that AD may be implicated in symptom burden beyond the common symptoms of fatigue, dryness, and pain.

References

1. Tarn *et al*.: Symptom-based stratification of patients with primary Sjögren's syndrome: multi-dimensional characterization of international observational cohorts and reanalyses of randomized clinical trials. *Lancet Rheumatol* 2019; 1: e85-94
2. Adler *et al*.: Symptoms of autonomic dysfunction in systemic sclerosis assessed by the COMPASS-31 Questionnaire. *J Rheumatol* 2018; 45: 8.

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DRY EYE SYMPTOMS STRONGLY CORRELATE WITH OCULAR AND EXTRAOCULAR PAIN IN PRIMARY SJÖGREN'S SYNDROME. INTERIM REPORT OF A PILOT CROSS-SECTIONAL MONOCENTRIC STUDY.

Moroni L.[1], Ferrari G.[2,3], Bonelli F.[3], Batani V.*[1], Bellone M.[1], Dagna L.[1]
[1]Unit of Immunology, Rheumatology, Allergy and Rare Diseases, Ospedale San Raffaele; Vita-Salute San Raffaele University, Milan, Italy, [2]Cornea and Ocular Surface Unit, Ospedale San Raffaele; Eye Repair Lab, Ospedale San Raffaele, Milan, Italy, [3]Eye Repair Lab, Ospedale San Raffaele, Milan, Italy

Background. Ocular involvement in primary Sjögren's Syndrome (pSS) has been traditionally assessed by Schirmer's test, Tear Break Up Time (TBUT) and Ocular Staining Score (OSS)[1]. The role of Ocular Surface Disease Index (OSDI), Visual Function Questionnaire-25 (VFQ-25) and Numerical Rating Scale (NRS) in measuring ocular pain and discomfort in pSS have not been investigated in detail.

Objectives. In this ongoing cross-sectionally study, we aim at exploring the prevalence of ocular pain in patients with pSS. Moreover, we investigated the potential correlations between dry eye, ocular pain, extraocular patient-reported outcomes and disease activity.

Methods. OSDI, VFQ-25 and NRS were administered to 19 consecutive patients with a definite diagnosis of pSS at our outpatient clinic. All patients signed an informed consent for the study. Pearson coefficients were obtained to assess correlation among EULAR Sjögren's Syndrome (SS) disease activity index (ESSDAI), EULAR SS Patient Reported Index (ESSPRI), erythrocyte sedimentation rate (ESR), TBUT, OSDI, VFQ-25 and NRS.

Results. Nineteen (19) consecutive patients have been enrolled in the study so far. The sample demographics and disease-related features are representative of a typical pSS population (10% male sex, median age at diagnosis 49 [IQR 24], median ESSDAI = 1 [IQR 6] being biological, haematological and glandular involvement the most represented). Prevalence of ocular pain of any grade (NRS>0) was 11/19 (58%). Six patients (33%) reported severe ocular pain (NRS≥5). Correlation analysis resulted strong and significant for patient-reported dryness (ESSPRId), ocular surface-associated symptoms (OSDI), and stability of the tear film (TBUT) with NRS for ocular pain. Interestingly, ocular pain also correlated with generalised pain (ESSPRIp) and fatigue (ESSPRIf). Moreover, a significant correlation was outlined for OSDI (but not TBUT) with ESSDAI and ESR. Detailed results are summarised in Table I.

Table I. Pearson r coefficients calculated for self-reported ocular pain (NRS), patient-reported outcomes (ESSPRI, OSDI, VFQ-25), physician-assessed dryness (TBUT), disease activity (ESSDAI) and erythrocyte sedimentation rate.
*p<0.05. **p<0.01.

	NRS	TBUT	ESSDAI	ESSPRId	ESSPRIp	ESSPRIf	OSDI	VFQ-25	ESR
NRS		-0.95**	+0.25	+0.73*	+0.69*	+0.59*	+0.68*	-0.54	+0.19
TBUT	-0.95**		+0.40	-0.56	-0.58	-0.64	-0.57	+0.24	-0.67
ESSDAI	+0.25	+0.40		+0.14	+0.43	+0.12	+0.77**	-0.33	+0.55*
ESSPRId	+0.73*	-0.56	+0.14		+0.73**	+0.36	+0.61*	-0.60*	+0.11
ESSPRIp	+0.69*	-0.58	+0.43	+0.73**		+0.53*	+0.51	-0.63*	+0.32
ESSPRIf	+0.59*	-0.64	+0.12	+0.36	+0.53*		+0.09	-0.31	+0.73
OSDI	+0.68*	-0.57	+0.77**	+0.61*	+0.51	+0.09		-0.60*	+0.56*
VFQ-25	-0.54	+0.24	-0.33	-0.60*	-0.63*	-0.31	-0.60*		+0.05
ESR	+0.19	-0.67	+0.55*	+0.11	+0.32	+0.73	+0.56*	+0.05	

Acronyms: NRS: Numerical Rating Scale (for ocular pain); TBUT: Tear Break Up Time; ESSDAI: EULAR Sjögren's Syndrome (SS) disease activity index; ESSPRI: EULAR Sjögren's Syndrome Patient Reported Index (d:dryness; p: pain; f: fatigue); OSDI: Ocular Surface Disease Index; VFQ-25: Visual Function Questionnaire-25; ESR: erythrocyte sedimentation rate.

Conclusions. ocular pain might represent an additional criterium for patient stratification in pSS. The association we observed between ocular pain and extra-ocular symptoms is novel and unexpected. It suggests that nociceptive mediators may have a key role in symptoms' pathogenesis of Sjögren's Syndrome[2]. OSDI may perform better than TBUT in assessing ocular surface disease involvement and mirrors systemic inflammatory activity.

References

1. Ramos-Casals M *et al*.: EULAR recommendations for the management of Sjögren's syndrome with topical and systemic therapies. *Ann Rheum Dis* 2020.
2. Gebreegziabher EA *et al*.: Neuropathic pain in the eyes, body, and mouth: insights from the Sjögren's International Collaborative Clinical Alliance. *Pain Pract* 2021.

Poster 85

ECOLOGICAL MOMENTARY ASSESSMENT OF THE SYMPTOMS IN SJÖGREN'S SYNDROME: DEVELOPMENT AND VALIDATION OF A DEDICATED WEBAPP

Georgel L.[1], Berrouiguet S.[1], Ben-Youssef A.[1], Guellec D.[1], Carvajal Alegria G.[2], Marhadour T.[1], Jousse-Joulin S.[1], Cochner-Lamard B.[3], Labetoulle M.[4], Saraux A.[1], Gravey M.[1], Devauchelle-Pensec V.[1], Seror R.[5], Cornec D.*[1]
[1]LBAI, UMR1227, Univ Brest, Inserm, Labex IGO, CHU Brest, Brest, France, [2]Rhumatologie, CHU Tours, Tours, France, [3]Latim, UBO, Inserm, Ophtalmologie, CHRU Brest, Brest, France, [4]Ophtalmologie, CHU Kremlin-Bicêtre, AP-HP, Kremlin-Bicêtre, France, [5]Rhumatologie, CHU KB, APHP, Kremlin-Bicêtre, France

Background. Primary Sjögren's syndrome (pSS) is a rare systemic autoimmune disease with no specific treatment at present. To better assess patient symptoms, we have developed in the context of the NECESSITY project a web application (WebApp) to collect patient symptom intensity on a daily basis.

Objectives. to measure the daily variability of symptoms using the WebApp. We also evaluated its ease of use.

Methods. 45 consecutive patients with pSS were included in 3 referral centers. Symptoms were assessed during the baseline and 3 month visits. Patients used the WebApp daily for 3 months to collect the VAS relating to fatigue, dryness and pain as well as the ESSPRI score. The variability of symptoms over time was assessed by the predicted median error. This value was determined using a linear regression model, in order to predict the value at the 3rd month, then this value was compared to the actual value collected at the 3rd month during the clinical visit. The ease of use of the WebApp was assessed using a satisfaction score (SUS score).

Results. Of the 45 patients included, 91.1% were women with an average age of 57 years, and low systemic disease activity (84.4% had an ESSDAI score below 5). The intensity of the symptoms collected during the clinical visits was similar at baseline and at 3 months. The values of the median error for each measurement are between 0.5 and 0.8. The 3-month predicted median error values ranged from 2 to -3. The patients all used the web application for 3 months with good attendance (80% of data completion) and were satisfied with this tool (median SUS score = 90).

Conclusions. Symptoms of pSS fluctuate from day to day in the majority of patients, making a point measurement imprecise. The developed WebApp is easy to use, and could allow more sensitive detection of the effect of a therapeutic intervention. This tool will soon be evaluated during prospective interventional clinical trials including the NECESSITY clinical trial.

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IN-DEPTH ANALYSIS OF SALIVARY GLAND BIOPSIES: DEVELOPMENT OF NEW TOOLS USING HYPERION MASS CYTOMETRY TO ACCURATELY DETERMINE SJÖGREN'S SEVERITY STATUS

Scuiller Y.*, Foulquier N., Hémon P., Pers J.O., Jamin C.
Lymphocytes B, Autoimmunité, et Immunothérapies (LBAI), UMR 1227, Université de Bretagne Occidentale, Brest, France

Background. Immunohistochemistry and immunofluorescence are the techniques primarily used for the analysis of patient biopsies. With the identification of four to six markers at a time, these techniques make large-scale analysis difficult. They appear to be insufficient for future effective approaches to personalized immunotherapy of patients suffering diseases such as Sjögren's syndrome.
Methods. An imaging mass cytometer (IMC, Hyperion) can circumvent this limitation allowing the simultaneous analysis of forty biomarkers on a single biopsy. However, exploiting this high dimensional information requires the development of powerful analysis software that integrates specific features. Particularly, cell segmentation from the images is a critical issue for the efficiency and quality of downstream analysis.
Results. We are currently developing a software including all the steps from image pre-processing to data analysis. The key step of cell segmentation is performed by a neural network with U-Net architecture that was trained on images from different tissues. Once the mask of the cell segmentation is obtained, a result file is generated. For each segmented cell, the file includes its centroid as well as the mean intensity of each marker expressed by the cell. With this valuable informations, our software can perform multiparametric analysis such as dimension reduction, clustering, manual gating and neighborhood analysis. All those results are exportable in CSV format for unsupervised studies.
Conclusions. We are currently using this software to identify specific signatures in Sjögren's syndrome patients through the implementation of unsupervised data driven approaches. Specifically, we are studying the marker expressions on salivary glands biopsies in order to characterize the evolution of Sjögren's severity towards lymphoma.

Poster 90

INFLUENCE OF EPIDEMIOLOGY AND ETHNICITY ON SYSTEMIC EXPRESSION OF PRIMARY SJÖGREN SYNDROME AT DIAGNOSIS: WORLDWIDE PATTERNS IN 14,836 PATIENTS (2022 SJÖGREN BIG DATA PROJECT)

Retamozo S.*[1], Szanto A.[2], Li X.[3], Rasmussen A.[4], Ng F.[5], Dong X.[6], Priori R.[7], Olsson P.[8], Baldini C.[9], Seror R.[10], Bootsma H.[11], Armagan B.[12], Gottenberg J.[14], Kruize A.[15], Hernandez-Molina G.[13], Paprovnik S.[16], Danda D.[17], Özkiziltas B.[18], Inanc N.[19], Quartuccio L.[20], Sebastian A.[21], Gerli R.[22], Romao V.C.[23], Rischmueller M.[24], Suzuki Y.[25], Kwok S.[26], Kvarnstrom M.[27], Solans R.[28], Pasoto S.G.[29], Galisteo C.[30], Sene D.[31], Moça Trevisani V.[32], Isenberg D.[33], Hofauer B.[34], Shimizu T.[35], Nordmark G.[36], Valim V.[37], Jurcut C.[38], Carubbi F.[39], González García A.[40], Devauchelle-Pensec D.[41], Melchor Díaz S.[42], Gheita T.A.[43], Brito-Zerón P.[44], López-Dupla M.[45], Fonseca-Aizpuru E.[46], Sánchez-Berná I.[47], Morel J.[48], Giacomelli R.[49], Atzeni F.[50], Consani C.[51], Vázquez M.[52], Akasbi M.[53], Flores-Chavez A.[54], Ramos-Casals M.[54]
[1]Sjögren Syndrome Research Group, GRESS-AGAUR, Dept. of Rheumatology, Hospital Parc Tauli, Barcelona, Spain, [2]University of Debrecen, Debrecen, Hungary, [3] Dept. of Rheumatology and Immunology, the First Affiliated Hospital of USTC, University of Science and Technology of China, Hefei, Anhui, China, [4]Oklahoma Medical Research Foundation, Genes and Human Disease Research Program, Oklahoma, USA, [5]The UK Primary Sjögren's Syndrome Registry, Newcastle, UK, [6]Dept. of Rheumatology, Peking Union Medical College Hospital, Beijing, China, [7]Rheumatology Clinic, Sapienza University of Rome, Rome, Italy, [8]Lund University, Malmö, Sweden, [9]Rheumatology Clinic of Pisa, Pisa, Italy, [10]Université Paris-Sud, Paris, France, [11]University Medical Center Groningen, Groningen, Netherlands, [12]Hacettepe University Faculty of Medicine, Division of Rheumatology, Ankara, Turkey, [13]Immunology and Rheumatology Department, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Ciudad de Mexico, Mexico, [14]Dept. of Rheumatology, Strasbourg University Hospital, Université de Strasbourg, CNRS, Strasbourg, France, [15]University Medical Center Utrecht (UMCU), Utrecht, Netherlands, [16]University Clinical Center Ljubljana, Ljubljana, Slovenia, [17]Medical College and Hospital, Tamil Nadu, India, [18]Dept. of Internal Medicine, Gazi University Faculty of Medicine, Ankara, Turkey, [19]Marmara University, School of Medicine, Istanbul, Turkey, [20]University Hospital "Santa Maria della Misericordia", Udine, Italy, [21]Dept. of Rheumatology and Internal Medicine, Wroclaw Medical Hospital, Wroclaw, Poland, [22]University of Perugia, Perugia, Italy, [23]Rheumatology Department, Hospital de Santa Maria, Lisboa, Portugal, [24]The Queen Elizabeth Hospital, Adelaide, Australia, [25]Kanazawa University Graduate School of Medicine, Kanazawa, Japan, [26]Seoul St. Mary's Hospital, College of Medicine, Seoul, Republic of Korea, [27]Karolinska Institutet Stockholm, Stockholm, Sweden, [28]Dept. of Internal Medicine, Hospital Vall Hebron, Barcelona, Spain, [29]Rheumatology Division, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, Brazil, [30]Dept. of Rheumatology, Hospital Parc Tauli, Barcelona, Spain, [31]Hôpital Lariboisière, Paris, France, [32]Divison of Health Based Evidence, Federal University of São Paulo, São Paulo, Brazil, [33]University College of London, London, UK, [34]University Hospital Klinikum Rechts der Isar, Munich, Germany, [35]Dept. of Immunology and Rheumatology, Unit of Advanced Preventive Medical Sciences, Division of Advanced Preventive Medical Sciences, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, [36]Uppsala University, Uppsala, Sweden, [37]Federal University of Espírito Santo, Vitoria, Espíritu Santo, Brazil, [38]Internal Medicine, Central University Emergency Military Hospital, Bucharest, Romania, [39]Internal Medicine and Nephrology Unit, Dept. of Life, Health & Environmental Sciences, University of L'Aquila, and Dept. of Medicine, ASL 1 Avezzano-Sulmona, L'Aquila, Italy, [40]Dept. of Internal Medicine Hospital Ramón y Cajal, Madrid, Spain, [41]Cavale Blanche-University Hospital, Brest, France, [42]Dept. of Rheumatology, Hospital 12 de Octubre, Madrid, Spain, [43]Faculty of Medicine, Cairo University, Cairo, Egypt, [44]Research and Innovation Group in Autoimmune Diseases, Millenium Balmes-Hospital CIMA Sanitas, Barcelona, Spain, [45]Dept. of Internal Medicine, Hospital Universitari Joan XXIII, Tarragona, Spain, [46]Unidad de Autoinmunes, del Hospital Universitario de Cabueñes, Gijón, Asturias, Spain, [47]Dept. of Internal Medicine Hospital Rey Juan Carlos de Móstoles, Madrid, Spain, [48]Montpellier Hospital, Montpellier, France, [49]Clinical Unit of Rheumatology and Clinical Immunology, University of Rome "Campus Biomedico" (former L'Aquila), Rome, Italy, [50]Rheumatology Unit, University of Messina and Milan, Milan, Italy, [51]Servicio Medicina Interna y de Enfermedades Autoinmunes. Hospital Maciel. Universidad de la República, Montevideo, Uruguay, [52]Dept. of Rheumatology of the Hospital de Clínicas de San Lorenzo, San Lorenzo, Paraguay, [53]Dept. of Internal Medicine Hospital Infanta Leonor, Madrid, Spain, [54]Sjögren Syndrome Research Group, GRESS-AGAUR, Dept. of Autoimmune Diseases, ICMiD, Hospital Clínic, University of Barcelona, Barcelona, Spain

Objectives. To analyse the influence of epidemiology and ethnicity on the clinical systemic presentation at diagnosis of primary Sjögren syndrome (SjS).
Methods. Following a worldwide data-sharing cooperative merging of international clinical SjS databases, the Big Data Sjögren Project Consortium was created in 2014 as an international, multicentre registry of patients fulfilling the 2002 classification criteria. Systemic involvement at diagnosis will be retrospectively evaluated according to the ESSDAI classification, which evaluates 12 domains or organ systems. Each domain is divided into 3-4 levels according to the degree of activity and scored as 0 (no activity), 1 (low activity), 2 (moderate activity) or 3 (high activity). Individual activity of every organ-by-organ ESSDAI domains were also collected as a dichotomic variable.
Patients. With respect to ethnicity, the highest mean ESSDAI scores were reported in Black/African American, followed by White, Asian and Hispanic patients (6.38 vs 5.83, 5.12 and 5.0, respectively, $p<0.001$). Men with primary SjS had a statistically significant higher mean ESSDAI score at diagnosis in comparison with women (7.28 vs 5.39, $p<0.001$).
In addition, people presenting without oral dryness at the time at diagnosis also showed a higher mean ESSDAI score (7.01 vs 5.38 in those presenting with dry mouth, $p<0.001$). Mean ESSDAI scores were also higher in people showing abnormal diagnostic tests at diagnosis, including ocular tests (5.77 vs 4.35 in people with normal results, $p<0.001$) and oral tests (5.77 vs 5.17, $p<0.001$), while the difference according to the result of salivary gland biopsy was not statistically significant (5.23 for positive vs 5.22 for negative biopsy). The presence of a positive immunological marker at diagnosis was homogeneously associated with a higher mean ESSDAI score in comparison with people with negative markers: positive ANA (6.01), RF (6.89), anti-Ro/SSA (5.96), anti-La/SSB (6.58), low C3 levels (9.78), low C4 levels (8.57) and cryoglobulins (14.40).
Conclusions. This study provides solid evidence for a strong influence of epidemiology, ethnicity, diagnostic tests and immunology on the systemic phenotype of primary SjS at diagnosis.

Poster 99

ESSPRI REFLECTS COMMON SYMPTOMS OF PRIMARY SJÖGREN'S SYNDROME BETTER THAN ESSDAI

Ilgen U.*[1], Erol Kalkan K.[2], Ademoglu Z.[3], Hakan E.[3]
[1]Rheumatology Clinic, Tatvan State Hospital, Bitlis, Turkey, [2]Rheumatology Clinic, Başakşehir Çam and Sakura City Hospital, İstanbul, Turkey, [3]Department of Rheumatology, Trakya University, Edirne, Turkey

Background. Most common symptoms of primary Sjögren's syndrome (pSS) are mucosal dryness, arthralgias, and fatigue. Other disease manifestations are present in less than one-third of the patients even throughout the entire disease course.
Objectives. This study aimed to assess the change in disease activity based on dryness, pain, and fatigue (ESSPRI) in a real-world cohort of pSS patients with an unchanged ESSDAI over time.
Methods. 94 consecutive pSS patients meeting the 2016 ACR/EULAR classification criteria were included in the study and followed up prospectively. Baseline and follow-up disease characteristics and ESSDAI and ESSPRI scores after a period of 11±2 months were evaluated. Institutional Review Board of Trakya University Medical School approved this study (TÜTF-BAEK 2021/79).
Results. Baseline disease characteristics were provided in Table I. Baseline ESSDAI was zero in 48 (51.1%) patients and changed by at least 1 point only in 10 (10.6%) during follow-up. In 84 patients with an unchanged ESSDAI score, 18 (21.4%), 24 (26.2%), and 31 (36.9%) reported 30% or more change in dryness, pain, and fatigue scores, respectively, corresponding to 30% or more change in the ESSPRI score in 25 (29.8%) (Figure 1). 30% or more change in patient and physician global assessment scores were notable in 20 (23.8%) and 12 (14.3%) patients with unchanged ESSDAI scores. Median disease duration was 26 (IQR: 29) and 44 (IQR: 38) months, respectively, in patients with and without improvement in ESSPRI despite no change in ESSDAI (p=0.008). Improvement of ESSPRI was mostly due to improvement of pain and fatigue scores particularly in patients with baseline arthritis and arthralgias. Worsening of ESSPRI was, on the other hand, due to worse dryness and fatigue scores.
Conclusions. ESSPRI was more sensitive than ESSDAI to change and reflected common symptoms of primary Sjögren's syndrome better. Improvement of ESSPRI was associated with shorter disease duration and baseline presence of arthritis and arthralgias.

Table I. Baseline demographic, clinical, and laboratory characteristics of the patients.

Age, *years*	54+11.4
Sex, *female n (%)*	89 (94.7)
Disease duration, *months*	36 (IQR: 40)
Minor salivary gland biopsy, *performed n (%)*	59 (62.8)
Focus score	2 (IQR: 3)
Clinical findings, *n (%)*	
Constitutional symptoms	3 (3.2)
Parotitis	2 (2.1)
Lymphadenopathy	1 (1.1)
Arthritis	23 (24.5)
Cutaneous involvement	2 (2.2)
Pulmonary involvement	2 (2.2)
Renal involvement	3 (3.2)
Peripheral nervous system involvement	3 (3.2)
Central nervous system involvement	3 (3.2)
Hematological involvement	11 (11.7)
Positive anti-nuclear antibody, *n (%)*	91 (96.8)
Positive anti-Ro, *n (%)*	57 (60.6)
Positive anti-La, *n (%)*	29 (30.9)
ESSDAI	0 (IQR: 2)
ESSPRI	5.5 (IQR: 2.1)
Dryness score (0-10)	7.8 (IQR: 3.3)
Pain score (0-10)	4 (IQR: 4)
Fatigue score (0-10)	5 (IQR: 4)
Patient Global Disease Assessment Score (0-10)	5 (IQR: 3.3)
Physician Global Disease Assessment Score (0-10)	2.5 (IQR: 2)

n= number; IQR= interquartile range; ESSDAI=EULAR Sjögren's syndrome disease activity index, ESSPRI=EULAR Sjögren's Syndrome Patient Reported Index. Continuous variables were expressed as medians with IQRs except for age.

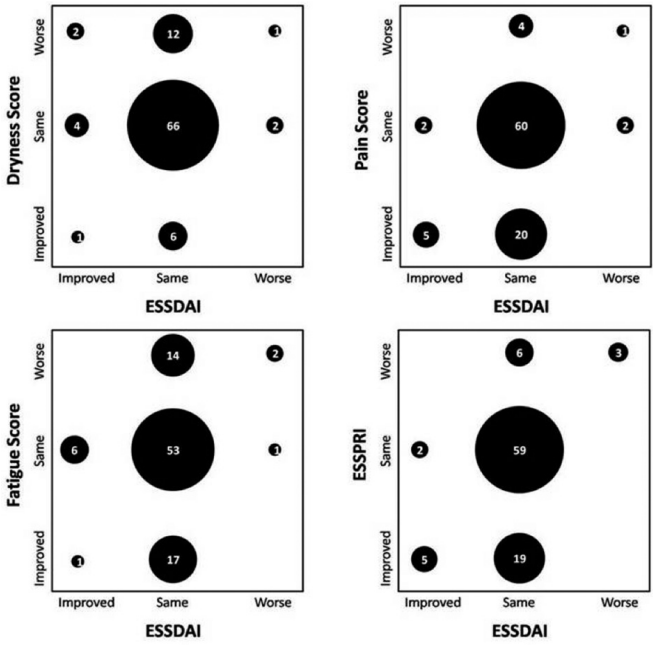

Fig. 1. Relationship between temporal changes in ESSDAI and ESSPRI.

Poster 111 (withdrawn by authors - late withdrawal)

THE RELATIONSHIP OF FDG PET-CT SALIVARY GLAND IMAGING TO ULTRASONOGRAPHIC SCORES AND SALIVARY FLOW RATE IN COMPARISON TO HEALTHY CONTROLS

Abacar K.Y.*[1], Kissa T.N.[2], Oksuzoglu K.[2], Ones T.[2], Mumcu G.[3], Bruyn G.A.[4], Inanc N.[1]
[1]Rheumatology Department, Marmara University School of Medicine, Istanbul, Turkey, [2]Nuclear Medicine Department, Marmara University School of Medicine, Istanbul, Turkey, [3]Health Management, Marmara University School of Health Sciences, Istanbul, Turkey, [4]Rheumatology, Reumakliniek Lelystad, Lelystad, Netherlands

Background. The use of salivary gland imaging modalities in patients with primary Sjögren's syndrome (pSS) has been increasing. Although ultrasound (US) and MRI are the most commonly used imaging modalities, the role of PET-CT for diagnosing pSS and determining glandular and extraglandular involvement has largely been neglected.
Objectives. To compare the sizes and metabolic activities of the major salivary glands in patients with pSS and healthy controls (HC). Correlation of the 18F-FDG PET-CT uptake characteristics with US scores and salivary flow rates (SFR) of the patients and HC was also determined.
Methods. 22 patients with pSS according to the 2016 ACR/EULAR Classification Criteria and 10 age/sex-matched HC were included in the study. The sizes and FDG uptakes of the parotid and submandibular glands of pSS patients and HC were assessed by PET-CT. The maximum standardized uptake value (SUVmax) was evaluated for FDG uptakes, and each patient's liver uptake and salivary gland uptake ratio were calculated. Correlations of gland sizes and FDG uptakes in PET-CT with OMERACT and Hocevar US scores, stimulated and unstimulated SFR, ESSPRI dryness scores and disease durations of pSS patients were calculated by Spearman test.
Results. The mean age (SD) of the patients was 58.6 years (10.5) versus 58.6 years (19.1) of HC; the mean (SD) disease duration was 8.96 (8.77) years. ANA was positive in all patients, anti-SSA positivity was present in 82.6%, and 30.4% of patients experienced ≥1 parotid swelling episode. Compared to HCs, the mean size of both submandibular glands (p=0.006 for left and p=0.032 for right) and SUVmax of the left submandibular gland (p=0.044) were significantly smaller in patients with pSS. In pSS patients, both right and left parotid sizes were smaller and SUVmax uptake was greater than in HC; these differences however did not reach statistical significance. When the PET-CT involvement characteristics of the patients were compared with the salivary gland US scores, there was a statistically significant negative correlation between the left parotid gland size in PET-CT and the

ultrasonographic inhomogeneity of Hocevar score and OMERACT score. There was a statistically significant negative correlation between right parotid gland size measured on PET-CT with ultrasonographic inhomogeneity, hyperechoic foci, parenchymal echogenicity, Hocevar total score, and OMERACT score. No statistically significant correlation was found between SUVmax scores detected by PET-CT and ultrasound scores in both parotid glands and submandibular glands.
A statistically significant positive correlation was found between the total gland size measured in PET-CT and the unstimulated salivary flow rate (p=0.038, r=0.604). There was a negative correlation between total gland size and ESSPRI dryness scores and symptom duration, which did not reach statistical significance.
Conclusions. PET-CT SUVmax measurements are insufficient to rule out major salivary gland involvement due to pSS. Second, PET-CT measurements of the parotid glands correlate with OMERACT ultrasound scores. Finally, the submandibular and parotid gland sizes are smaller than HC.

Table I. Correlations of gland sized and ultrasonographic scores.

Gland Size (PET/CT)		OMERACT Score	Parenchymal Echogenicity	Homogeneity	Hypoechoic Areas	Hiperechoic Foci	Visibility of Gland Border	Parenchymal Inhomogeneity	Total
R-Parotis	r	-.699*	-.717*	-.704*	-0,598	-.656*	-0,368	-.758**	-.645*
	p	0,017	0,013	0,016	0,052	0,028	0,266	0,007	0,032
L-Parotis	r	-.699*	-.717*	-.704*	-0,598	-.656*	-0,368	-.758**	-0,482
	p	0,017	0,013	0,016	0,052	0,028	0,266	0,007	0,134
R-Subm	r	-0,011	0.118	-0,011	-0,270	0,203	-0,006	0,247	0.024
	p	0,972	0.714	0,972	0,397	0,526	0,986	0,439	0.942
L-Subm	r	0,245	0,306	0,245	0,071	0,327	0,118	0,306	0,435
	p	0,443	0,333	0,443	0,826	0,300	0,714	0,333	0,158

Poster 113

SERUM BETA2-MICROGLOBULIN AS A MARKER OF ACTIVE PRIMARY SJÖGREN'S SYNDROME AND EXTRAGLANDULAR INVOLVEMENT

Bueno I.B.*, Oliveira M.C., Oliveira F.R.
Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto, Brazil

Background. Primary Sjögren's syndrome (SSp) is frequently associated with extraglandular manifestations and lymphoma. Only a few predictive factors of these complications have been identified to date. Beta2-microglobulin (B2M), a subunit protein of HLA that indicates adaptive immune activation, may be used as a marker for hematologic malignancies and renal dysfunction. This study aimed to evaluate B2M serum levels in SSp patients and analyze how they correlate with disease activity and traditional prognostic biomarkers.
Patients and methods. In this cross-sectional study conducted at the rheumatology outpatient clinic of a university hospital, 225 patients fulfilling the AECG criteria for SSp were evaluated for subjective complaints, disease activity, and damage indices (ESSPRI, ESSDAI, and SSDDI), B2M and conventional biomarkers serum levels. Statistical analysis used GraphPad Prism, version 9.0, and data were expressed as percentages or as means and standard deviation and analyzed by Mann-Whitney and Spearman's correlation tests.
Results. The mean age was 54±14 years, with 95% female, and the mean disease duration was 5.7±5 years. Fourteen patients (6.7%) had kidney disease, and 8 patients (3.7%) had a confirmed diagnosis of lymphoma. Anti-SSA/Ro and anti-SSB/La were positive in 71% and 43% of patients, respectively, and 90.5% (n=181/200) had a focus score ≥1. B2M levels were increased in 39.1% (n=74/189) of cases. Patients with ESSDAI scores <4 had lower B2M than patients with ESSDAI ≥5 (p=0.0245). There were positive correlations between B2M and disease activity measured by total ESSDAI (r=0.23; p=0.006), B2M and damage measured by SSDDI (r=0.33; p=0.011). In the ESSDAI, the agreement was greater between B2M levels and constitutional (r=0,17; p=0.031), renal (r=0.24; p=0.002), hematological (r=0.17; p=0.035), and biological (r=0.33; p<0.0001) domains. There were also significant correlations between B2M and gamma globulin serum levels (r=0.29; p<0.0001), C4 serum levels (r=-0.26; p=0.001), erythrocyte sedimentation rate (r=0.27; p<0.002), and creatinine serum levels (r=0.32; p<0.0001). Patients with positive anti-SSA/Ro (p=0.0014), anti-SSB/La (p=0.0002), and rheumatoid factor (p<0.0001) had higher B2M than those with negative autoantibodies. Patients with renal impairment had higher B2M levels than patients without kidney disease (p<0.0001). There were no associations between B2M and ANA, cryoglobulins, CRP, focus score, ESSPRI, or presence of lymphoma.
Conclusions. Beta2-microglobulin serum levels are elevated in SSp patients with active disease measured by ESSDAI, especially in those with higher scores in the constitutional, renal, hematological and biological domains, with disease damage (SSDDI), and hypergammaglobulinemia. Our results suggest that serum B2M may be a biomarker of disease activity and extraglandular involvement in SSp.

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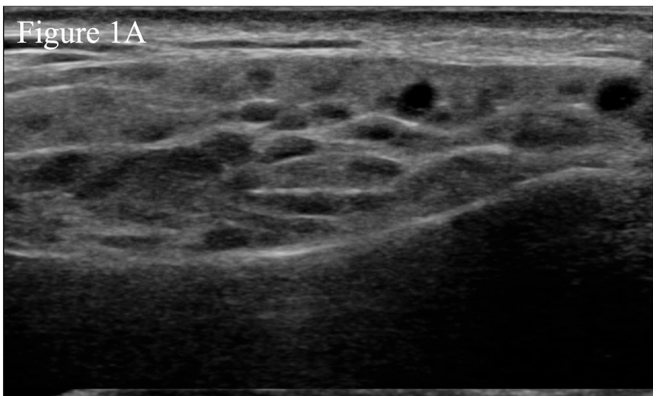
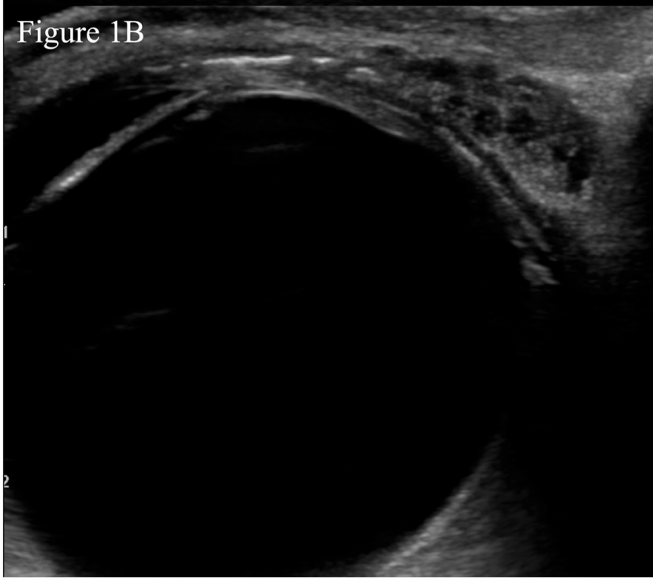
ULTRASONOGRAPHY OF LACRIMAL GLANDS: UNDERESTIMATE TOOL IN PRIMARY SJÖGREN'S SYNDROME: A CASE REPORT

Giovannini I.[1], Zandonella Callegher S.[2], Longhino S.*[1], Manfrè V.[1], De Vita S.[1], Zabotti A.[1]
[1]Rheumatology Clinic, Azienda Sanitaria Universitaria Friuli Centrale c/o University of Udine, Udine, Italy, [2]Department of Rheumatology, Hospital of Bruneck, Brunico, Italy

Introduction. Primary Sjögren's syndrome (pSS) is a systemic autoimmune disease which primarily targets salivary (SGs) and lacrimal glands (LGs) leading to oral and ocular dryness. Although major salivary gland ultrasonography (SGUS) has not been introduced in 2016 ACR/EULAR Sjogren Classification Criteria, it is now a well-established tool with a high inter-rater reliability for evaluating even early pSS salivary gland involvement. However, the data on the assessment of LGs by ultrasonography is scarse.
Case report. A 48-year-old man presented at our department with a long history of fever, myalgias, inflammatory arthralgias and symmetric purpuric lesions in lower limbs. Patient reported also persistent parotid swelling, previously diagnosed as bacterial sialadenitis. He did not complain of sicca symptoms. We performed sialometry and Schirmer's test which resulted normal. The patient presented rheumatoid factor positivity, type II cryoglo-





bulinemia, hypocomplementemia and a high titer ANA positivity (1:1280 speckled) with anti-Ro52/60 and anti-La specificity. Despite the absence of subjective and objective ocular and oral dryness, we programmed an US assessment of SGs and LGs to evaluate the parenchymal involvement. In this context, SGUS showed moderate/severe parenchymal inhomogeneity (OMERACT score 3 for parotid glands and OMERACT score 2 for submandibular glands, see Figure 1A) while LG ultrasound (LGUS) showed bilateral glandular enlargement with severe parenchymal inhomogeneity due to the presence of hypoechoic lesions (Figure 1B) and features very similar to those found in major SGs.

Considering the US involvement of major SGs and LGs, even in the absence of minor salivary gland biopsy, we concluded for pSS with associated cryoglobulinemic vasculitis.

Conclusions. Literature about the use of LGUS in pSS is scant but it could represent an objective, easy-to-perform, non-invasive, and repeatable test for the evaluation of lacrimal glands. Our case report highlights the role of lacrimal glands ultrasonography (LGUS) in a clinical context in which, despite a highly informative serologic data, functional glandular impairment was absent. Through US, an easy, non-invasive and repeatable tool, we were able to demonstrate involvement of both salivary and lacrimal glands, strongly supporting pSS diagnosis. LGUS might be implemented along with SGUS as routinary procedure in evaluating patients with suspected or definite diagnosis of pSS.

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VALIDITY OF THE NOVEL OMERACT ULTRASOUND SCORING SYSTEM FOR SALIVARY GLANDS TARGET LESIONS IN SJÖGREN'S SYNDROME

Inanc N.*[1], Jousse-Joulin S.[2], Abacar KY..[1], Cimsit Ç.[3], Cimsit C.[3], D'Agostino M.[4], Naredo E.[5], Hocevar A.[6], Finzel S.[7], Terslev L.[8], Pineda C.[9], Keen H.[10], Iagnocco A.[11], Hanova P.[12], Schmidt W.A.[13], Mumcu G.[14], Bruyn G.A.[15]

[1]Rheumatology Department, Marmara University School of Medicine, Istanbul, Turkey, [2]Rheumatology Department, Cavale Blanche Hospital and Brest Occidentale University, Brest, France, [3]Radiology Department, Marmara University School of Medicine, Istanbul, Turkey, [4]Hôpital Ambroise Paré, Boulogne-Billancourt, Versailles Saint Quentin University, Versailles, France, [5]Rheumatology Department, Joint and Bone Research Unit, Hospital Universitario Fundación Jiménez Díaz, Universidad Autónoma, Madrid, Spain, [6]Rheumatology Department, University Medical Centre, Ljubljana, Slovenia, [7]Department of Rheumatology and Clinical Immunology, Medical Center, University of Freiburg, Medical Faculty, University of Freiburg, Freiburg, Germany, [8]Centre for Rheumatology and Spine Diseases, Rigshospitalet, Copenhagen, Denmark, [9]Rheumatology Department, Instituto Nacional de Rehabilitacion, Mexico, Mexico, [10]Medicine and Pharmacology Department, The University of Western Australia, Murdoch, Perth, Australia, [11]Academic Rheumatology Centre, Università degli Studi di Torino, Turin, Italy, [12]Rheumatology, First Faculty of Medicine, Charles University, Prague, Czech Republic, [13]Immanuel Krankenhaus Berlin, Medical Center for Rheumatology Berlin-Buch, Berlin, Germany, [14]Health Management, Marmara University School of Health Sciences, Istanbul, Turkey, [15]Rheumatology, Reumakliniek Lelystad, Lelystad, Netherlands

Background. Imaging techniques such as salivary gland ultrasound and magnetic resonance imaging (MRI) are able to diagnose primary Sjögren syndrome (pSS) patients with high sensitivity and specificity. Recently, the OMERACT ultrasound novel scoring system for major salivary gland (SG) lesions in patients with pSS was developed showing good inter-reader and excellent intra-reader reliability.

Objectives. The aim of the OMERACT Sjögren ultrasound subtask group exercise was to assess the validity of the OMERACT ultrasound novel scoring system for major salivary gland (SG) lesions compared with MRI of parotid (PGs)/submandibular glands (SMGs) and salivary flow rates (SFRs) in patients with pSS.

Methods. Nine sonographers and two radiologists participated in the validity exercise, evaluating the parenchymal changes of bilateral PGs and SMGs in 11 pSS patients using greyscale ultrasound and MRI. Nine sonographers examined the superficial lobe of the PGs in both longitudinal and transverse plane, while the SMGs were evaluated in longitudinal plane only. Machine settings were not allowed to modify during scanning. The OMERACT novel four grade semiquantitative ultrasound score was applied: Grade 0, normal parenchyma; Grade 1: minimal change: mild inhomogeneity without anechoic/hypoechoic areas; Grade 2: moderate change: moderate inhomogeneity with focal anechoic/hypoechoic areas; Grade 3: severe change: diffuse inhomogeneity with anechoic/hypoechoic areas occupying the entire gland surface or fibrous gland. MRI images were evaluated by two radiologists with at least ten years of expertise in head and neck practice. The PGs parenchyma were graded by modifying the protocol as proposed by Kojima *et al*., *i.e*. grade 0 definitely normal, grade 1 slightly heterogeneous, grade 2 clearly abnormal, and grade 3 severely heterogeneous destroyed parenchyma. Differences in opinion between radiologists, if any, were resolved by reevaluating those cases. Furthermore, both stimulated and unstimulated salivary flow rates (SFRs) were assessed in 11 pSS patients.

Results. OMERACT novel ultrasound score was strongly correlated with MRI score for the PGs and for the SMGs (Table I). Correlation was similar for both the PGs and the SMGs combined (r:0,8 p=0.002). Moreover, both unstimulated and stimulated SFRs as objective criteria were associated with total OMERACT novel ultrasound score (r:0,7 p=0.04; r: 0,7 p=0.027) and total MRI score (r:0,8 p=0.004; r: 0,8 p=0.013). Similar trend was observed in PGs and SMGs (Table II).

Conclusions. The OMERACT novel ultrasound scoring system for the evaluation of SG in pSS showed strong correlation with MRI assessment. Furthermore, both imaging methods strongly correlate with unstimulated and stimulated SFRs.

Table I. Spearman's rho correlation coefficients for salivary gland target lesions scored by ultrasound and MRI.

		r	p
Total MRI Score	Total-OMERACT SGUS Score	0,8	0.002
MRI R PG	US R PG	0,7	0.004
MRI L PG	US L PG	0,9	0.000
MRI R SMG	US R SMG	0,7	0.017
MRI LSMG	US LSMG	0,6	0.046

Table II. Spearman's rho correlation coefficients of MRI and US scores of salivary glands with salivary flow rates (SFR).

	MRI Score					OMERACT SGUS Score				
	TOTAL	R PG	L PG	R SMG	LSMG	TOTAL	R PG	L PG	R SMG	LSMG
Unstimulated SFR	r:-0,8 p: 0.004	r:- -0,8 p: 0.009	r:- -0,8 p: 0.009	r:- -0,9 p: 0.001	r:- -0,9 p: 0.001	r:-0,7 p=0.04	r:- -0,8 p: 0.009	r:- -0,7 p: 0.03	r:- -0,8 p: 0.012	r:- -0,9 p: 0.001
Stimulated SFR	r:-0,8 p: 0.013	r:- -0,7 p: 0.024	r:- -0,7 p: 0.024	r:- -0,8 p: 0.003	r:- -0,8 p: 0.003	r:-0,7 P=0.027	r:- -0,7 p: 0.024	r:- -0,7 p: 0.024	r:- -0,7 p: 0.02	r:- -0,8 p: 0.003

Oral communication 141

THE USEFULNESS OF ULTRASOUND-GUIDED CORE NEEDLE BIOPSY OF THE PAROTID GLAND FOR THE DIAGNOSIS OF PRIMARY SJÖGREN'S SYNDROME

Manfrè V.*[1], Giovannini I.[1], Lorenzon M.[2], Pegolo E.[3], Hocevar A.[4], Dejaco C.[5], Quartuccio L.[1], De Vita S.[1], Zabotti A.[1]

[1]Rheumatology Clinic ASUFC, Udine, Italy, [2]Institute of Radiology, ASUFC, Udine, Italy, [3]Institute of Anatomic Pathology, ASUFC, Udine, Italy, [4]Department of Rheumatology, University Medical Centre Ljubljana, Ljubljana, Slovenia, [5]Department of Rheumatology, Hospital of Bruneck, Bruneck, Italy

Background. To date, histopathological diagnosis of primary Sjögren's syndrome (pSS) relies on labial biopsy, whereas open surgical parotid biopsy is mainly reserved to evaluate lymphoproliferative complications.(1) Lately, parotid gland (PG) sampling as a diagnostic tool for pSS is gaining interest as specific classification criteria were composed for applying open parotid biopsy as histopathological criterion for pSS.(1,2) Ultrasound-guided Core Needle Biopsy (US-guided CNB) is a novel and safe technique proven to be useful in PG lymphoma diagnosis in pSS patients with salivary gland enlargement.(3) Besides, its potential role for the diagnosis of pSS has never been assessed.

Objectives. This study explores the value of US-guided CNB of the PG as a diagnostic tool for pSS.

Methods. 28 patients with clinical diagnosis of pSS underwent US-guided CNB due to chronic or recurrent PG swelling suspected for lymphoma. In 27/28 patients, tissue sampling was adequate for histopathological diagnosis. 1 patient was excluded for a different final diagnosis, 15 for a diagnosis of PG lymphoma. 9/27 patients were included for evaluation of US-guided CNB efficacy in histopathological diagnosis of pSS. The following histological features related to pSS were studied: Focus score (FS); germinal centers (GCs); lymphoepithelial lesions (LELs); MALT acquisition; presence of focal lymphocytic (FLS) or Myoepithelial/lymphoepithelial sialadenitis (MESA/LESA).

Results. 8/9 patients satisfied pSS 2016 ACR/EULAR classification criteria at diagnosis, 9/9 after the procedure. 3 cases showed FLS, of which 2/3 had FS ≥1, 1/3 had FS <1 with concomitant GCs and MALT acquisition, still supporting pSS diagnosis. The other 6 cases showed MESA/LESA, with multiple GCs and LELs and FS=12. The patient not classified as pSS had histological features of MESA/LESA, confirming pSS diagnosis (Tab. I).

Table I. Description of histopathological features of 9 parotid gland US-guided core needle biopsies of pSS patients. LELs: lymphoepithelial lesions; GCs: germinal centers; MALT: mucosa-associated lymphoid tissue; MESA/LESA: myoepithelial/lymphoepithelial sialadenitis; FLS: focal lymphocytic sialadenitis.

#Patient	Focus score	LELs	GCs	MALT acquisition	MESA/LESA	FLS
#1	12	✓	✓	✓	✓	X
#2	1,35	✓	✓	✓	X	✓
#3	12	✓	✓	✓	✓	X
#4	0,465	X	✓	✓	X	✓
#5	12	✓	✓	✓	✓	X
#6	1	X	X	X	X	✓
#7	12	✓	✓	✓	V	X
#8	12	✓	✓	✓	V	X
#9	12	✓	✓	✓	V	X

Conclusions. The reported histological features allow a pathological diagnosis of pSS also in patients in which labial biopsy was not performed. Therefore, US-guided CNB of PG may represent a potential novel diagnostic tool for pSS. CNB can be US-guided in focal glandular areas with different sonographic features, consistent with different histopathology, further supporting its role as diagnostic tool in pSS. The next step will be to evaluate US-guided CNB in pSS cases without PG swelling and compare the results with labial biopsy.

References

1. Spijkervet FKL *et al*.: Parotid gland biopsy, the alternative way to diagnose Sjögren syndrome. *Rheum Dis Clin North Am* 2016.
2. Pijpe J *et al*.: Parotid gland biopsy compared with labial biopsy in the diagnosis of patients with primary Sjogren's syndrome. *Rheumatology* (Oxford) 2007.
3. Giovannini I *et al*.: Safety, patient acceptance and diagnostic accuracy of ultrasound core needle biopsy of parotid or submandibular glands in primary Sjögren's syndrome with suspected salivary gland lymphoma. *RMD Open* 2022.

Poster 142

ULTRASOUND EVALUATION OF MAJOR SALIVARY GLANDS IN AN ITALIAN COHORT OF PRIMARY SJÖGREN'S SYNDROME PATIENTS: A MONOCENTRIC STUDY

Giardina F.*[1], Gattamelata A.[1], Colafrancesco S.[1], Mastromanno L.[1], Villa M.[1], Simoncelli E.[1], Izzo R.[1], Conti F.[1], Priori R.[2]

[1]Rheumatology Unit, Department of Clinical Internal, Anaesthesiologic and Cardiovascular Sciences, Sapienza University of Rome, Rome, Italy, [2]Saint Camillus International University of Health Science, UniCamillus, Rome, Italy

Objectives. Ultrasound (US) of the major salivary glands is gaining an important role in the evaluation of patients with primary Sjögren's syndrome (pSS). The aim of this study is to assess the correlation between ultrasound characteristics and clinical-laboratory features of the disease.
Methods. consecutive patients with pSS (ACR/EULAR 2016 criteria) underwent US examination of the major salivary glands. Data about sociodemographic status, disease duration, serological characteristics, disease activity assessed by ESSDAI, patients' symptoms as calculated by ESSPRI, and subjective evaluation of ocular and oral dryness using dedicated VAS scales were collected. The ultrasound evaluation was performed through the use of Esaote MyLab ™ Gamma equipment with a 4-13 Mhz linear probe. Ultrasound data were evaluated by applying OMERACT1 (Grade from 0 to 3) and De Vita2 scores (Grade from 0 to 3). Fibrosis and glandular size were also considered. Continuous variables were summarized as median (1st and 3rd quartiles), while categorical variables as absolute and relative frequencies. Correlations were made using Spearman's non-parametric test. The main statistical analyzes were performed using linear and logistic regression models adjusted for the main clinical confounders (significance level=0.05).
Results. A total of 35 patients (34 F, 1 M; median age 60) with pSS were enrolled. There were no significant correlations between OMERACT and De Vita Scores and the risk of glandular swelling, leukopenia, disease duration and ESSDAI index. A significant association (p<0.05) emerged between glandular scores and the presence of anti-SSA, anti-SSB and rheumatoid factor (RF), as well as between glandular fibrosis and anti-SSB and rheumatoid factor. Hypergammaglobulinemia had a significant direct relationship with OMERACT parotid score. A significant inverse correlation was also found between ESSPRI and ultrasound scores, but not for xerostomia.
Conclusions. Our study does not show a correlation between disease activity and glandular ultrasound features, while the negative correlation between the extent of glandular involvement and ESSPRI might suggest that a greater glandular commitment is not necessarily an expression of the patient's symptom burden. The evidence of an association between ultrasound scores and the presence of autoantibodies, as well as between glandular fibrosis and anti-SSB and RF, would suggest that specific glandular ultrasound patterns might allow the identification of patients with more aggressive disease phenotypes. Further studies are needed to validate these data on larger case series.

Poster 162 (withdrawn by authors - late withdrawal)

QUALITY OF LIFE AND PHYSICAL/MENTAL PERFORMANCE IN MALE AND FEMALE PATIENTS WITH PRIMARY SJÖGREN'S SYNDROME: A PROSPECTIVE MONOCENTRIC STUDY ON 60 PATIENTS SURVEYED BY VALIDATED QUESTIONNAIRE

Angeli F.*[1], Nalli C.[1], Vojinovic T.[2], Andreoli L.[1], Franceschini F.[1]

[1]Rheumatology and Clinical Immunology, ASST Spedali Civili, Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy, [2]Laboratory of Experimental Rheumatology and Academic Division of Clinical Rheumatology, Department of Internal Medicine and Specialties, University of Genova, IRCCS Polyclinic San Martino, Genova, Italy

Background. Frailty is a condition associated with an increase vulnerability derived by a reduction in reserve of various physiological system, and it's most associated with aging. There are few data about the impact of Sjögren's syndrome on frailty and daily life activities.
Objectives. To evaluate the clinical course of a monocentric cohort of primary Sjögren's syndrome (pSS) and the disease impact on the quality of life of patients through validated questionnaires.
Methods. Questionnaires were administered to patients in follow-up at our Center for pSS between December 2019 and November 2021. We administered the "profile of fatigue and discomfort questionnaire" and the Short-Form 12 (SF-12) for the evaluation of the impact of pSS on quality of life, daily life activities and physical and psychological health. We compared female and male patients. Clinical data were retrieved from medical charts.
Results. Sixty patients (6 males) were evaluated. The mean age at diagnosis was 46.5±13.8 years for females and 45.7±14.1 years for males, with a disease durat.on of 165.4±110.5 months and 160±111.1 months, respectively. At the moment of diagnosis, ESSDAI was 3.6±3,4 in males, and 3.2±3,2 for females (p=ns), while at the moment of the survey it was 2.6±3.5 for males and 2.2±3,1 for females (p=ns). By means of a VAS scale between zero and one hundred we evaluated: 1) dryness, with a mean score of 55.5±27.8 in females and 50.9±27.4 in males; 2) fatigue, 49,1±31.4 for females and 46,3±30,8 for males; 3) pain, 39.3±33.5 in females and 39.5±33.2 in males. The mean ESSPRI for females was 5.1±2.7 and for males 5.0±2.8. The mean of Frailty Index was 0.166±0.705 in males and 0.137±0.603 in females. Results of SF-12 questionnaire: mean PCS (physical component score) was 46.2±9.5 and 45.1±9.8 in males and females, respectively. Mean MCS (mental component score) was 48.3±9.8 and 47.4±10.6 in males and females, respectively. Charlson comorbidity index was 1.54±0.92 in males and 1.51±0.91 in females.
Conclusions. In our monocentric prospective cohort, most patients were female (90%). Although the number of male patients was low and this did not allow a proper statistical analysis, we reported no differences between males and females with regard to age of onset, duration and disease activity at onset and at date of clinical evaluation. Clinical manifestations of pSS and its chronicity have an impact on daily activities with a moderate fatigue, pain and dryness (mean ESSPRI 5.1). There is also a slight mean reduction on SF-12 questionnaire (considering a cut-off of 50 for both components) more in PCS than MCS.

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COMPREHENSIVE ASSESSMENT OF PATIENTS WITH SUSPECTED SJÖGREN'S SYNDROME: 5-YEAR RESULTS OF A MULTIDISCIPLINARY SJÖGREN'S SYNDROME CLINIC

Romão V.C.*[1], Bandeira M.[1], Silvério António M.[1], Simão R.[2], Pinto J.[3], Gonçalves A.I.[3], Gonçalves M.J.[1], Martins A.L.[2], Lopes P.[3], Morena Bueno Silva L.[1], Lança M.[1], Coutinho G.[2], Esteves Marques R.[3], Macieira C.[1], Khmelinskii N.[1], Rodrigues W.[3], Salvado F.[2], Fonseca J.E.[1]

[1]Rheumatology Department, Hospital de Santa Maria, Centro Hospitalar Universitário Lisboa Norte, & Instituto de Medicina Molecular, Faculdade de Medicina, Universidade de Lisboa, Lisbon Academic Medical Centre, Lisbon, Portugal, [2]Stomatology Department, Hospital de Santa Maria, Centro Hospitalar Universitário Lisboa, Lisbon Academic Medical Centre, Lisbon, Portugal, [3]Ophthalmology Department, Centro Hospitalar Universitário Lisboa Norte, Lisbon Academic Medical Centre, Lisbon, Portugal

Background. Primary Sjögren's syndrome (pSS) is a systemic rheumatic disease that affects several organ systems, most frequently the ocular, oral and musculoskeletal domains. Multidisciplinary care is thus crucial in the optimal management of SS patients.
Objectives. To report the clinical impact of a Multidisciplinary SS Clinic (MSSC) over a 5-year period.
Methods. We prospectively included patients assessed in the MSSC from September 2015 to October 2020. All patients had a full clinical evaluation, including disease-related questionnaires, specialized oral/ocular assessment, salivary gland biopsy (SGB) and ultrasound (SGUS), tear and salivary flow and ocular staining scores. We compared the results of patient-reported outcomes, comprehensive clinical assessments and specialized complementary exams in patients with pSS and other diagnoses.
Results. 445 patients (96% women, mean age 57±14 years) with sicca symptoms underwent complete multidisciplinary evaluation. Patients were most frequently referred from Rheumatology (91%), but also from Stomatology (n=5%), Ophthalmology (n=2%), Internal Medicine (1%) and other medical specialties (1%). Most patients were diagnosed with pSS (n=221; 50%), followed by non-Sjögren sicca syndrome (nSSS, n=134; 30%), secondary SS (sSS, n=60; 13%) and undifferentiated connective tissue disease (n=30; 7%). Positive sicca tests were present in 217/385 patients (56%): unstimulated salivary flow (USF) ≤0.1ml/min in 84/317 (27%); Schirmer's test ≤5mm/5min in 163/354 (46%); van Bijsterveld score ≥4 in 42/349 (12%); Ocular Staining Score (OSS) ≥5 in 36/343 (11%). Subjective complaints assessed by the EULAR Sjögren Syndrome Patient Reported Index (ESSPRI), the EULAR Sicca Score (ESS), the Profile in Fatigue and Dryness in SS Index (PROFAD-SSI), the Xerostomia Inventory (XI), and the Ocular Surface Disease Index (OSDI) did not differ between patients with pSS and other diagnoses. However, objective dryness measures such as USF (31vs20%, p=0.028), Schirmer's test (51vs40%, p=0.040), and OSS (14vs7%, p=0.048) were significantly associated with pSS. A positive SGB (focus score≥1) was seen in 48% of patients with a clinical diagnosis of pSS (p<0.001 vs. other diagnoses), with a mean focus score of 1.1±1.6. Instead, 94% of patients with nSSS had grade 0-1 biopsies. Mean SGUS scores (p=0.006) and the frequency of moderate/severe changes (p<0.001) were higher in pSS patients.
Conclusions. Multidisciplinary evaluation was crucial in the assessment of patients with similar sicca complaints and in the management of ocular/oral/systemic involvement. Objective measurements and specialized complementary exams greatly contribute to establishing or confirming the diagnosis of pSS.

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NOVEL AUTOANTIBODIES IDENTIFY SJÖGREN'S DISEASE IN PATIENTS LACKING SERUM IGG SPECIFIC FOR RO/SS-A AND LA/SS-B

Longobardi S.[1], Lopez-Davis C.[1], Khatri B.[1], Georgescu C.[1], Lawrence C.[1], Rasmussen A.[1], Radfar L.[2], Scofield R.H.[1], Axtell R.C.[1], Pardo G.[1], Wren J.D.[1], Koelsch K.A.[1], Guthridge J.[1], James J.A.[1], Lessard C.J.[1], Farris A.D.*[1]

[1]Oklahoma Medical Research Foundation, Oklahoma City, USA, [2]University of Oklahoma Health Sciences Center, Oklahoma City, USA

Objectives. Classification of Sjögren's disease (SjD) requires either Ro/SS-A autoantibodies or minor salivary gland biopsy positive for focal lymphocytic infiltrates. Up to 40% of SjD cases lack Ro autoantibodies. Here we used human proteome arrays to identify autoantibodies in Ro antibody negative SjD.
Methods. A discovery dataset was generated by testing SjD salivary gland plasmablast-derived monoclonal antibody pools (n=83 mAbs in 14 pools), stimulated parotid saliva (n=11 SjD), and plasma (n=30 SjD, n=15 HC) on human proteome arrays containing 15,500-19,500 proteins. A validation dataset was generated by testing plasma and stimulated parotid saliva from additional SjD cases (n=46 anti-Ro+, n=50 anti-Ro–), HC (n=42), and other disease (OD) controls (n=54) on custom arrays containing 150 proteins. For each protein, the mean + 3SD of the HC value was used as the threshold for positivity. Differences from HC were determined by Fisher's Exact test at p<0.1 and by random forest machine learning and receiver operative curve (ROC) analysis, using 2/3 of the validation dataset to train and 1/3 of the validation dataset to test the ability of the model to assign subject status. Select proteins were additionally validated by capillary Western blot. Relationships among antigens were explored using STRING interactome analysis.
Results. Ro+ SjD parotid saliva contained antibodies binding to Ro60, Ro52, La/SS-B, and muscarinic receptor 5 (MR5). SjD plasma contained 13 novel autoantibody specificities, 12 of which were detected in both discovery and validation datasets. Binding to ≥1 of the novel antigens identified 45% of Ro+ SjD cases and 52% of Ro– SjD cases. ROC analysis using binary (positive/negative) data and excluding binding to the canonical Ro60, Ro52 and La antigens showed ROC area under the curve (AUC) of 0.82 (95% CI 0.62-0.92) for distinguishing Ro– SjD cases from HC. Non-canonical autoantibodies could also distinguish Ro+ SjD cases (AUC 0.74, 95% CI 0.61-0.9) and OD cases (AUC 0.65, 95% CI 0.45-0.76) from HC. STRING interactome analysis filtered on pathways including ≥2 novel antigens identified leukemia cell, ubiquitin mediated proteolysis, antiviral defense, and cytosolic DNA sensing as possible pathways targeted by the autoimmune response in Ro– SjD.
Conclusions: We have identified novel antigenic targets of the autoantibody response in SjD that may be useful for identifying a substantial proportion of Ro seronegative SjD cases without a lip biopsy.

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DOES EULAR SJÖGREN'S SYNDROME PATIENT REPORTED INDEX (ESSPRI)-PAIN MODERATE DAILY ACTIVITY IMPAIRMENT IN PATIENTS WITH PRIMARY SJÖGREN SYNDROME?

Yenisoy Y.[1], Altingöz E.N.[1], Kapusuz A.[1], Abacar K.Y.[2], Tatli I.[3], Türe-Özdemir F.[3], Karacayli U.[4], Yay M.[5], Direskeneli H.[2], Fortune F.[6], Inanc N.*[2], Mumcu G.[7]

[1]Marmara University, MSc student, Institute of Health Sciences, Istanbul, Turkey, [2]Marmara University, School of Medicine, Division of Rheumatology, Istanbul, Turkey, [3]Marmara University Medical School, Department of Heamatology and Immunology, Istanbul, Turkey, [4]Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Health Sciences University, Ankara, Turkey, [5]Department of Statistics, Mimar Sinan Fine Art Faculty, Istanbul, Turkey, [6]Barts and The London School of Medicine and Dentistry, Centre Immunobiology and Regenerative Medicine, Queen Mary University of London, London, UK, [7]Faculty of Health Sciences, Department of Health Management, Marmara University, Istanbul, Turkey

Objectives. The aim of the present study was to examine the effects of EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) on Daily activity impairment by using the moderation analysis (MA) in patients with primary Sjögren Syndrome (pSS).

Materials and methods. In this cross-sectional study, 86 patients (M/F: 5/81; mean age: 52.4±11.6 years) were included in the study. Complex interrelations were evaluated by using MA which evaluates whether a moderator variable affects the relationship between independent and outcome variables. The patients were divided into two groups; using salivary gland hypofunction (unstimulated salivary flow rate <0.1 ml/min) was present (n=33, 38.4%) or not (n=53 38.4%) as the independent variable. Patients' Daily activity impairment was evaluated by using the Work Productivity and Activity Impairment scale (WPAI) as an outcome variable. Patients' symptoms were evaluated by using ESSPRI-Dryness, -Pain, -Dryness (0-10 points for each) as potential moderators.
Results. The WPAI-Daily activity score was significantly higher in patients with Hyposalivation (87.57±22.22) than patients without Hyposalivation (43.77±23.87). The WPAI-Daily activity score was correlated with ESSPRI-Pain, -Fatigue and Dryness in patients without Hyposalivation (p<0.05). Using MA, the presence of Hyposalivation, the WPAI-Daily activity score increased significantly (p=0.0000). Besides, ESSPRI-Pain was the only significant moderator variable for poor WPAI-Daily activity impairment in patients without Hyposalivation using three cut-off points defined statistically (p=0.0000 for 2 points, 5 points: p=0.0002 for 9 points). Interestingly, similar results were not found in patients with Hyposalivation (p>0.05).
Conclusions: Daily activity impairment was associated with Hyposalivation and moderated by Pain in patients without Hyposalivation.

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POSTURAL TACHYCARDIA AND SJÖGREN DISEASE

Goodman B.*, Arca K.
Mayo Clinic, Scottsdale, USA

Introduction. Dysautonomia is a common extra-glandular manifestation of Sjögren Disease (SD) that is heterogenous, under-recognized, and has been suboptimally characterized. One of the more common forms of dysautonomia in SD is what appears phenotypically to resemble postural tachycardia syndrome (POTS). POTS, the most common form of dysautonomia in the young, is defined by the presence of an excessive postural tachycardia, absence of orthostatic hypotension, symptoms of orthostatic intolerance, and absence of a systemic condition that could result in dysautonomia (such as SD). The purpose of this study is to report the features of overlapping POTS and SD.
Methods. We report the clinical, laboratory, pathological, and autonomic testing features in a cohort of 60 patients who were evaluated for dysautonomia, otherwise met criteria for POTS, but also were diagnosed with SD.
Results. All but 2 of the patients in this cohort were female with a mean age of 33, and 92% were diagnosed with SD following their diagnosis of dysautonomia. Mean dysautonomia symptom duration prior to the diagnosis of SD was 11 years. All patients in this cohort underwent comprehensive autonomic testing, with all patients by definition demonstrating an excessive postural tachycardia with head-up tilt; but were further characterized based upon conventional criteria as having a concomitant autonomic neuropathy (25/60), hyperadrenergic features in 7/60 patients, and 2 patients had a combination of both features. Importantly, formal motility testing was performed in 28 patients, and was abnormal in 22 of the testing patients, with evidence of gastroparesis in 14 patients, small intestinal dysmotility in 6 patients, esophageal dysmotility in 6 patients, and 6 patients with multiple areas of dysmotility. Laboratory studies showed evidence of abnormal mast cell activation in 30% of patients.
Conclusions. Some individuals with a phenotype typical of POTS, either have or will be diagnosed with SD. These individuals are mostly female, have a long duration of autonomic symptoms, can have neuropathic or hyperadrenergic features on autonomic testing, frequently have dysmotility, and not infrequently have signs and symptoms of mast cell activation.

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THE SJÖGREN'S TOOL FOR ASSESSING RESPONSE (STAR): ASSESSMENT OF RESPONSE RATES OVERALL, ACCORDING TO BASELINE ACTIVITY AND BY DOMAIN: REANALYSIS OF 9 CLINICAL TRIALS IN PRIMARY SJÖGREN'S SYNDROME

Seror R.*[1], Baron G.[2], Cornec D.[3], Perrodeau E.[2], Camus M.[1], Bowman S.J.[4], Bombardieri M.[5], Bootsma H.[6], Arends S.[6], Gottenberg J.E.[7], Fisher B.A.[8], Hueber W.[9], Roon J.V.[10], Devauchelle-Pensec V.[3], De Wolff L.[6], Gergely P.[9], Mariette X.[1], Porcher R.[2]
[1]Department of Rheumatology, Université Paris-Saclay, APHP Hôpital Bicêtre, Le Kremlin Bicêtre, Paris, France, [2]AP-HP Hôtel Dieu Hospital, Université Paris Descartes, Paris, France, [3]LBAI Université de Brest, Brest, France, [4]4Rheumatology Department, Milton Keynes University Hospital, Milton Keynes, UK, [5]Experimental Medicine and Rheumatology, William Harvey Research Institute, Queen Mary University, London, UK, [6]Rheumatology and Clinical Immunology, University Medical Center Groningen, Groningen, Netherlands, [7]Rheumatology, CHU de Strasbourg, Strabourg, France, [8]National Institute for Health Research (NIHR) Birmingham Biomedical Research Centre and Rheumatology Research Group, Birmingham, UK, [9]Novartis Pharma, Basel, Switzerland, [10]Rheumatology and Clinical Immunology, University of Utrecht, Utrecht, Netherlands

Background. The ESSDAI and ESSPRI, used alone, are not able to capture all features of primary Sjögren's syndrome (pSS). The NECESSITY consortium developed the Sjögren's Tool for Assessing Response (STAR), a composite index comprising 5 domains to assess response to treatments on all disease aspects in clinical trials.
Objectives. To assess STAR response according to baseline systemic activity, and in each of its 5 domains; and to evaluate the added value of ocular staining score (OSS), salivary gland ultra-sound (SGUS) and rheumatoid factor (RF) in STAR scoring and compare with CRESS.
Methods. This study relies on the 9 randomized controlled trials (RCTs) used for STAR development. OSS, SGUS and RF were not available for most trials.

Table I. Response rate and netween arm difference with full and concise version of STAR and CRESS in 9 randomized controlled trials.

		EXPERIMENTAL	CONTROL	RISK DIFFERENCE (95%CI)
ABATACEPT (ASAP3)	**cSTAR**	**21/40 (53)**	**8/36 (22)**	**30 (7 ; 51)**
W24	**fSTAR**	**27/40 (68)**	**12/37 (32)**	**35 (11 ; 55)**
	cCRESS	**18/38 (47)**	**3/35 (9)**	**39 (17 ; 57)**
	fCRESS	**28/40 (70)**	**6/37 (16)**	**54 (31 ; 71)**
BAMINCERCEPT	cSTAR	6/28 (21)	5/16 (31)	-10 (-39 ; 17)
W24	fSTAR	7/28 (25)	6/16 (38)	-13 (-42 ; 16)
	cCRESS	13/26 (50)	5/16 (31)	19 (-13 ; 47)
	fCRESS	15/27 (56)	6/16 (38)	18 (-14; 47)
HYDROXYCHLOROQUINE (JOQUER)	cSTAR	13/46 (28)	8/45 (18)	11 (-7 ; 29)
W24	fSTAR	-	-	-
	cCRESS	**22/40 (55)**	**10/38 (26)**	**29 (6; 49)**
	fCRESS	-	-	-
LEFLU + HYDROXY (REPURPSS)	**cSTAR**	**12/21 (57)**	**0/7 (0)**	**57 (9; 79)**
W24	fSTAR	-	-	-
	cCRESS	**12/21 (57)**	**0/7 (0)**	**57 (9; 79)**
	fCRESS	-	-	-
IANALUMAB (ANTI BAFFR)	cSTAR	-	-	-
W24	fSTAR	12/18 (67)	3/9 (33)	33 (-8; 66)
	cCRESS	-	-	-
	fCRESS	6/18 (33)	2/9 (22)	11 (-30; 44)
ISCALIMAB (ANTI CD40)	**cSTAR**	**15/20 (75)**	**4/11 (36)**	**39 (1; 69)**
W12	**fSTAR**	**16/20 (80)**	**4/11 (36)**	**44 (3; 73)**
	cCRESS	11/20 (55)	2/11 (18)	37 (-3; 65)
	fCRESS	**12/18 (67)**	**2/11 (18)**	**48 (9; 77)**
RITUXIMAB (TRACTISS)	cSTAR	26/57 (46)	19/56 (34)	12 (-6; 30)
W48	fSTAR	26/57 (46)	20/56 (36)	10 (-8; 28)
	cCRESS	**34/56 (61)**	**20/51 (39)**	**22 (2; 40)**
	fCRESS	**35/56 (63)**	**20/52 (38)**	**24 (4; 42)**
RITUXIMAB (TEARS)	**cSTAR**	**24/55 (44)**	**9/49 (18)**	**25 (5; 42)**
W24	**fSTAR**	**25/55 (45)**	**9/49 (18)**	**27 (7; 44)**
	cCRESS	**29/54 (54)**	**12/48 (25)**	**29 (7 ; 46)**
	fCRESS	**31/54 (57)**	**12/48 (25)**	**32 (10; 50)**
TOCILIZUMAB (ETAP)	cSTAR	24/45 (53)	16/44 (36)	17 (-4; 37)
W12	fSTAR	-	-	-
	cCRESS	13/40 (33)	11/42 (26)	6 (-14; 26)
	fCRESS	-	-	-

Thus, concise STAR (cSTAR) was calculated without these items at all available visits in each trial. A trial was categorized as positive if showing a significant between-arm difference in at least one visit. Stratified analyses according to baseline clinESSDAI (<5 vs ≥5) were performed whenever possible. The response rate in each STAR domain was calculated, along with a full STAR (fSTAR) including OSS, SGUS and RF when available to determine whether they affected the scoring. SGUS response was defined as a 25% improvement of the available scoring, since only 1 trial used Hocevar score. The same analyses were run for the concise Composite of Relevant Endpoints for Sjögren's Syndrome (cCRESS) and full CRESS (fCRESS).
Results. cSTAR and cCRESS, classified identically 6/9 trials. Abatacept (ASAP-III), leflunomide+hydroxychloroquine and rituximab (TEARS) trials were categorized as positive trials with both scores. By contrast, the hydroxychloroquine (JOQUER) and rituximab (TRACTISS) trials were positive with cCRESS only and the iscalimab trial with cSTAR only. Stratified analyses according to baseline activity showed similar between group difference in both subgroups (clinESSDAI < or ≥5) with cSTAR.
For the systemic domain, CRESS definition (final clinESSDAI<5) classified patients with low activity as responders (even if no decrease in clinESSDAI) compared to STAR definition (decrease of clinESSDAI ≥3 points), leading to increased overall responder rates, particularly for treatment with biologic activity (rituximab, hydroxychloroquine). In patients with moderate to high activity, a larger rate of response was observed in both arms with STAR definition, both definitions displaying similar between arm difference. For other domains, adding RF to IgG response improved between arm differences in 3/5 trials. Adding OSS to Schirmer's test made no obvious difference in between-arm differences, in the 2 trials available. Adding SGUS scoring to whole saliva slightly increased between arm differences in the 3 available trials.
Conclusions. cSTAR and cCRESS responses were consistent across most of the trials. Some differences were observed mainly driven by the definition of systemic response; CRESS classified patients with low activity as responders even in the absence of improvement of ESSDAI or ESSPRI. Adding RF and SGUS seemed to increase the overall responsiveness of the STAR and CRESS.

Poster 183

COMPARISON OF ULTRASOUND AND SIALOGRAPHY OF MAJOR SALIVARY GLANDS IN PRIMARY SJÖGREN'S SYNDROME

Khvan Y.*, Torgashina A., Chaltsev B.
V.A. Nasonova Research Institute of Rheumatology, Moscow, Russian Federation

Background. At the present time, salivary glands ultrasonography (SGUS) is not a criterion position in the ACR 2012 and ACR/EULAR 2016 criteria primary Sjögren's syndrome (pSS), however, when this imaging method was added to the current criteria, there was demonstrated an increase in their sensitivity and specificity.
Objectives. to compare the diagnostic value of ultrasound and sialography of major salivary glands.
Methods. From 2016 to 2020, we examined 94 patients (93 women, 1 man) with the mean age 48.6±14.3 years (minimum 18, maximum 78) with newly diagnosed pSS according to Russian criteria 2001, 86% of patients fulfilled ACR 2012 criteria and 87% - the ACR/EULAR 2016 criteria. All patients underwent classical examination (stomatological, ophthalmological, immunological), and SGUS was performed using GE LOGIQ 9 on the two parotid and two submandibular glands. Ultrasound images were evaluated with the OMERACT SS severity scoring system (SGUS SS) from grades 0 to 3. Statistical analyses (Spearman coefficient $p<0.05$) were performed using STATISTICA version 12.
Results. Detailed characteristics of patients are presented in Table I. In our study 86 patients in SGUS had inhomogeneity structure from mild to diffuse with hypoechoic areas. 4 patients had no signs of sialectasia on sialography, however, in ultrasound we found SGUS SS grade 2.
In 3 patients with SGUS grade 0 we determined globular sialectasia Among 12 patients with sialectasia on parotid sialography, 5 patients had SGUS SS grade 0, 1 – grade 1, 2 – grade 2, 4 – grade 3.
Correlation was calculated for each SGUS SS (0-3) with clinical and classical methods of examination of the salivary glands.
Changes in SGUS SS 3 correlated with recurrent parotitis r=0.22 (p=0.03), enlargement of parotid salivary glands r=0.23 (p=0.02) and cavitary sialectasia r=0.23 (p=0.02).

Table I.

Parameters	N	%
Oral dryness	78	83,0
Enlargement of parotid salivary glands	32	34,0
Recurrent parotitis	19	20,2
Retention pain	31	33,0
RF positive >2UNL (>30 IU/ml)	51	54,2
anti-SSA (anti-Ro) positive (>25 IU/ml)	81	86,1
anti-SSB (anti-La) positive (>25 IU/ml)	48	51,0
ANA ≥ 1:320	94	100,0
SGUS SS 0	8	8,5
SGUS SS 1	1	1,0
SGUS SS 2	20	21,2
SGUS SS 3	65	69,1
Stimulated SFT < 2,5ml/5 min	59	62,8
Sialectasia on parotid sialography	90	94,7
Punctate sialectasia	12	12,6
Globular sialectasia	63	66,3
Cavitary sialectasia	10	10,5
Distructive sialectasia	6	6,3
FS ≥ 1foci/4 mm2	83	88,2

Histological changes FS ≥1 correlated with all grades on ultrasound (SGUS SS 0 r= -0.24 (p=0.01), SGUS SS 1 r=0.41 (p=0.000027), SGUS SS 2 r= - 0.21 (p=0.03), SGUS SS 3 r=0.40 (p=0.00006)).
The punctate sialectasia correlated with SGUS SS 1 r= -0.28 (p=0.005) and SGUS SS 0 r=0.45 (p=0.000004). Stimulated SFT did not correlate with ultrasound changes.
Conclusions. Based on our study, we can suppose that sialography and ultrasound are not interchangeable methods, but complementary. Probably, in everyday clinical practice, SGUS can be used as an additional method for salivary gland assessment, given the availability and safety of the method. The most convenient system for assessing the salivary glands, at present, is the OMERACT SS severity scoring system, however, now we do not have score for the complete differentiation in pSS and lymphoproliferative complications.

Poster189

ULTRASOUND OF SALIVARY GLANDS IN PATIENTS WITH POSITIVE AND NEGATIVE ANTICENTROMERE ANTIBODIES PRIMARY SJÖGREN'S SYNDROME

Khvan Y., Torgashina A., Chaltsev B.*
V.A. Nasonova Research Institute of Rheumatology, Moscow, Russian Federation

Background. The salivary gland ultrasonography (SGUS) is widely used to assess the structure of the salivary gland in primary Sjögren's syndrome (pSS). At the present time there are few publications about SGUS changes in a special subtype of pSS with anticentromere antibodies (ACA).
Objectives. to study SGUS changes in ACA (ACA+) positive pSS patients and ACA-negative (ACA–) and to compare them.
Methods. We examined 145 patients with pSS, including 105 ACA– patients (pSS-ACA–) with the mean age 46.8±14.5 years and 40 ACA+ positive (pSS-ACA+) with the mean age 58.2±11.3 years. All patients underwent standard examination for the diagnosis of pSS (stomatological, ophthalmo-

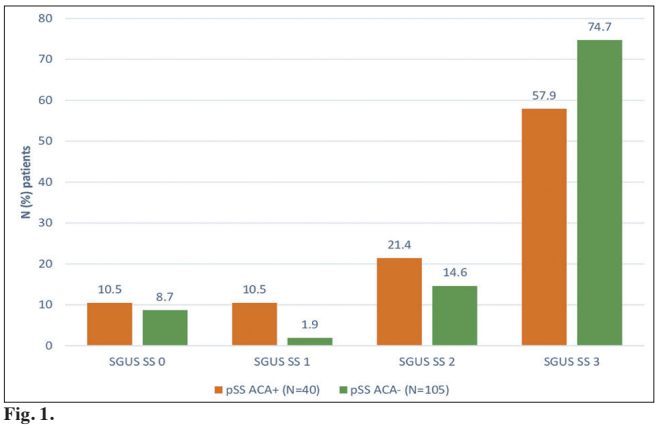


Fig. 1.

Table I.

Parameters	ACA–		ACA+	
	N	%	N	%
Oral dryness	86	83,5	36	94,7
Ocular dryness	76	73,8	30	78,9
Enlargement of parotid salivary glands	36	34,9	7	18,4
Recurrent parotitis	23	22,3	7	60,5
ANA ≥1:320	105	100	40	100
Stimulated saliva flow test < 2.5 ml/5 min	65	63,1	30	78,9
Sialectasia on parotid sialography	105	100	40	100
Stimulated Schirmer's test <10 mm/5 min	67	65,0	26	68,4
Tear breakup time <10 seconds	59	57,3	20	52,6
Focus score ≥ 1foci/4 mm2	94	91,3	12/13	92,3
MALT-lymphoma	8	7,7	5	13,1

logical, immunological), and SGUS performed using GE LOGIQ 9 of two parotid and two submandibular glands. Ultrasound images were evaluated with the OMERACT SGUS scoring system (SGUS SS) from grades 0 to 3. Statistical analyses (chi-squared test, $p<0.05$) were performed using STATISTICA version 12.

Results. Characteristics of patients with pSS-ACA+ and pSS-ACA– are presented in Table I. Characteristics of SGUS SS in pSS-ACA+ and pSS-ACA– are shown in Fig. 1. We did not find any significant differences when comparing SGUS SS in patients with pSS-ACA+ and pSS-ACA–.

Conclusions. We did not find any significant differences in SGUS and SGUS SS in patients with pSS-ACA+ and pSS-ACA–.

Poster 190 (withdrawn by authors - late withdrawal)

SCLERODERMA CAPILLAROSCOPIC PATTERNS IN AUTOIMMUNE DISEASES WITH RAYNAUD'S PHENO MENON: REPORT OF 100 PATIENTS

Chetouane R.*, Rahal F., Hanni F.
EHS BenAknoun, Algiers, Algeria

Objectives. Research the scleroderma capillaroscopic patterns in the various autoimmune diseases with Raynaud's phenomenon. - prevalence of the other nonspecific capillaroscopic anomalies.

Patients and methods. One hundred patients were investigated: 26 cases with undifferentiated connective tissue disease (UCTD), 20 patients with systemic lupus erythematosus (SLE), 4 patients with dermato/polymyositis, 10 with rheu- matoid arthritis, 16 cases with primary Sjögren's syndrome and 24 patients with systemic sclerosis (SSc). Ninety-nine of these patients are female, the average age is 40,3 years. These patients were all explored by capillarmicroscopy.

Results. All patients (100%) with dermatomyositis showed the scleroderma capillaroscopic pattern, 70.8% of systemic sclerosis, 42.3% of undifferentiated connective, 30% of lupus disease, 31.2% of Sjögren's syndrome and one case (10%) of patients with rheumatoid arthritis also exhibited the same pattern.

Conclusions. Scleroderma capillaroscopic pattern is often present in systemic sclerosis and dermatomyositis. Furthermore, it has also been described in other autoimmune disease such as Sharp syndrome, patients with Raynaud's phenom- enon and UCTD may also exhibit this pattern. Therefore, capillarmicroscopy seems to be a useful tool for the early selection of those patients who are potential candidates for developing scleroderma spectrum disorders.

Poster 191

CASE SERIES OF EXTRAGLANDULAR MANIFESTATIONS OF PRIMARY SJÖGREN SYNDROME IN A UNIVERSITY HOSPITAL OF BOGOTÁ, COLOMBIA

Borda Samper C.*, Navarrete Motta L.E., Bernal Macias S., Fernández Ávila D.G., Diaz M.C., Gutierrez Davila J.M., González Rojas B.J.
Pontificia Universidad Javeriana - Hospital Universitario San Ignacio, Bogotá, Colombia

Background. Primary Sjögren syndrome (SSp) is an autoimmune disease characterized by inflammation of exocrine lacrimal and salivary glands. There is a small percentage of patients that present with extraglandular disease, including multisystemic organ involvement, and a broad spectrum of hematological abnormalities which increases the risk of hematologic malignancies. Extraglandular SSp is difficult to diagnose, due to its diverse form of presentation and its high prevalence in overlap syndromes. There is a high spectrum of disease, with no information regarding mortality nor severe organ involvement. The main objective of this work is to describe a case series of patients with extraglandular involvement of SSp and offer a global view of the large spectrum of disease, its characteristics and highlight the importance of these manifestations related with SSp.

Patients and methods. During the month of May of 2022, we conducted a retrospective study of case series in which all hospitalized patients with diagnosis of SSp (according to classification criteria ACR/EULAR 2016) with extraglandular manifestations were included. We selected patients who were treated as inpatient in a university hospital in Bogotá-Colombia during a 10-month period (August 2021 to mid-May 2022). We analyzed medical records of these patients, extracting our variables.

Results. We documented 20 patients with SSp diagnosis with extraglandular involvement. The average median age was 59 years. 18 patients were women (90%). The most frequent extraglandular manifestation was nervous system in 11 patients (55%), 6 who had central involvement and 5 peripheral manifestations, followed by pulmonary manifestations (n=9, 45%), lymphadenopathies (n=7, 35%), and articular involvement (n=8, 40%). Usual interstitial pneumonia was the most common lung involvement. Two cases associated with lymphoma (10%) were documented. Additionally, 2 patients had antiphospholipid syndrome (aPL) with a triple positive aPL antibody profile. Regarding our laboratory findings, 85% (n=17) were anti-Ro/SSA positive and 25% (n=5) were anti-La/SSB positive, all of them with high titers of antinuclear antibodies, 45% of these patients (n=9) with speckled pattern. Complement (C3 and C4) consumption was found in 35% of cases (n=7). Regarding treatment, the medication most commonly used were glucocorticoids (n=16, 80%), followed by antimalarial treatment (n=14, 70%), cyclophosphamide (n=5, 25%) and rituximab (n=2, 10%). Within these group of patients, during their inpatient assessment, mortality rate was found to be 10% (n=2), both of them associated with bacteriemia.

Conclusions. We present clinical information of a case series of patients with SSp with extraglandular involvement, who required inpatient assessment in a high complexity institution in Colombia. The main extraglandular manifestation was central and peripheral nervous system involvement and the most frequent treatment prescribed in our institution were corticosteroids. We documented a 10% inpatient mortality rate. More studies are needed with larger sample size in order to provide more accurate characteristics of this population.

ASSOCIATION OF SS WITH OTHER DISEASES: IMPLICATIONS IN DISEASE BIOLOGY AND MANAGEMENT

Poster 2

SEX HORMONES AND RELATED COMORBIDITIES ARE ASSOCIATED WITH DEVELOPING SJÖGREN'S DISEASE: A POPULATION-BASED NESTED CASE-CONTROL STUDY

McCoy S.*[1], Hetzel S.[1], Vanwormer J.[2], Bartels C.[1]
[1]*University of Wisconsin, Madison, USA,* [2]*Marshfield Clinic Research Institute, Marshfield, USA*

Sjögren's is the most female predominant systemic autoimmune disease, with peak onset around perimenopause. Estrogen appears to protect against SjD when compared to controls with dryness, but prior studies lack a healthy control comparison group and granular details about exogenous and endogenous exposures. Our objective was to determine how specific endogenous and exogenous hormone exposures contribute to Sjögren's risk.

We performed a retrospective case-control study of adult women, nested within a defined population of patients in north-central Wisconsin. Sjögren's cases one Sjögren's diagnosis by a rheumatology provider or two Sjögren's diagnoses > 4 weeks apart from a non-rheumatology provider. Those with overlapping autoimmune diseases were excluded. Three controls were included for each Sjögren's case and were matched on age. We calculated a modified composite estrogen score (mCES) for each patient, with one point for: 1) body mass index (BMI) ≥30 kg/m2, 2) menopause ≥55 years, 3) hormone replacement therapy >90 days, and 4) hysterectomy, which was considered a marker of high estrogen because hysterectomy is most often performed for fibroids and post-surgical management often includes exogenous hormones. Risk ratios for Sjögren's were reported, adjusted for demographics.

Of 546 Sjögren's cases and 1,637 age-matched controls, mCES was not significantly associated with SjD in adjusted models (Figure 1). The top individual hormone exposures associated with Sjögren's included estrogen replacement therapy (ERT; RR 1.78 [95% CI 1.47-2.14]), polycystic ovarian syndrome (1.65 [1.28-2.12]) and hysterectomy without bilateral oophorectomy (1.51 [1.13-2.03]) (Figure 2). We identified comorbidities preceding Sjögren's including fibromyalgia, pulmonary disease, diabetes, lymphoma, osteoporosis, peripheral vascular disease, and renal disease (Figure 3). Taking comorbidities into account, we developed a predictive model for Sjögren's that included fibromyalgia (2.50 [1.93-3.25]), osteoporosis (1.84 [1.27-2.66]), hormone replacement therapy (HRT) (1.61 [1.22-2.12]), diabetes (0.27 [0.13-0.50]), and body mass index (BMI) (0.97 [0.95-0.99]) (Table I).

We report a novel algorithm to improve identifying patients at risk for SjD and describe sex hormone association with SjD. Finally, we report new comorbidities associated with SjD decrease, BMI and diabetes, and increase, lymphoma and osteoporosis.

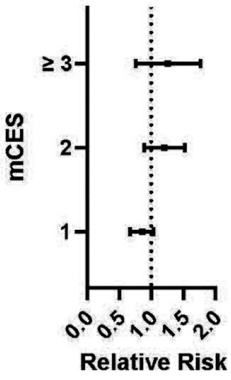


Fig. 1. Relative risk of Sjögren's by modified momposite estrogen score.
Our primary exposure of interest was the mCES. Given few patients with mCES of 4 (n=8), we combined mCES levels 3 and 4. Patients with mCES of ≥3 were older and h ad different medical insurance (*e.g.* more medicare; Table II). Other co-variates, including race, ethnicity, tobacco use, and alcohol use were not significantly different between-mCES levels. BMI was highest in mCES ≥3 with 85% of these subjects categorized as obese, compared to mCES=0 with 0%, mCES=1 with 55% and mCES=2 with 63%.

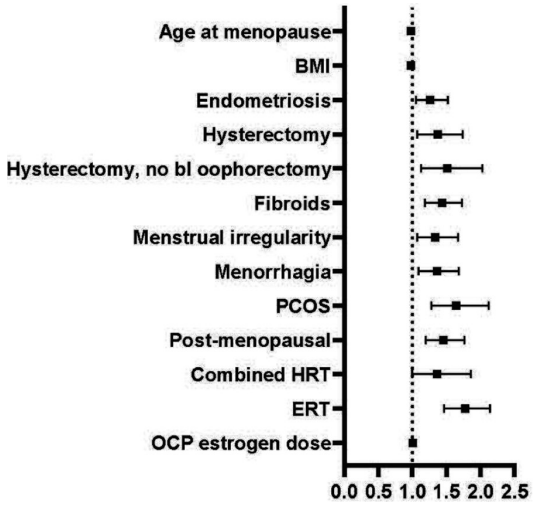


Fig. 2. Risk ratio of Sjogren's with endogenous and exogenous sex hormone exposure. BMI: body mass index; PCOS: polycystic ovarian syndrome; HRT: hormone replacement therapy; ERT: estrogen replacement therapy; OCP: oral contraceptive pill;multivariable model adjusted for age, race, ethnicity, and insurance. All reported values have adjusted $p \leq 0.05$.

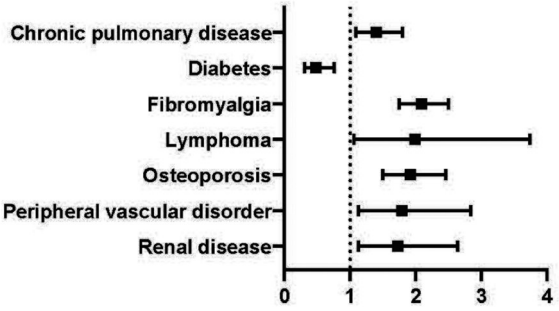


Fig. 3. Risk ratio of Sjögren's with baseline comorbidities.
Multivariable model adjusted for age, rae, and insurance All reported values have adjusted $p \leq 0.05$.

Poster 4

(withdrawn by authors)

Poster 10

MALIGNANCIES AMONG PATIENTS WITH SJÖGREN'S SYNDROME

Szántó A.*, Aradi Z., Orosz V.
University of Debrecen, Faculty of Medicine, Division of Clinical Immunology, Debrecen, Hungary

Background. Increased lymphoma risk is well-known in patients with Sjögren's syndrome (SS), however, data concerning the prevalence of solid tumors are sparse. The aim of this study was to evaluate the occurrence of malignancies in patients followed-up because of SS.

Methods. Data of 374 SS patients were retrospectively analyzed. Demographic data, autoantibodies, blood parameters and preceding immunosuppressive treatment of patients were evaluated.

Results. Malignant disease occurred in 25 patients (6.6%). Twenty-four age and gender-matched SS patients without malignancies served as controls. Solid tumor developed in 18 patients (4.8%): types of tumors were urogenital (n=8), breast (n=6) and gastrointestinal (n=4) cancers. Urogenital tumors were clear-cell kidney cancer (n=3), transitiocellular urinary bladder cancer (n=2), cervix cancer (n=2) and prostate cancer (n=1). Seven patients (1.8%) suffered from hematological malignancy (1 myeloproliferative and 6 lymphoproliferative).

Upon diagnosis of SS, in patients with future hematological diseases, anti-Ro/SS-A positivity was significantly more frequent and RF concentration was significantly higher than either in controls (p=0.026 and 0.024, respectively) or in patients with solid tumors (p=0.02 each).

Hematocrit (0.36±0.03 vs 0.39±0.03, p=0.035) and platelet counts (178.71±59.8 vs 263.95±58.5 G/L, p=0.029) at diagnosis were significantly lower in patients later suffering from hematological malignancies, compared to the control group. No significant correlation was found between the previous immunosuppressive treatment and the development of either hematological or solid malignant disease.

Conclusions. Based on our results, unlike in the general Hungarian population, in patients with SS, most frequent tumors are urogenital and breast cancers. Although there are well-defined biomarkers indicating the risk of lymphoma development, such biomarkers for solid tumors do not exist. In Hungary, there is a population-based screening for breast cancer, but screening for urogenital neoplasms also seems to be reasonable during the follow-up of patients with SS.

Poster 29

SALIVARY GLANDS ULTRASONOGRAPHY VALUE IN RHEUMATOID ARTHRITIS PATIENTS WITH DRY SYNDROME

Rabault R.*, Jousse-Joulin S., Saraux A., Courtois-Communier E., Cornec D., Guellec D., Marhadour T., Houssais C., Tison A., Devauchelle-Pensec V.
CHRU Cavale Blanche, Brest, France

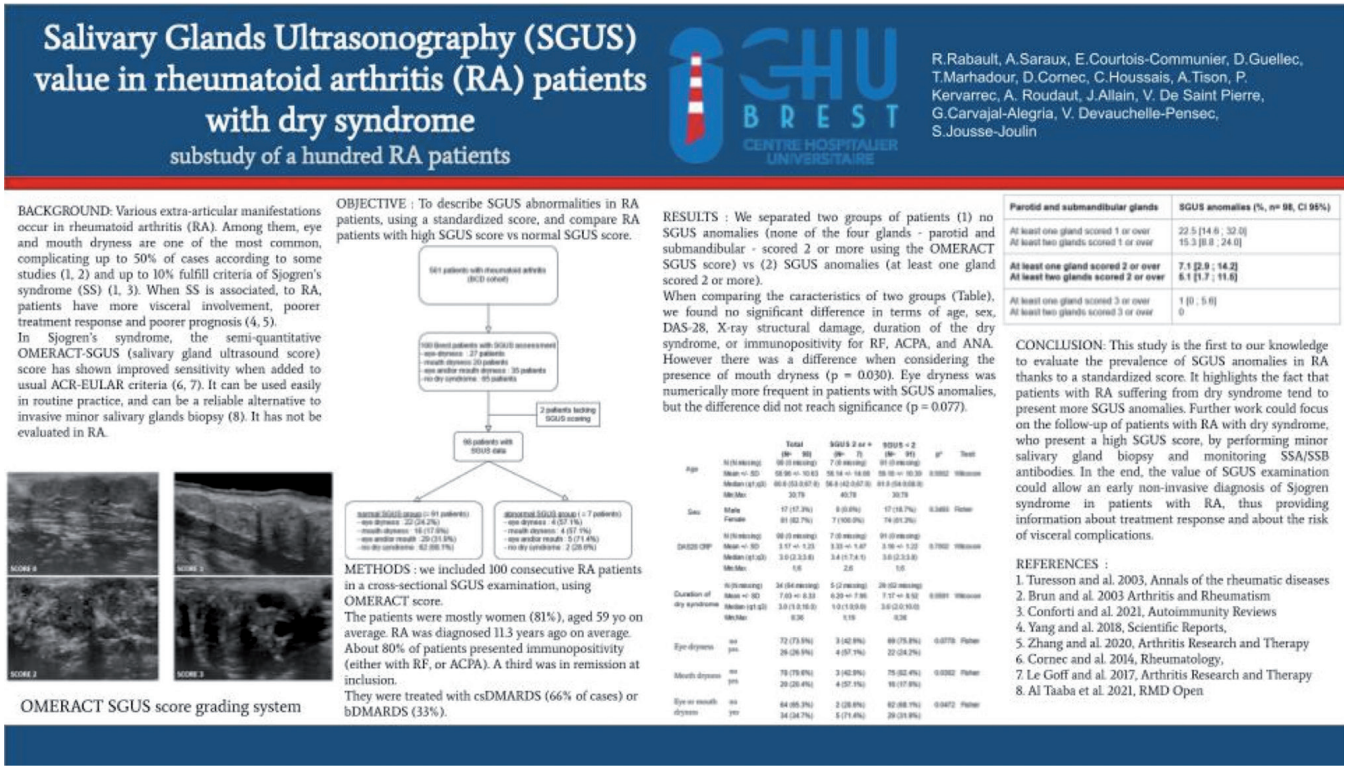
Background. The prevalence of salivary glands ultrasound (SGUS) abnormalities in Sjögren's syndrom (SS) is well described (2). However, the prevalence is still unknown in rheumatic inflammatory conditions such as rheumatoid arthritis (RA).

Objectives. The main objective of this study was to describe the prevalence of SGUS parenchymal structural abnormalites in patients with RA. Secondary objectives were: i) to study correlation between disease duration and the SGUS OMERACT score and ii) to study correlation between duration of sicca syndrome and the SGUS OMERACT score.

Methods. 561 patients with RA satisfying ACR/EULAR 2010 classification criteria were included in 10 French centers in a prospective cohort to compare joint ultrasonography and clinical follow-up. Cross-sectional SGUS examination (parotid and submandibular) was performed in a substudy of this cohort. The new OMERACT-SGUS scoring system (1) was used and clinical, biological, immunological and radiological data were collected. 100 patients agreed to be included in this sub-study of BCD, and a total of 98 SGUS patients' data were evaluated. Most patients were women (81%), mean age 59 years, with time from RA diagnosis of 11 years on average. The mean CRP-DAS-28 at baseline was at 3.2 with a third of patients in remission at inclusion. Anti-CCP antibody or RF was positive in 92 patients (92%). 27 patients (27%) complained of eye dryness and 20 (20%) of mouth dryness. 12 (12%) suffered from both. Two thirds of patients benefited from csDMARDs, with a third treated with bDMARDs. 33 (33%) also benefited from a corticosteroid treatment.

Results. Among 98 patients, 22 (22.5%) had at least one salivary gland scored grade 1 or more, this number was reduced at 18 (18.4%) when considering only the parotid glands. 7 patients (7.1%) had at least one salivary gland score grade 2 or more, with a number reduced to 4 (4.1%) when considering only the parotids. Only one patient (1%) had a parotid gland scored 3. In the 7 patients presenting significant abnormalities in SGUS (grade 2 or more), 5 patients had either dry eye or dry mouth symptoms (71.4%).

Conclusions. Our findings suggest that 7% of RA patients present significant SGUS abnormalities according to OMERACT scoring system, associated with clinical sicca syndrome in 71% of cases. There was no significant association between the duration of rheumatoid arthritis and the grade in OMERACT score (Spearman coefficient for correlation -0,028, p=0.99). There was also no significant association found between the duration of sicca symptoms and the OMERACT score (Spearman coefficient for correlation 0,025, p=0.89). This study highlights the importance of SGUS assessment in RA sicca patients to improve monitoring and follow-up in routine clinical practice.



Poster 33

SIGNIFICANCE OF RHEUMATOID FACTOR ISOTYPES IN PATIENTS WITH SJÖGREN'S SYNDROME WITH JOINT COMPLAINTS OF DIFFERENT ETIOLOGY

Aradi Z.*[1], Nagy G.[2], Szántó A.[1]
[1]University of Debrecen Faculty of Medicine, Division of Clinical Immunology, Debrecen, Hungary, [2]University of Debrecen, Institute of Laboratory Medicine, Debrecen, Hungary

Objectives. Examining rheumatoid factor (RF) isotypes among patients with Sjögren's syndrome (SS) and cases associated with polyarhthritis and rheumatoid arthritis, we aimed to determine whether there is a difference between the RF isotype patterns of the groups of SS patients with joint complains of different origin.
Methods. We compared 3 patient groups: patients with Sjögren's syndrome without joint complaints, patients with Sjögren's syndrome associated with rheumatoid arthritis and primary SS with polyarthritis as an extraglandular manifestation. Patients were also grouped according to their IgG levels (normal vs. high).
Results. Based on our results, we can see that high total IgG levels are associated with significantly higher RF median levels (29 vs. 129 IU/ml, respectively, $p<0.001$). This is true for all three RF isotypes, with a significant difference for RF IgA. Examining the 3 patient groups, the highest RF levels were found in the group without joint complaints (231.85 IU/ml), RF levels were moderate in polyarthritis (141.58 IU/ml), and the lowest values were measured in the group with associated rheumatoid arthritis (103.36 IU/ml). However, the difference was significant only regarding IgA isotypes between patients free of articular pain and patients with associated rheumatoid arthritis ($p=0.002$).
Conclusions. In patients with Sjögren's syndrome, high RF levels might contribute to hypergammaglobulinaemia. High RF levels are rather the consequence of Sjögren's syndrome activity than signs of a co-existing rheumatoid arthritis. In patients with joint involvement of Sjögren's syndrome, high RF IgA isotype tends to support the polyarthritis activity of Sjögren's syndrome. If associated rheumatoid arthritis is suspected, other markers (e.g., antibodies to citrullinated peptide) may be more helpful in the daily routine for distinguishing between the two types of joint complaints.

Oral communication 56

CHARACTERIZATION OF THE MUSCLE INFLAMMATORY INFILTRATE BY HYPERION TECHNOLOGY IN INCLUSION MYOSITIS ASSOCIATED WITH SJÖGREN'S SYNDROME, COMPARISON WITH SPORADIC FORMS

Quéré B.*[1], Bourhis A.[2], Hemon P.[3], Pers J.O.[3], Noury J.[1], Marcorelles P.[2], Guellec D.[2], Devauchelle-Pensec V.[1], Allenbach Y.[4], Kuberaka M.[4], Leonard-Louis S.[4], Sanges S.[5], Maurage C.[6], Nocturne G.[7], Adam C.[7], Meyer A.[8], Lannes B.[8], Urbanski G.[9], Croue A.[9], Uguen A.[2], Cornec D.[1]
[1]Hospital Cavale Blanche, Brest, France, [2]Hospital Morvan, Brest, France, [3]LBAI, UMR 1227, Brest, France, [4]Hospital Pitié-Salpêtrière, Paris, France, [5]Hospital Huriez, Lille, France, [6]Hospital Degand, Lille, France, [7]Hospital Bicêtre, Kremlin-Bicêtre, France, [8]Hospital Civil, Strasbourg, France, [9]Hospital, Angers, France

Introduction. Within the group of inflammatory myopathies, Inclusion-Body Myositis (IBM) is a distinct pathology with clinical and histological features very different from other entities. In the literature, an association between primary Sjögren's syndrome (pSS) and IBM has been demonstrated by several works. The aim of our study was to characterize the inflammatory infiltrate of IBM associated with pSS, comparing it to that of patients with sporadic forms of the disease.
Materials and methods. We conducted a translational research project, from formalin-fixed and paraffin-embedded muscle biopsies of patients from six expert centers. Fourteen patients with inclusion myositis associated with Sjögren's syndrome (IBM-pSS) were included and compared with seven patients with sporadic inclusion myositis (IBMs). HYPERION imaging mass cytometry (IMC) technology was used for study of the inflammatory infiltrate by multiplex immunostaining (37 markers) (Figure 1). After histological comparison in IHC, supervised and unsupervised statistical analyses were performed in the comparison of IMC data between IBM- pSS and IBMs patients.

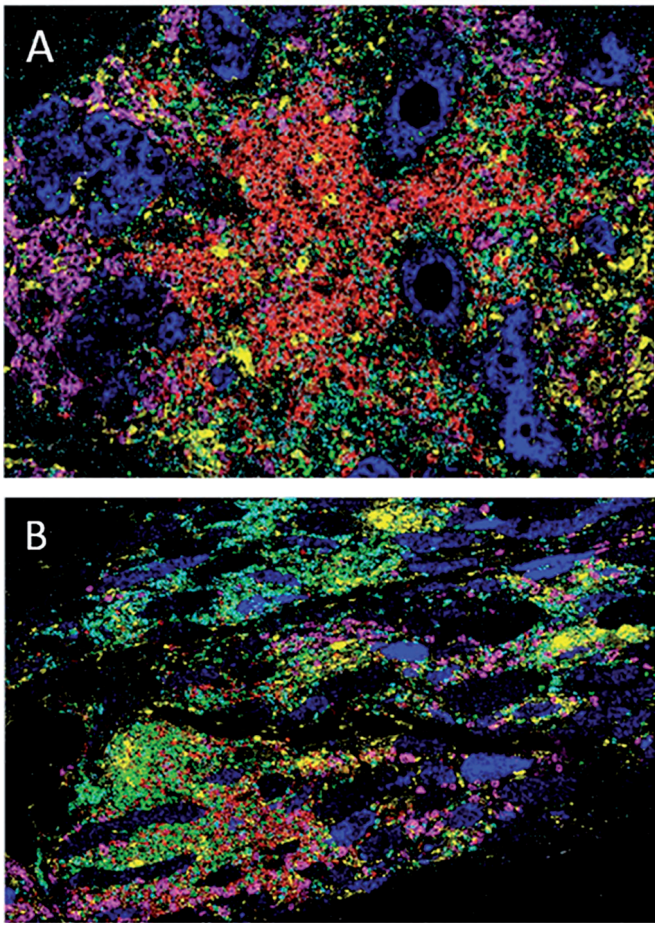


Fig. 1. Example of markers of multiplex immunostaining in salivary glands (A) and in muscle (B).

Results. Biopsies from IBM-pSS patients showed more inflammatory infiltrate than those from IBMs patients with a relative surface occupied by inflammatory infiltrate of 4.8% versus 1.4% respectively. Macrophages and T lymphocytes were the predominant populations within the muscle inflammatory infiltrate in both groups (with a median of 52.7% and 35.0% respectively in the IBMs group and 49.1% and 17.8% in the IBM + pSS group). The proportion of plasma cells ($CD138^+$ $CD38^+$ CD27+) in the IBM + pSS group was higher than in the IBMs group (median 14.7% and 8.5%, respectively), as was the proportion of B cells, which was higher in the IBM + pSS group (median 3.1% and 0.5%, respectively). Concerning T lymphocytes (LT), CD8+ LTs predominated compared to $CD4^+$ LTs in both groups.
Discussion. Compared to IBM patients, infiltrate in IBM + pSS patients is globally characterized by a predominance of same cell types as in IBM patients with, as described in the literature of IBM patients, a predominance of macrophages and T lymphocytes. However, infiltrate seems to be more abundant in IBM + pSS patients, in who there is also an increase in proportion of B lymphocytes and plasma cells compared with IBMs patients. This muscle infiltrate of IBM + pSS patients presents characteristics that may be similar to the lymphophasmacytic infiltrate observed in the salivary glands of pSS patients.
Conclusions. This first study using IMC in muscles, suggests an increase in the proportion of B lymphocytes and plasma cells in the inflammatory infiltrate of IBM + pSS patients, compared with patients with sporadic forms of the disease.

Poster 57

MYOSITIS IN PATIENTS WITH PRIMARY SJÖGREN'S SYNDROME: DATA FROM A FRENCH NATIONWIDE SURVEY

Houssais C.[1], Noury J.[1], Allenbach Y.[2], Gallay L.[3], Quéré B.*[1], Assan F.[4], Benveniste O.[2], Broner J.[5], Duffau P.[6], Espitia A.[7], Grasland A.[8], Sanges S.[9], Hachulla E.[9], Hayem G.[4], Le Guern V.[10], Martis N.[11], Mariampillai K.[2], Mulleman D.[12], Nocturne G.[13], Mariette X.[13], Meyer A.[14], Devauchelle-Pensec V.[1], Cornec D.[1], Guellec D.[1]
[1]Hospital Cavale Blanche, Brest, France, [2]Hospital Pitié-Salpêtrière, Paris, France, [3]Hospital Herriot, Lyon, France, [4]Hospital Ambroise Paré, Boulogne-Billancourt, France, [5]University Hospital, Nimes, France, [6]University Hospital, Bordeaux, France, [7]Hospital Hötel-Dieu, Nantes, France, [8]Hospital Mourier, Colombes, France, [9]Hospital Huriez, Lille, France, [10]Hospital Cochin, Paris, France, [11]Hospital L'Archet, Nice, France, [12]Hospital, Tours, France, [13]Hospital Kremlin, Kremlin-Bicêtre, France, [14]Hospital Civil, Strasbourg, France

Rational. Myositis is an uncommon manifestation of primary Sjögren's syndrome (pSS). Gradation of muscle involvement using the ESSDAI score does not require biopsy-proven myositis or immunological investigations. The objective was to investigate the nature of inflammatory muscle involvement in pSS-associated myositis.
Methods. We conducted a French nation-wide survey between May 2017 and December 2018. Patients with physician-based diagnosis of pSS and myositis were included.
Results. 60 cases were identified. Patients were mostly female (86.7%) and pSS classification criteria were met in 71.7%. Myalgia was identified in 59.6%, muscular weakness in 56.4% and elevated CK-levels in 74.5% cases. Muscle biopsy was performed in 83.3% patients and showed inflammatory lesions in 80% of cases. An associated condition likely to explain myositis was identified in 31 patients: typical dermatomyositis rash (n=8), anti-RNP antibodies (n=11), myositis specific antibodies (n=10), and systemic lupus erythematosus, scleroderma or ANCA associated vasculitis specific antibodies in favor of an overlap syndrome (n=7). Among the 29 patients without associated condition likely to explain myositis, 17 had a biopsy-proven myositis, showing histopathologic features consistent with IBM in 5 cases. Worsening of muscular involvement despite treatment was reported in 4 of these 5 patients. Comparative analysis showed a lower ESSDAI (p=0.001) among patients without an associated condition.
Conclusions. In most cases of concurrent pSS and myositis, inflammatory muscle involvement is explained by a context of overlap syndrome or has a histological pattern consistent with IBM. Extensive investigations appear to be necessary in these patients, in order to avoid misclassification and/or ineffective treatments.

Poster 72

PRIMARY SJÖGREN'S SYNDROME PRESENTING AS THROMBOTIC THROMBOCYTOPENIC PURPURA IN A MALE PATIENT WITH PREVIOUS KIKUCHI-FUJIMOTO DISEASE

Silvério-António M.[1], Alves Ribeiro L.[2], Medeiros J.[2], Romão V.C.*[1], Fonseca J.E.[1]
[1]Rheumatology Department, Hospital de Santa Maria, Centro Hospitalar Universitário Lisboa Norte, Lisbon Academic Medical Centre. Rheumatology Research Unit, Instituto de Medicina Molecular, Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal, [2]Hematology and Hematopoietic Cell Transplantation Department, Hospital de Santa Maria, Centro Hospitalar Universitário Lisboa Norte, Lisbon Academic Medical Centre, Lisbon, Portugal

A 28-year-old Caucasian man, with a past medical history of isolated self-limited cervical Kikuchi-Fujimoto Disease (KFD) 9 years before, presented with a 5-day history of fatigue, fever and mucocutaneous pallor. Two days later, he developed headache, progressive weakness of right upper limb, confusion and slurred speech. The patient had mild xerostomia and extensive teeth lack. Laboratorial investigation showed intravascular haemolytic anaemia (haemoglobin [Hb] 7.0 g/dL, total bilirubin 1.7 mg/dL, lactate dehydrogenase [LDH] 1400 IU/L, haptoglobin <10 mg/dL) and thrombocytopenia (platelets 11,000/mm^3). Blood smear revealed anisocytosis and poikilocytosis with schistocytes and polychromatic erythrocytes. Erythrocyte sedimentation rate was 94 mm/1sth and C-reactive protein was normal range.
Creatinine was mildly raised at 1.14 mg/dL and general biochemistry was otherwise unremarkable. Prothrombin time, partial thromboplastin time, fibrinogen and D-dimers were normal. Cultures and serology did not reveal any acute infection. Cranial and thoraco-abdominal CT scans were unremarkable. A diagnosis of thrombotic thrombocytopenic purpura (TTP) was suspected (PLASMIC score of 6). The patient started daily plasma exchange (PEX) with resolution of neurologic defects and laboratorial improvement. The TTP diagnosis was subsequently confirmed by a severe deficiency of ADAMTS13 activity (<1%) and anti-ADMATS13 IgG autoantibodies (>95 UI). At 7th day of PEX there was a laboratorial disease relapse treated with high-dose glucocorticoid therapy and rituximab. The patient had also positive ANA (1:320 speckled), anti-Ro-52 and anti-Ro-60 antibodies. He had a high clinical oral dryness score (CODS=7) and diminished unstimulated whole salivary flow rate at 0.1 mL/min. Schirmer's test (15mm/5'), ocular staining score (0) and tear break-up time were unremarkable. Salivary gland ultrasound revealed grade 2 changes in parotid glands. Salivary gland biopsy showed focal lymphocytic sialadenitis with a focus score <1/4 mm^2.
Steroids were tapered and discontinued after 6 months. At 2 months normalization of Hb, platelets, LDH and ADAMTS13 activity were observed and anti-ADAMTS13 auto-antibodies were negative. There were no signs of TTP relapse after one year of follow-up.
There are 16 reports of TTP associated with pSS: mostly female patients (14/16) and with SS diagnosis prior to TTP in less than 50%. Studies in systemic lupus erythematosus (SLE) and other autoimmune diseases suggest that older age and female sex are risk factors for TTP. Our case presents uncommon features, such as young age, male sex and presentation with the 5 typical clinical manifestations.
Only 10 case reports linked KFD with SS, mostly in women (9/10), with the KFD diagnosis generally preceding SS onset (7/10). As for SLE, patients with KFD and SS have a higher recurrence rate than reported for idiopathic forms (7/10 patients vs 3–4%). Our patient had some atypical features such as male gender and lack of recurrences.
This report presents the first association between these three clinical entities and highlights the possibility of atypical characteristics of TTP and KFD in patients with SS.

Poster 81

CHARACTERIZATION OF THE ASSOCIATION BETWEEN PRIMARY SJÖGREN'S SYNDROME AND SYSTEMIC LUPUS ERYTHEMATOSUS (PSS/SLE)

De Marchi G.[1], Baldini C.[2], Elefante E.[2], Manfrè V.[1], Navarro Garcia I.C.[2], Giovannini I.[1], Treppo E.[1], Zabotti A.[1], Quartuccio L.*[1], De Vita S.[1]
[1]Azienda Sanitaria Universitaria Friuli Centrale, Udine, Italy, [2]Rheumatology Unit, University of Pisa, Pisa, Italy

Objectives. To better characterize overlap syndrome Sjögren's syndrome + systemic lupus erythematosus (SLE/SS).
Methods. We evaluated all patients with SLE/SS overlap syndrome, afferent to two Italian rheumatology centers. Patient selection envisaged a first phase of patient reclassification by reapplying the pSS and SLE classification criteria (1, 2). Clinical, clinimetric, functional, ultrasound and histological data of the patients were compared with pSS and SLE patients.
Results. 45 patients with overlap syndrome (F: M 44: 1) were compared with 79 pSS (F: M 72: 7) and 83 SLE (F: M 70:13) patients. They had younger at onset than pSS (35.18±10.77 vs. 53.68±11.41 years; $p<0.0001$) but older than the SLE group (35.18±10, 77 vs. 32.33±16.07 years; $p=0.044$). Compared to the pSS group, the SLE/SS patients had similar subjective oral and ocular sicca and Schirmer's test while unstimulated sialometry was more altered in the pSS group (82.3% vs. 35.6%; p 0.0001). There were no differences in relation to the parotid swelling (ever or persistent). SLE/SS patients had greater joint involvement (77.8% vs. 53.9%; $p=0.009$), mucocutaneous (60.0% vs. 13.2%; $p<0.0001$), renal (27, 3% vs 5.3%; $p=0.001$) and serotic (31.1% vs. 3.9%;$p<0.0001$) compared to pSS, while the latter presented thyroid disease (39.2% vs. 22.2 %; $p=0.053$). Ultrasound changes in the major salivary glands were prevalent in pSS patients compared to SLE/SS patients. In contrast, histological changes were similar between SLE-SS patients and pSS patients, both in terms of compatible biopsy (83.3% vs. 85.2%; $p=0.518$) and biopsy grade ($p=0.496$). SLE/SS patients have a higher prevalence of anti-SSA (100.0% vs. 78.5%; $p<0.0001$) and a lower positive RF (19.5% vs. 50.6%; $p=0.008$) and serum cryoglobulins (4.8% vs. 25.3%; $p=0.035$).
The ESSPRI index was comparable between cases and controls while ESSDAI was significantly more altered in overlap patients. In comparison with SLE patients, the extra-glandular manifestations were comparable, with the exception of a greater serositis involvement in the overlap group (31.1% vs. 15.7%; $p=0.041$). SLE/SS patients had a higher prevalence of anti-SSA (100.0% vs. 31.3%; $p<0.0001$) anti-SSB antibodies (57.8% vs. 7.2%; $p<0.0001$), C4 reduction (40.0% vs. 19.3%; $p0.011$) and the reduction in white blood cell count (48.9% vs. 28.9%; $p=0.025$) compared to SLE. The SLEDAI-2k activity index was higher among overlap patients ($p=0.009$).
Conclusions. Our data support the hypothesis that patients with SLE/SS represent a distinctive clinical entity, rather than the mere overlap of two independent connective tissue diseases. Faced with a clinical and histological involvement comparable to pSS, these patients are characterized by less ultrasound involvement and a reduced presence of FR and cryoglobulins; it is unclear whether this could translate into a lower lymphoproliferative risk. Clinical extraglandular activity appears globally superior to pSS and at least comparable to SLE, including renal involvement, and this could stimulate new and more targeted therapeutic approaches in these patients.

Poster 102

CLINICAL AND HISTOLOGICAL FEATURES OF PATIENTS WITH PRIMARY SJÖGREN SYNDROME AND AUTOIMMUNE THYROIDITIS: A NATIONAL MULTICENTRIC CROSS-SECTIONAL STUDY

Celia A.I.*[1], Colafrancesco S.[1], Villa M.[1], Gattamelata A.[1], Izzo R.[1], Giardina F.[1], Simoncelli E.[1], Mastromanno L.[1], Baldini C.[2], Bartoloni Bocci E.[3], Carubbi F.[4], Quartuccio L.[5], Orlandi M.[6], Gerli R.[3], Giacomelli R.[7], De Vita S.[5], Alessandri C.[1], Conti F.[1], Priori R.[8]
[1]Rheumatology Unit, Department of Clinical Internal, Anaesthesiological and Cardiovascular Sciences, Sapienza University of Rome, Rome, Italy, [2]University of Pisa, Pisa, Italy, [3]University of Perugia, Perugia, Italy, [4]University of L'Aquila, L'Aquila, Italy, [5]University of Udine, Udine, Italy, [6]University of Florence, Florence, Italy, [7]Campus Biomedico University of Rome, Rome, Italy, [8]Saint Camillus International University of Health Science, UniCamillus, Rome, Italy

Objectives. Autoimmune thyroiditis (AT) is frequently associated with primary Sjögren syndrome (pSS) and the high coexistence seem to suggest a similar pathogenic background. The aim of this study was to assess the prevalence of AT in a large multicentric cohort of patients with pSS and to characterize the clinical-serological phenotype of this subgroup of patients.
Methods. The prevalence of AT was evaluated on a multicentric Italian cohort (Italian Research Group on Sjögren's syndrome - GRISS) of patients with pSS (AECG criteria). Patients were divided in two groups, with (group 1) or without (group 2) AT. Most relevant clinical [xerophthalmia, xerostomy, arthralgia, extraglandular involvement, purple, lymphoma, use of DMARDs, coeliac disease (CD) and fibromyalgia (FM)] and serological features (ANA, anti-Ro/SSA, anti-La/SSB, rheumatoid factor (RF), hypergammaglobulinemia, leukopenia, hypocomplementemia) were compared between the two groups. For the univariate analysis, Mann-Whitney and Chi-square tests were used. To account for most relevant clinical and serological features (age, sex, anti-Ro/SSA, anti-La/SSB, RF), multivariable logistic regression analyses was performed to confirm differences between groups 1 and 2. Logistic regression with interaction terms was performed to identify in group 1 patients more likely to experience specific outcomes.
Results. 2546 patients with pSS were enrolled. The prevalence of AT was (550/2546) 19.6%. In patients with AT a lower prevalence of lymphoma ($p=0.03$), male sex ($p=0.009$) and use of DMARDs ($p=0.016$) was detected;

Multivariable models	Lymphoma (NHL)		Celiac Disease		Fibromyalgia		Use of DMARDs	
	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value
Patients pSS & AT SS	**0.56** (0.29 – 1.05) ref	0.070 -	**1.87** (1.02 – 3.22) ref	0.022 -	**1.37** (1.09 – 1.73) ref	0.007 -	**0.69** (0.51 – 0.92) ref	0.012 -
Age	0.99 (0.97 – 1.00)	0.26	1.00 (0.97 – 1)	0.890	0.99 (0.98 – 1.00)	0.390	1.00 (1.00 – 1.01)	0.035
Sex Male Female	3.79 (0.47 – 0.95) ref	<0.0001 -	2.91 (0.00 – inf) ref	0.981 -	0.27 (0.13 - 0.58) ref	0.0006 -	1.75 (1.11 – 2.77) ref	0.015 -
Anti Ro/SSA Positive Negative	1.17 (0.62 – 2.22) ref	0.62 -	0.99 (0.53 – 1.87) ref	0.990 -	1.05 (0.83 – 1.33) ref	0.660 -	1.11 (0.84 – 1.46) ref	0.440 -
Anti-La/SSB Positive Negative	1.49 (0.9 – 2.49) ref	0.11 -	1.63 (0.9 – 2.49) ref	0.110 -	0.68 (0.53 - 0.87) ref	0.002 -	1.12 (0.87 – 1.45) ref	0.350 -
Rheumatoid Factor Positive Negative	4.17 (2.3 – 7.36) ref	<0.0001 -	0.39 (2.3 – 7.36) ref	0.001 -	0.97 (0.78 – 1.2) ref	0.807 -	1.39 (1.1 – 1.75) ref	0.005 -

Fig. 1. (Poster 102).

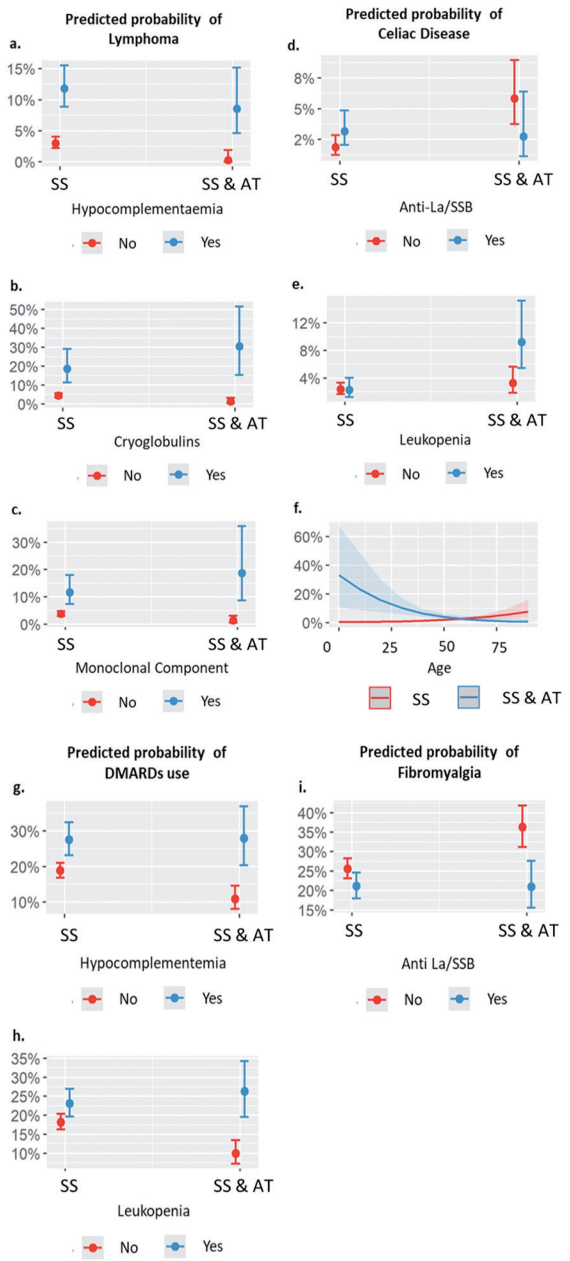


Fig. 2.

conversely, a higher prevalence of FM (p=0.0006), CD (p=0.004) and hypergammaglobulinemia (p=0.018) was identified. Multivariable analysis confirmed a higher prevalence of FM and CD and a lower use of DMARDs in patients with pSS and AT (Figure 1). In pSS and AT, the prevalence of lymphoma was higher in those with hypocomplementemia (p=0.050), cryoglobulins (p=0.009) and monoclonal component (p=0.018) (Figure 2 a-c). In the same subgroup, the predicted probability of CD was higher in those without anti-La/SSB (p=0.027) and with leukopenia (p=0.035) (Figure 1 d-e) and decreased over age (p<0.0001) (Figure 1 f). Finally, in pSS and AT the predicted probability to use DMARDs was higher in those with hypocomplementemia (p=0.030) and leukopenia (p=0.002) (Figure 1 g, h) while the predicted probability of FM was higher in patients with positive anti-La/SSB antibodies (p=0.041) (Figure 1 i).

Conclusions. This is the largest cross-sectional study describing the prevalence, phenotype and outcome of associated AT in patients with pSS. We confirm a high prevalence of AT in pSS. Such coexistence seems to identify a different subset of patients characterized by higher CD and FM. Although not confirmed by multivariable analysis, patients with pSS and AT appear to have a lower tendency to develop lymphoma and use DMARDs, possibly suggesting a better outcome.

Oral communication 104

SJÖGREN'S COEXISTING WITH AUTOIMMUNE DISEASES: A SYSTEMATIC LITERATURE REVIEW INFORMING THE INTERNATIONAL TASK FORCE OF SJÖGREN'S NOMENCLATURE AND CLASSIFICATION ROME 2022

Retamozo S.*[1], Baer A.N.[2], Brito-Zerón P.[3], Akpek E.[4], Baldini C.[5], Bootsma H.[6], Bowman S.J.[7], Dörner T.[8], Fisher B.A.[7], Hammitt K.M.[9], Laing Gibbard L.P.[14], Lieberman S.[15], Mariette X.[13], Pflugfelder S.C.[10], Sankar V.[16], Tzioufas A.G.[11], Ramos-Casals M.[12]

[1]Sjögren Syndrome Research Group, GRESS-AGAUR, Barcelona, Spain, [2]Johns Hopkins University School of Medicine, Baltimore, MD, USA, [3]Research and Innovation Group in Autoimmune Diseases, Millenium Balmes-Hospital CIMA Sanitas, Barcelona, Spain, [4]Ocular Surface Disease and Dry Eye Clinic, The Wilmer Eye Institute, The Johns Hopkins University School of Medicine, Baltimore, Maryland, USA, [5]Department of Clinical and Experimental Medicine, Rheumatology Unit, University of Pisa, Pisa, Italy, [6]Rheumatology and Clinical Immunology, University of Groningen, University Medical Centre Groningen, Groningen, Netherlands, [7]Rheumatology Department, University Hospitals Birmingham NHS Foundation Trust, Birmingham; Institute of Inflammation and Ageing, College of Medical and Dental Sciences, University of Birmingham; National Institute for Health Research Birmingham Biomedical, [8]Department of Rheumatology and Clinical Immunology, Charité-Universitätsmedizin Berlin, Berlin, Germany, [9]Sjögren's Foundation, Reston, Virginia, USA, [10]Department of Ophthalmology, Baylor College of Medicine, Houston, USA, [11]Department of Pathophysiology, School of Medicine, University of Athens, Athens, Greece, [12]Sjögren Syndrome Research Group, GRESS-AGAUR; Department of Autoimmune Diseases, ICMiD, Hospital Clínic; University of Barcelona, Barcelona, Spain, [13]Deparment of Rheumatology, Université Paris-Saclay, Hôpital Bicêtre, Assistance Publique-Hôpitaux de Paris, Paris, France, [14]Faculty of Dentistry, University of Toronto, Toronto ON, Canada, [15]Division of Rheumatology, Allergy, and Immunology, Stead Family Department of Pediatrics, Carver College of Medicine, University of Iowa, Iowa, USA, [16]Division Director for Oral Medicine, Department of Diagnostic Science Tufts University School of Dental Medicine, Boston, USA

Objectives. To evaluate current evidence on the epidemiological, clinical and immunopathological profile of Sjögren's disease (SjD) coexisting with other autoimmune diseases to inform the International Task Force of Sjögren's Nomenclature and Classification Rome 2022.

Methods. The MEDLINE, EMBASE and Cochrane databases were searched for studies characterizing the coexistence between SjD and other autoimmune diseases, including both systemic (systemic lupus erythematosus -SLE-, systemic sclerosis, rheumatoid arthritis, Still disease, sarcoidosis, inflammatory myopathies, antiphospholipid syndrome, anti-neutrophilic cytoplasmic autoantibody -ANCA- vasculitis, giant cell arteritis, IgG4-related disease-RD-, amyloidosis, spondyloarthritis -SpA-, Behcet disease) and organ-specific (autoimmune hepatitis -AIH-, primary biliary cholangitis -PBC-, autoimmune thyroiditis, multiple sclerosis -MS-, neuromyelitis optica spectrum disease -NMOSD-, celiac disease, inflammatory bowel disease -IBD, type I diabetes mellitus). Studies were eligible when the study population fulfilled the current classification criteria for both SjD (2002/2016) and for the co-existent autoimmune disease. The epidemiological, clinical and immunopathological features in SjD patients with a coexisting autoimmune disease were compared with those reported in the Sjögren Big Data Project that included 15,652 patients with primary SjD.

Results. We identified 134 studies including 2304 SjD patients with coexisting autoimmune diseases. The prevalence of women was higher in SjD co-existent with AIH and thyroiditis and lower in SjD co-existent with SpA and sarcoidosis (Figure 1). Mean age at SjD diagnosis was lower in SjD co-existent with SLE or MS and higher in SjD co-existent with ANCA vasculitis (Figure 2). The highest frequencies of specific phenotypic features were as follows: a positive minor salivary gland biopsy in SjD co-existent with autoimmune digestive diseases (IBD and celiac disease) (Figure 3), anti-Ro antibodies in SjD co-existent with NMOSD and inflammatory myositis (Figure 4), and anti-La antibodies in SjD co-existent with celiac disease and inflammatory myositis (Figure 5). In general, the highest frequencies of positive biopsy were found in co-existent diseases with lower frequencies of anti-Ro antibodies, and vice versa, reflecting the cardinal role of these phenotypic features in the fulfillment of Sjögren's classification criteria.

Conclusions. The epidemiological profile of SjD is clearly modified when another autoimmune disease is present, with age at diagnosis and sex distribution approaching that typically reported for the coexistent autoimmune disease. Anti-Ro antibodies were most prevalent in SjD co-existent with autoimmune diseases characterized by a higher frequency of Ro autoantibodies, such as NMOSD and inflammatory myopathies. The frequency of positive salivary biopsy and anti-Ro antibodies seems to be modulated by their key role in fulfilling the current SjD classification criteria.

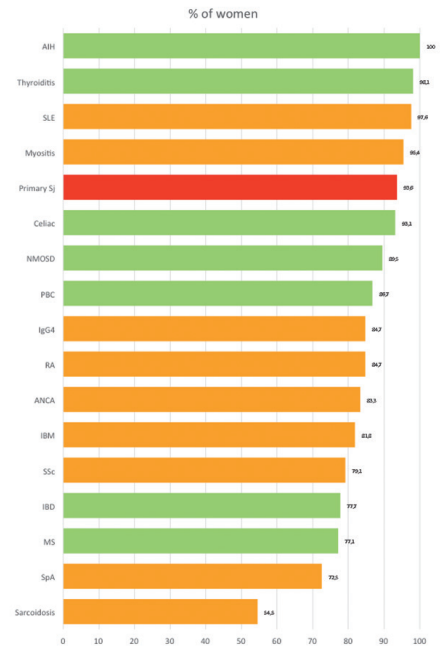


Fig. 1.

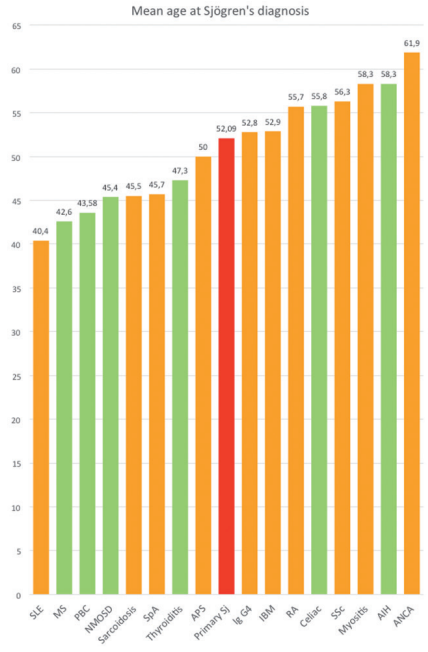


Fig. 2.

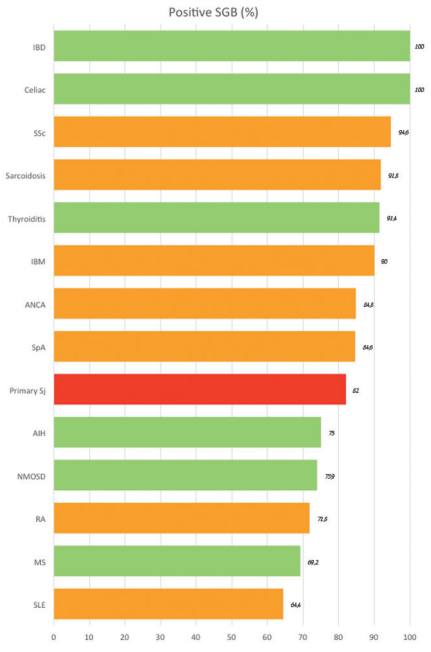


Fig. 3.

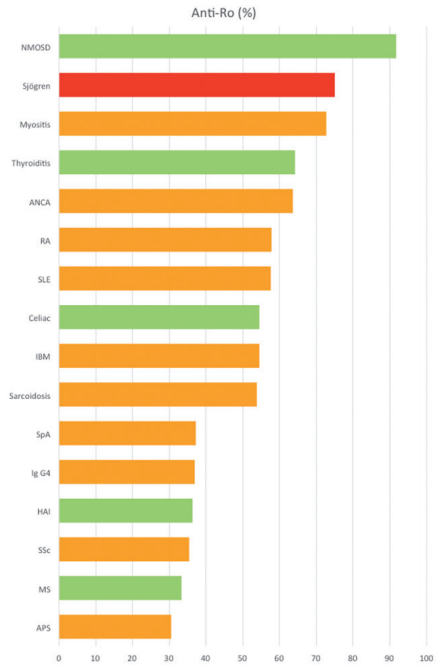


Fig. 4.

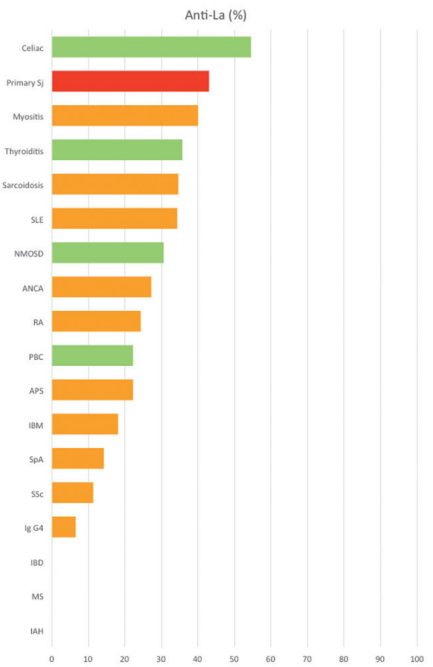


Fig. 5.

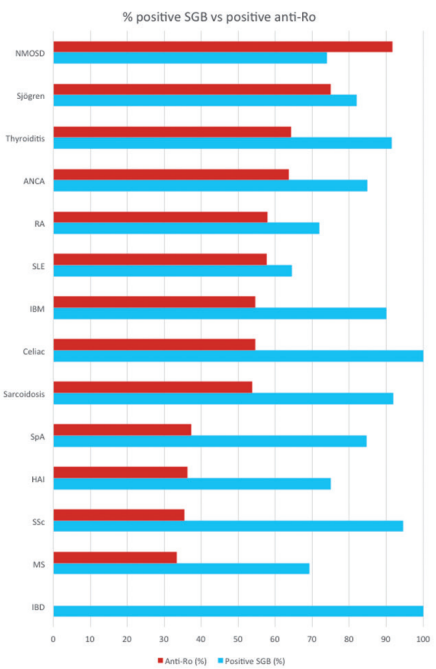


Fig. 6.

Poster 108

IMMUNOPATHOLOGICAL SCENARIOS DEFINING COEXISTENCE BETWEEN SJÖGREN SYNDROME AND SARCOIDOSIS

Flores-Chavez A.*[1], Ng F.[2], Alunno A.[4], Inanc N.[3], Abacar K.Y.[3], Feijoo-Masso C.[5], Seror R.[6], Hernandez-Molina G.[18], Hofauer B.[8], Pasoto S.G.[9], Robles A.[10], Akasbi M.[11], Brito-Zerón P.[12], Lopez-Dupla M.[13], Retamozo S.[14], Bandeira M.[15], Romão V.C.[16], Devauchelle-Pensec V.[7], Carubbi F.[4], Mariette X.[17], Ramos-Casals M.[14]

[1]Department of Autoimmune Diseases, ICMiD, Hospital Clínic, Barcelona, Spain, [2]The United Kingdom Primary Sjögren's Syndrome Registry, UK, [3]Marmara University, School of Medicine, Istanbul, Turkey, [4]Internal Medicine and Nephrology Unit, Department of Life, Health & Environmental Sciences, University of L'Aquila, and Department of Medicine, ASL 1 Avezzano-Sulmona-L'Aquila, Italy, [5]Internal Medicine, Hospital Parc Taulí, Sabadell, Spain, [6]Rheumatologye Department, Université Paris-Sud, Paris, France, [7]Cavale Blanche-University hospital, Brest, France, [8]University Hospital Klinikum Rechts der Isar, Germany, [9]Rheumatology Division, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [10]Internal Medicine, Hospital La Paz, Madrid, Spain, [11]Department of Internal Medicine Hospital Infanta Leonor, Madrid, Spain, [12]Research and Innovation Group in Autoimmune Diseases, Millenium Balmes-Hospital CIMA Sanitas, Barcelona, Spain, [13]Department of Internal Medicine, Hospital Universitari Joan XXIII, Tarragona, Spain, [14]Sjögren Syndrome Research Group, GRESS-AGAUR, Barcelona, Spain, [15]Rheumatology Department, Centro Hospitalar Universitário Lisboa Norte, Centro Académico de Medicina de Lisboa (CAML); Rheumatology Research Unit, Instituto de Medicina Molecular, Faculdade de Medicina, CAML, Lisboa, Portugal, [16]Lisboa, Portugal, [17]Rheumatologie Department, Université Paris-Saclay, Paris, France, [18]Immunology and Rheumatology Department, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Ciudad de Mexico, Mexico

Objectives. The recent 2016 classification criteria for Sjögren syndrome (SjS) include sarcoidosis as an exclusion criterion for the diagnosis of the disease. However, several studies have supported a true coexistence between the two diseases with nearly 30 cases being reported.

Methods. Members of the Sjögren Big Data Project Consortium were contacted searching for potential cases of coexistence between SjS and sarcoidosis seen in daily practice. Inclusion criteria were the fulfilment of the current classification criteria both for SjS (2016 ACR/EULAR) and sarcoidosis (WASOG). A combination of non-caseating granulomas (NCG, in non-exocrine organs) with focal lymphocytic sialadenitis (FLS) and/or positive anti-Ro antibodies was considered a definitive immunopathological scenario of coexistence. Since granuloma may be observed in patients with SjS, patients with defined SjS and isolated granuloma on labial biopsy without any other signs of sarcoidosis were not included.

Patients. We received the data from 49 cases that were evaluated for inclusion in the study: 7 were excluded after confirming the lack of fulfilment of the 2016 SjS criteria. Therefore, a total of 42 patients were included in the study (36 women, with a mean age of 53.1 years at diagnosis of SjS and of 51.6 years at diagnosis of sarcoidosis). In 16 patients, SjS was diagnosed first, in 15 sarcoidosis was the first disease diagnosed, and in 11 the two diseases were diagnosed concomitantly. We had histopathological confirmation of sarcoidosis in all cases but 4, while for SjS, a minor salivary gland biopsy was carried out in 22 cases showing FLS in 19 (86%). SjS-related autoantibodies included anti-Ro in 29 (69%) and anti-La in 16 (38%). Elevated serum angiotensin-converting enzyme was reported in 12/29 (41%) cases, and hypercalcemia in 5 (12%) cases.

Organ-specific involvement of sarcoidosis defined according to the WASOG criteria included hilar/mediastinal enlarged lymph nodes in 29 (69%) cases, pulmonary involvement in 19 (45%), cutaneous involvement in 11 (26%), extrathoracic lymphadenopathy in 10 (24%), ocular involvement in 7 (17%), liver involvement in 6 (14%) and bone/joint involvement in 6 (14%). Cardiac sarcoidosis was diagnosed in 4 (10%) cases and neurosarcoidosis in 2 (5%). Sarcoidosis therapy included corticosteroids in 25 (59%) cases, oral immunosuppressants in 10 (24%) and biological therapies in 4 (10%, two patients received adalimumab and 2 rituximab).

Conclusions. We describe 42 unpublished cases of patients fulfilling the current classification for both Sjögren syndrome and sarcoidosis. This implies that sarcoidosis and not just the presence of granuloma on labial biopsy may, like other systemic autoimmune diseases, coexist with SjS, and that having a diagnosis of sarcoidosis does not rule out a further development of SjS.

Poster 112

HIGH PREVALENCE OF SJÖGREN'S SYNDROME AMONG PRIMARY IMMUNODEFICIENCIES: A STUDY IN A TERTIARY CENTER OF NORTH-EASTERN ITALY

Longhino S., De Marchi G., Fabro C., Rizzo M.T.*, Manfrè V., Quartuccio L., De Vita S.

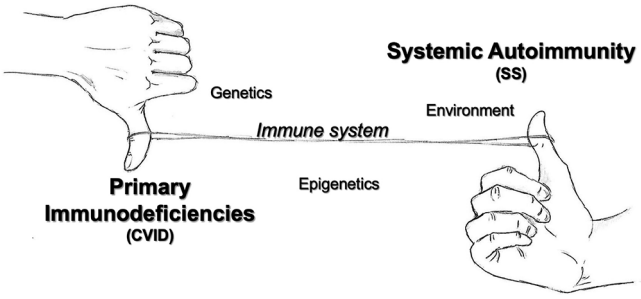
Rheumatology Clinic, Udine, Italy

Background. Autoimmunity and primary immunodeficiencies (PIDs) have long been regarded as antithetical and mutually exclusive entities. Recently, a greater understanding of the pathogenetic mechanisms has overturned this ancient perspective, suggesting a deep interconnection between them. In the wake of this new vision, we conducted a study aimed at 1) evaluating the prevalence of Sjögren's syndrome (SS) and secondly other systemic autoimmune diseases in a group of patients with PIDs 2) identifying peculiarities of SS patients with concomitant PIDs.

Objectives. To study the prevalence of autoimmune manifestations, and in particular SS, as classified according to the 2016 ACR/EULAR or 2002 AECG classification criteria in a cohort of PID patients followed in a tertiary center of North-Eastern of Italy.

Patients and methods. All patients suffering from PIDs and followed at our Clinic were studied. Only descriptive analyses were performed due to the small sample. All the available data, such as clinical, serological, ultrasonography and histological data when available, were collected.

Results. 34 patients with PIDs were recruited (25 females and 9 males) with mean age of 61.4±11.8 years and mean follow-up of 10.3±7.9 years. Among them, 24/34 (71%) were CVID and 10/34 (29%) were IgGSD. The prevalence of SS estimated in all the patients with PIDs was 12/34 (35%) divided as follows: 7/24 (29%) among patients with CVID and 5/10 (50%) among patients with IgGSD. Regarding other systemic autoimmune diseases, the overall prevalence was 8/34 (23%) divided as follows: 2 Systemic Lupus Erythematosus, 4 seronegative spondyloarthritis (SpA) and 2 eosinophilic granulomatosis with polyangiitis; all these autoimmune diseases were diagnosed in the CVID group except 1 SpA belonging to the IgGSD group. Concerning SS characteristics in PIDs 1) all patients experienced sicca symptoms with at least one objective test (*e.g.* Schirmer's test, unstimulated whole salivary flow, ocular staining or salivary scintigraphy/sialography); 2) anti-Ro52/60 and anti-La were negative in almost all SS-PIDs patients unless 1 CVID with anti-SSA positivity, despite the compatibility with SS diagnosis of lip biopsies (Focus Score ≥1 in all seronegative patients) and salivary gland ultrasonography (OMERACT score 2 in 4 CVID and 1 IgGSD respectively, and OMERACT score 3 in 3 CVID and 4 IgGSD respectively).



Conclusions. besides the limitation of the small sample and selection bias, this study suggests that SS is one of the most represented systemic autoimmune diseases in PIDs and in particular in CVID, highlighting possible common pathogenic features between these two conditions (1). Notably, the peculiar seronegative status of SS-PID patients underscores the importance of a complete disease assessment that should include lip biopsy and salivary gland ultrasonography in these patients in whom antibodies production is impaired.

Reference

1. Quartuccio L, De Marchi G, Longhino S, Manfrè V, Rizzo MT, Gandolfo S, Tommasini A, De Vita S, Fox R: Shared pathogenetic features between CVID and Sjögren's syndrome: clues for a personalized medicine. *Front Immunol* 2021.

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RESPIRATORY PATTERNS IN PATIENTS WITH SJÖGREN'S SYNDROME AND POSTURAL TACHYCARDIA

Arca K.*, Goodman B.
Mayo Clinic Arizona, Scottsdale, USA

Background. Postural orthostatic tachycardia syndrome (POTS) has been associated with Sjögren's syndrome (SS), though it is not fully understood if SS is causative of POTS. Neurologic and autonomic signs can occur prior to development of sicca symptoms and antibody positivity. Upper and lower airway disorders are common in SS, including interstitial lung disease. Conversely, patients with POTS may exhibit dysfunctional breathing patterns resulting in symptoms of breathlessness in the absence or excess of underlying respiratory or cardiac disease. Respiratory patterns in patients with POTS and SS have not been characterized.
Methods. A chart review of 60 patients diagnosed with POTS and SS was performed. All patients underwent standardized autonomic testing including blood pressure and heart rate responses to Valsalva maneuver, heart rate variability during deep breathing, blood pressure and heart rate responses to head-up tilt (HUT), and sudomotor testing. Respiratory responses were recorded using respiratory inductive plethysmography. Average respiratory rates (RR) were obtained from two one-minute epochs in the supine position and three one-minute epochs in the upright position. Postural tachypnea was defined as respiratory rate doubling from supine to upright. Rate and amplitude of respirations were assessed for conformity. Also assessed were presence of apnea (absent respiration for at least 10 seconds), Cheyne-Stokes patterns, frequent 'sighs', and dyssynchrony between abdominal and thoracic respirations.
Results. 53 patients with SS and POTS were included in the analysis. 51/53 (96%) were female and the average age was 31 years. The median duration from symptom onset to diagnosis of Sjögren's was 7 years (range 0.5-42 years). No patients had evidence of interstitial lung disease but 22/53 (42%) had asthma. 21/53 (40%) had neuropathic findings on autonomic testing and 5/53 (9%) were hyperadrenergic. Average Composite Autonomic Symptom Score (CASS) was 1 (range 0-5). Average supine RR was 15 (range 5-30), average RR during HUT was 16 (range 6-39). 3/53 (6%) demonstrated postural hyperventilation. 43/53 (81%) demonstrated irregular rate and/or amplitude of breaths supine or upright. 17/53 (32%) had apneic periods (range 1-5 events) and 14/53 (26%) showed dyssynchrony between abdominal and thoracic respirations supine or upright. Two patients (4%) demonstrated a Cheyne-Stokes pattern. 14/53 (26%) reported shortness of breath during HUT. Of those who reported shortness of breath (n=14), the median RR's supine and during HUT were similar to the full cohort, as was the proportion of irregular rate and/or amplitude during HUT (11/14; 79%).
Conclusions. In the absence of interstitial lung disease, patients with POTS and SS demonstrate signs of dysfunctional breathing. While these findings do not directly correlate with symptoms of shortness of breath during HUT, day-to-day symptoms of breathlessness are not accounted for in this study. Future studies should include patient reported symptoms outside of autonomic testing as well as testing for hypocapnia to better understand the significance of abnormal breathing patterns.

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SINGLE CELL ATLAS OF MINOR SALIVARY GLANDS REVEALS KEY DIFFERENTIAL CELLULAR AND FUNCTIONAL PLAYERS IN SJÖGREN'S AND SICCA SYNDROME

Nayar S.*[1], Turner J.D.[1], Asam S.[1], Smith C.G.[1], Colfrancesco S.[2], Iannizzotto V.[1], Teodósio A.[3], Flint J.[3], Gardner D.H.[3], Bowman S.J.[4], Croft A.P.[1], Filer A.[1], Fisher B.A.[4], Buckley C.D.[5], Barone F.[6]
[1]Rheumatology Research Group, Institute of Inflammation and Ageing, Birmingham Tissue Analytics, Institute of Translational Medicine University of Birmingham, Birmingham, UK, [2]Rheumatology Unit, University of Rome, Sapienza, Rome, Italy, [3]Birmingham Tissue Analytics, Institute of Translational Medicine University of Birmingham, Birmingham, UK, [4]Rheumatology Research Group, Institute of Inflammation and Ageing, National Institute for Health Research (NIHR) Birmingham Biomedical Research Centre and Dept. of Rheumatology, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK, [5]Kennedy Institute of Rheumatology, University of Oxford, Oxford, UK, [6]Candel Therapeutics, Needham, Massachusetts, USA

Introduction. Sjögren's syndrome (SjS) shares a series of symptoms with non-SjS Sicca syndrome, a salivary gland disease characterised by glandular dysfunction and dryness. However, unlike SjS, Sicca is not defined by tertiary lymphoid structure (TLS) formation in the salivary glands. TLS germinal centres provide a local hub for the maturation and proliferation of auto-reactive B-cells and expansion of malignant B-cell clones. TLS that form within salivary glands (SGs) of SjS patients are associated with poor disease outcome, autoantibody production and lymphoma development. In contrast, some Sicca cases may be associated with poorly defined T cell infiltration in the absence of clear T/B cell aggregation without TLS formation. The cellular and biological processes that drive organ permissiveness for TLS establishment in SjS as opposed to Sicca are largely unclear, but could act as an exemplar for TLS formation at other sites.
Methods: Single cell atlases of minor SGs were generated from SjS and sicca (n=eight per group) patients using the 10x scRNAseq Genomics platform. SjS patients fulfilled 2016 ACR/EULAR classification criteria. Sicca patients were anti-Ro and biopsy negative for FLS, but displayed scattered T cell infiltration in some cases. Data analysis was performed using R and the harmony, Seurat and Cellchat packages. Multiplex IHC, RNAscope and quantitative-PCR were used to validate scRNAseq findings.
Results. Cell clustering of SjS and Sicca SGs unveiled key differences in both immune cells and stromal cell compartment between the two disease groups. Sicca samples had significant differences in the immune-cell compartment, in particular, sicca SGs lacked activated $ICOS^+IL17^+IFNG^+TNF^+$ CD4 T helper and presented major differences in the $IL7R^+CD8^+$ T and Treg population. Small numbers of poorly differentiated populations of B cells and plasma cells were detected in Sicca, as compared to SjS SGs. Both disease groups had populations of $CD8^+GranzymeK^+CD8$ T cells.
Sicca SGs lacked crucial alterations in their stromal cell populations including an absence of $CXCL9^+BAFF^+CCL19^+CCL21^+CD40^+$ immunofibroblasts that are classically associated with SjS TLS. Whilst CD40 expression was broadly expressed across SjS cell clusters, limited expression of both CD40 and CD40L was observed in Sicca SG, supporting the clinical observations on the importance of the CD40/CD40L pathway in SjS pathology. Cellular interactome and in vitro analysis revealed complex interplay between LTBR, TNF, IFNγ and CD40 signals on both immune and stromal cell populations for TLS establishment. No major differences were observed in the presence of myeloid and pericyte populations between the two disease groups. Analysis of differentially expressed genes highlighted variances in activation and function of epithelial and endothelial cells. Interestingly, sicca presented a significant inflammatory signature on endothelial cells.
Conclusions. Our work is the first, systematic map and atlas of micro-anatomical and functional differences between SjS and Sicca providing critical insight in pathogenic players and therapeutic targets in these two different conditions.

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COMPARISON OF SALIVARY EXOSOMAL-RNA IN SJÖGREN'S, RHEUMATOID ARTHRITIS AND LUPUS

Singh M.[2], Sawicki B.[1], Chakrabortty S.[1], Cole J.[1], Lang S.[1], Yu S.*[1], Johan S.[1], Papas A.[2]
[1]Exosome Diagnostic, Waltham, USA, [2]Tufts School of Dental Medicine, Boston, USA

Introduction. Sjögren's Disease (SjD) is particularly difficult to diagnose due to overlapping symptoms with associated autoimmune disorders leading to an average diagnosis time of 3 years. A non-invasive salivary exosomal-RNA (exoRNA) based test capable of diagnosis for SjD would be highly desirable. This research presents a Sjögren's-specific gene signature, obtained from non-invasively collected salivary exoRNA, which is unique and different from Rheumatoid Arthritis and Lupus.
Methods. A novel, long RNA-Seq workflow incorporating a targeted hybrid-capture to selectively enrich and profile human exosomal mRNAs and long non-coding RNAs (lncRNAs) from saliva was first developed. Salivary exoRNA from 45 disease samples (including SjD, systemic lupus erythematosus, and Rheumatoid arthritis) and 40 healthy, matched controls were profiled then. Differential gene expression analysis, followed by feature

selection using machine learning algorithms was performed to identify a SjD-specific exoRNA signature. A validation study was conducted with 12 SD,10 Heathy, 5 RA and 5 Lupus subjects.
Results. RNA-Seq data analysis demonstrated highly efficient enrichment, with over 75% of sequencing reads mapping to the human transcriptome. Further RNA biotype analysis revealed over 60% of transcriptome reads mapping to protein coding genes and lncRNA. At a conservative threshold of 1 read per million (RPM), over 12,000 mRNAs and approximately 500 lncRNAs were detected. Most importantly, using a machine learning algorithm, we identified a 4-gene signature, and validated this cohort with an AUC of 0.86. see Table I.

Table I. Differential gene expression analysis of SD vs. Rheumatoid Arthritis and Lupus.

Disease vs Healthy	Differentially Expressed Genes	Genes Upregulated in Disease
Sjögren's Disease	70	64
Rheumatoid Arthritis	8	2
Lupus	9	5
Sjögren's Disease	Differentially Expressed Genes	Genes Upregulated in Disease
Rheumatoid Arthritis	105	19
Lupus	4	1

Conclusions. The gene signature identified in this current study provides an efficient, non-invasive, and molecular means of diagnosing Sjögren's Disease. This validation study has demonstrated that the signature is uniquely distinguishable from other autoimmune diseases.

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FEATURES OF JOINT MANIFESTATIONS IN PATIENTS WITH RHEUMATOID ARTHRITIS IN COMBINATION WITH SJÖGREN'S SYNDROME

Torgashina A.*, Matianova E., Gordeev A.
V.A. Nasonova Research Institute of Rheumatology, Moscow, Russian Federation

Background. A growing number of cross-sectional studies have shown that patients with rheumatoid arthritis (RA) in combination with Sjögren's syndrome (SjS) tend to have more severe arthritis and visceral involvement than those without.
Objective. To characterize the activity of RA as an independent disease and in combination with SjS.
Methods. we analyzed information on 650 patients with RA (according to ACR/EULAR 2010 RA criteria) who were hospitalized in V.A. Nasonova Research Institute of Rheumatology, from January 2021 to May 2022 inclusive, these patients were approved for prescribing biological treatment. Among these patients, 193 (29,7%) had a combination RA with SjS (according to ACR/EULAR 2016 SjS criteria). Patients younger than 40 years and male patients were excluded from subsequent analysis. Thus, we obtained groups matched by sex, age and duration of RA: group RA+SjS (S) (n=150) and group patients with RA as a control group (C) (n=255).
Results. Median age was 57±9.2 in group S and 56±9.4 in group C. The duration of RA was 12 years. The period from the first articular manifestations to the diagnosis of RA averaged 10 months. The main clinical indicators of arthritis activity were lower in the group S: swollen joints score, VAS of pts, ESR, CRP, as well as calculated activity indices (DAS28ESR, DAS28CRP, CDAI and SDAI) (p<0.05). The distribution of patients by radiographic stages did not differ significantly between the groups, X-ray stage 4 RA was observed in 26% in both groups. Systemic manifestations such as rheumatoid nodules and interstitial lung disease occurred with the same frequency in the groups.
The mean value of the total CIRS comorbidity index in group S was higher than in group C (p=0.03) due to the greater number of organ systems involved in the pathological process p=0.0001). At the same time, the CIRS severity index, which reflects the severity of existing concomitant pathologies, in group S was lower (p<0.0001). Statistically significant differences in the incidence of individual pathologies between groups were not identified.
The duration of RA before the start of biological therapy (bDMARDs), in group S was higher (p=0.04) according to the anamnesis. Duration of therapy with bDMARDs, number of drug changes per the anamnesis in the groups were comparable.
Rituximab (p<0.0001) was more frequently prescribed as the first bDMARDs in group S, TNF-alpha inhibitors – in group C (p=0.0001). During the current hospitalization, the expert panel also prescribed rituximab significantly more often (p<0.0001) in S group. Other bDMARDs (ing TNF-alpha, IL6 blockers, inhibitors T-cell co-stimulation) and Janus kinases inhibitors were prescribed to single patients in group S.
Conclusions. According to the results of our research, the combination of diseases leads to a milder course of the articular syndrome. The choice of the bDMARDs in these patients is also determined by the clinical manifestations of the SjS.

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EVALUATION OF SOME IMMUNOLOGICAL MARKERS IN RHEUMATOID ARTHRITIS IN COMBINATION WITH SJÖGREN'S DISEASE

Torgashina A.*, Matianova E.
V.A. Nasonova Research Institute of Rheumatology, Moscow, Russian Federation

Objectives. to compare main serological parameters in patients with rheumatoid arthritis (RA) with and without Sjögren's syndrome (SjS).
Methods. in observational cross-sectional study enrolled 343 patients (pts) with RA according to the 2010 ACR/EULAR criteria, who had been examined and treated in our clinic in 2021 year. Of these SjS was diagnosed on ACR/EULAR 2016 criteria in 96 (28%) pts. Thus, 2 groups were identified for comparative analysis: pts with RA in combination with SjS (n=96) (S group) and pure RA (n=247) as a control group (C group).
The study was based on the analysis of a database of patients with RA treated bDMARDs in our clinic. To obtain comparable data, we left in the study female patients older than 40 years at the time of the study.
Results. Mean age in S group was 58±9.3, in C - 56±9.4 years old. Median age at first onset of arthritis was 44 years. The time to diagnosis of RA did not differ significantly and was 7.5 (4-36) months in S group and 10 (4-48) months in C group. Their RA disease activity, estimated by DAS28-ESR, DAS28-CRP was higher in C group (p<0.003).
ANA-positivity was more common in RA patients with SjS than in those without SS (90.5% vs. 72.6%, p<0.0001). Median titers ANA in these patients were also significantly higher (1/640 [1/320;1/1280]), than in C group (1/160 [0;1/640], p<0.0001). Speckled and cytoplasmic glow was observed more often in group S than in the control group (p<0.0001). In group C, patients with ANA were younger (p=0.04). The time to diagnosis was not longer in patients with ANA in C group.
As expected, in group C, only 2 patients were weakly positive for anti-Ro-antibody and 1 for anti-La-antibody, no more than 2 upper limits. In group S, about 80% of patients had high levels of these antibodies. RF and ACCP levels and frequency of detection of these markers did not differ between groups (p>0,1).
In group S, the level of inflammatory activity in terms of CRP was significantly lower (6.1 [1.6-20] and 14,1 [3-5–34], p=0,008), but the level of IgG was significantly higher in the same time (p=0-001).
Conclusions. Patients with both RA and SjS showed a higher rate of positive ANA and anti-Ro/La antibody tests, lower CRP but higher IgG values. The presence of ANA in patients with RA determines the need for a more detailed examination to exclude SjS.

INVOLVEMENT OF DIFFERENT SPECIALITIES IN THE CARE OF SS

Poster 9 (withdrawn by authors - late withdrawal)

ATYPICAL GLOMERULAR DAMAGE IN THE PRIMARY GOUGEROT-SJÖGREN SYNDROME: ABOUT 2 CASES

Chawad W.*, Ammouri W., Choukair S., Fari Firdaous S., Ibourk Idrissi F., Taouch A., Belkhettab S., Talebi H., Mouatassim N., Khibri H., Maamar M., Harmouche H., Tazi Mezalek Z., Adnaoui M.
Department of Internal Medicine and Clinical Hematology, Ibn Sina's Hospital, Rabat, Morocco

Introduction. Sjögren-gougerot syndrome (SS) is a systemic autoimmune disease characterized by lymphoid infiltration of the exocrine glands, and by the production of autoantibodies. It is the second most common connective tissue disease, after rheumatoid arthritis. Kidney involvement in primary SS is rare and was first described in 1960 on reports of kidney biopsies showing tubulointerstitial inflammation. Tubulointerstitial nephropathy is the most common kidney disease. Glomerular damage is much rarer and is dominated by membrano-proliferative glomerulonephritis (MPGN) and Membranous glomerulonephritis (MGN). We report two observations of patients with pSS who presented glomerular involvement during the course of their disease; a typical MGN in one case, and a Focal Segmentary Glomerular Hyalinosis (FSGH) in the other, with a favorable evolution under corticosteroids, immunosuppressants.

Case n 1. A 44-year-old woman was hospitalized for the assessment of an edematous syndrome. She had been followed for a SS retained on: a keratoconjonctivitis sicca, a positive testing for anti-Ro/SSA antibodies and a focal sialadenitis. The biological assessment found total proteins at 46 g/l, albumin at 18 g/l and a proteinuria at 4.38 g/24 h. Renal function was preserved. The urine sediment test identified the presence of albumin, leukocytes and red blood cells. The kidneys were at a normal size and differentiation. The biopsy of the kidney revealed a membranous glomerulonephritis. Corticosteroid therapy was started along with an angiotensin receptor blocker. Cyclophosphamide was added at the rate of 6 monthly boluses of 1g, with a relay by a perfusion every 3 months. The clinical evolution was favorable and proteinuria turned negative.

Case n 2. A 49-year-old patient was followed for Sjögren's syndrome based on the presence of a dry oculo-buccal syndrome, of anti-SSA and anti-SSB antibodies, and a lymphocytic sialadenitis. The patient also had neurological damage in the form of chronic polyradiculoneuritis. A renal screening test found positive proteinuria at 1.5 g/l with preserved renal function. Renal biopsy highlights a morphological aspect of mesangiopathy with a segmental deposit of IgM in immunofluorescence, suggesting FSGH. A bolus of methylprednisolone was instituted, followed by cyclophosphamide with a relay by Azathioprine (AZA). Control proteinuria was negative. The evolution was marked by neurological relapses, and the installation of a hepatic cytolysis under AZA, which led to it interruption. The patient was then put on rituximab every six months. He is currently in renal and neurological remission.

Conclusions. Renal p sS is an underdiagnosed problem that can present itself in different ways. If the tubulo-interstitial lesions represent 2/3 of renal lesions, glomerular nephropathies are much rarer. They often correspond to MPGN, secondary to cryoglobulinemia. If suspected, renal biopsy should be performed quickly. Any discovery of renal involvement in a patient with pSS should lead to a search for differential diagnoses such as lupus, hepatitis C and IgG 4-associated disease.

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DISTINGUISHING CHILDHOOD SJÖGREN'S DISEASE IN PATIENTS PRESENTING WITH SIALADENITIS TO A PEDIATRIC MULTIDISCIPLINARY OTOLARYNGOLOGY/RHEUMATOLOGY CLINIC

Holley A.*, Park A., Stern S.
University of Utah School of Medicine, Salt Lake City, USA

Background/Purpose. Sialadenitis is a common distinguishing manifestation of Childhood Sjögren's Disease (SD). A pediatric multidisciplinary otolaryngology/rheumatology clinic (PMORC) was founded in December 2019 at the University of Utah. Our aim was to compare initial clinical characteristics of patients with and without SD seen in this PMORC.

Methods. Retrospective analysis of patients (pt) seen in this PMORC presenting with chronic sialadenitis was performed. Pt were split into two groups: children diagnosed with SD and children with chronic sialadenitis not diagnosed with SD. A diagnosis of SD was made per expert pediatric rheumatology opinion. These two groups were compared based on demographic information, systemic symptoms, dryness features, areas of glandular swelling, basic laboratory manifestations, ultrasound results, salivary gland biopsy results, and sialendoscopy findings. The framework of this PMORC included a new pt evaluation, a biopsy and therapeutic sialendoscopy with triamcinolone acetonide injection, and a follow up visit.

Results. Twenty-seven pt were evaluated in the PMORC over twenty-eight months. Twenty-two of these patients received official diagnoses. Sixteen (59%) of the pt were female. The median age of symptom onset was 7 years (stdev 3.57, IQR 4) and the median age of the first PMORC visit was 10 years (stdev 4.22, IQR 6). Eleven pt were diagnosed with SD, and eleven pt received a diagnosis that was not SD. 8/11 SD and 5/16 non-SD pt presented with swelling of more than one gland (p=0.19). 7/11 SD and 2/11 non-SD pt presented with joint pain (p=0.03). 5/11 SD and 3/11 non-SD pt presented with dry eyes. 3/11 SD and 6/11 non-SD pt presented with dry mouth.

Only 1 pt was SSA+ and was diagnosed with SD. All 11 pt diagnosed with SD and 6/11 non-SD pt had abnormal ultrasounds (p=0.01).

Of the 11 pt with SD, 10 showed focal lymphocytic infiltration on their minor or major salivary gland biopsy and the remaining 1 pt showed a diffused lymphocytic infiltration (p=0.0004). 4 pt had a focus score ≥1, 2 patients showed focal inflammation with a focus score <1, and 5 pt underwent parotid biopsies. Only 2 pt not diagnosed with SD showed focal inflammation (focus score <1) on their biopsy. 1 of these pt had recurrent sialolithiasis and the other pt had recurrent ear infections and semicircular canal dysplasia.

Of the 18 sialendoscopies performed, 12 pt reported improvement and/or temporary relief. Only 2 pt reported no improvement and 4 outcomes are unknown.

Conclusions. Given the many atypical features of Childhood SD, there is a need for a validated pediatric criterion. While dry mouth, dry eyes, and a positive SSA/SSB are common indicators of adult SD, they were less common in this pediatric cohort presenting with sialadenitis. Instead, we reported statistically significant differences in frequency of joint pain, ultrasound findings, and focal lymphocytic infiltration on biopsy. These parameters could be used to create a pediatric criterion for Childhood SD.

Symptom	Patients w/ SD (n = 11)	Patients w/o SD (n = 11)	P-Value
Glandular swelling: 2+ glands involved	8 (73%)	5 (45%)	0.19
Systemic symptoms	10 (91%)	8 (73%)	0.27
Fatigue	6 (55%)	4 (36%)	0.39
Joint pain	**7 (64%)**	**2 (18%)**	**0.03**
Dry eyes	5 (45%)	3 (27%)	0.38
Dry mouth	3 (27%)	5 (45%)	0.38
Dry skin	1 (9%)	3 (27%)	0.27
Cavities	6 (55%)	6 (55%)	1.0
SSA/SSB positive	1 (9%)	1 (10%) (n = 10)	0.94
Ultrasound Abnormal	**11 (100%)**	**6 (55%)**	**0.01**
Focal Lymphocytic Infiltration on Biopsy	**10 (91%)**	**2 (20%) (n = 10)**	**0.0004**
Improvement of symptoms after sialendoscopy	5 (83%) (n = 6)	7 (88%) (n = 8)	0.83

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OUTCOME OF PREGNANCY IN WOMEN WITH PRIMARY SJÖGREN'S SYNDROME COMPARED TO THE GENERAL POPULATION: THE FRENCH MULTICENTER PROSPECTIVE GR2 STUDY

Martin De Frémont G.*[1], Costedoat-Chalumeau N.[1], Belkhir R.[1], Guettrot-Imbert G.[1], Morel N.[1], Nocturne G.[1], Goulenok T.[1], Diot E.[2], Lazaro E.[3], Perard L.[4], Ferreira N.[2], Le Besnerais M.[5], Limal N.[1], Martis N.[6], Abisror N.[1], Debouverie O.[7], Richez C.[3], Sobanski V.[8], Maurier F.[9], Sauvetre G.[5], Levesque H.[5], Timsit M.A.[10], Tieulié N.[6], Orquevaux P.[11], Bienvenu B.[12], Mahevas M.[1], Lartigau-Roussin C.[13], Chauvet E.[14], Berthoux E.[4], Sarrot-Reynauld F.[15], Raffray L.[16], Couderc M.[17], Martin Silva N.[18], Jourde-Chiche N.[19], Jego P.[20], Thomas T.[21], Poindron V.[22], Queyrel-Moranne V.[6], Le Ray C.[1], Mariette X.[1], Le Guern V.[1], Seror R.[1]

[1]APHP, Paris, France, [2]CHU Tours, Tours, France, [3]CHU Bordeaux, Bordeaux, France, [4]CH Saint Joseph Saint Luc, Lyon, France, [5]CHU Rouen, Rouen, France, [6]CHU Nice, Nice, France, [7]CHU Poitiers, Poitiers, France, [8]CHU Lille, Lille, France, [9]Hôpitaux Privés de Metz, Metz, France, [10]CHU Brest, Brest, France, [11]CHU Reims, Reims, France, [12]Hôpital Saint Joseph, Marseille, France, [13]CH Gabriel Martin, Saint Paul, France, [14]CH Perpignan, Perpignan, France, [15]CHU Grenoble, Grenoble, France, [16]CHU La Réunion, Saint Denis de la Réunion, France, [17]CHU Clermont Ferrand, Clermont Ferrand, France, [18]CHU Caen, Caen, France, [19]APHM, Marseille, France, [20]CHU Rennes, Rennes, France, [21]CHU Saint Etienne, Saint Etienne, France, [22]CHU Strasbourg, Strasbourg, France

Background. If the outcome of SLE pregnancies has largely been studied, in primary Sjögren's syndrome (pSS), a few retrospective studies, using heterogeneous methods, investigated the risk of adverse pregnancy outcomes (APO) with inconsistent results (similar frequency to the general population to ≥50% of pregnancies). Moreover, these studies rarely analyzed the impact of pregnancy on the course of pSS.
Objectives. To describe evolution and prognosis of pregnancies in pSS and compare them to the general population.
Methods. The GR2 study is a French prospective cohort of pregnancies in women affected with auto-immune diseases involving 76 centers. The ENP is a French national perinatal survey on a sample of around 14.000 births, every 5 years. We included GR2 pSS women fulfilling ACR/EULAR 2016 criteria and having an ongoing pregnancy at 13 weeks of gestations. EULAR Sjögren's Syndrome Disease Activity Index and Patient Reported Index (ESSDAI and ESSPRI) were recorded at the first trimester of each pregnancy (baseline ESSDAI or bESSDAI), at each trimester and at delivery, and a cumulative ESSDAI (cESSDAI) was calculated, defined as the sum of each domain maximum score during follow-up before pregnancy. A pSS flare was defined as an increase ≥3 points of the ESSDAI. APO were defined as the occurrence of any of the following events: unexplained intrauterine foetal death (IUFD) ≥13 weeks, neonatal death (≤28 days), placental insufficiency (intrauterine growth restriction (IUGR), preeclampsia/eclampsia, HELLP syndrome, and/or placental abruption) leading to a premature delivery <37 weeks, small-for-gestational-age (SGA) birth weight (≤3rd percentile according to the French AUDIPOG curve) or the occurrence of a congenital atrio-ventricular block. We compared the risk of APO between pSS pregnancies and a general population sample of pregnancies from the 2016 ENP report, after matching 1 pSS woman for 4 women from the ENP on age, parity and residential area.
Results. 106 pregnancies occurred in 96 pSS women. pSS flares occurred in 14 (13.2%) pregnancies. Analyses did not identify any baseline parameter associated with the risk of pSS flare, in particular no association with ethnicity, cESSDAI, bESSDAI, or bESSPRI, biological markers of activity or type of autoantibodies. APO occurred in 14 (13.2%) pregnancies including only one pregnancy having pSS flare. Women with and without APO had comparable age, weight, smoking status, pSS duration, cESSDAI, bESSDAI or bESSPRI at inclusion. However, women with APO were more often Afro-Caribbean (38.5% vs 14.4%, p=0.05) and had more often anti-RNP antibodies (28.6% vs 6.5%, p=0.03). Treatment exposure did not differ between groups. The comparative study with the general population is ongoing and will be presented during the symposium.
Conclusions. APO and pSS flares were both observed in 13.2% of pregnancies but did not occur together. Afro-Caribbean origin and anti-RNP antibodies were associated to a higher risk of APO, whereas no factor was associated with pSS flare.

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SALIVARY FLOW RATE AND ORAL STATUS IN PATIENTS WITH PRIMARY SJÖGREN SYNDROME AND DIFFUSE CUTANEOUS SYSTEMIC SCLEROSIS: A CROSS-SECTIONAL STUDY

Glavina A.[1], Parat K.[1], Bozic I.[2], Perkovic D.[2], Biocina-Lukenda D.[1], Martinovic Kaliterna D.[3], Radic M.*[2]

[1]Department of Oral Medicine and Periodontology, Study of Dental Medicine, School of Medicine, University of Split, Split, Croatia, [2]Division of Rheumatology and Clinical Immunology, Center of Excellence for Systemic Sclerosis in Croatia, University Hospital Split, Split, Croatia, [3]University of Split, School of Medicine, Split, Croatia

Background. Sjögren's syndrome (SjS) and systemic sclerosis (SSc) are systemic autoimmune diseases that may have their manifestations in the oral cavity.
Objectives. Determine salivary flow rates and oral status in patients with primary Sjögren Syndrome (pSjS) and diffuse cutaneous systemic sclerosis (dcSSc) and comparison to control subjects.
Subjects and methods. This single-center, cross-sectional study included 31 patients with pSjS, 28 patients with dcSSc, and 28 control subjects. There were no significant differences between the groups with regards to age and gender. Unstimulated whole salivary flow rate (UWSFR) and stimulated whole salivary flow rate (SWSFR), pH value of saliva, DMFT index, periodontal pocket depth (PPD), clinical attachment level (CAL), interincisal distance were analyzed in all three groups of subjects.
Results. Patients with pSjS and dcSSc had statistically significant lower values of UWSFR (0.20; 0.38 vs. 0.91 ml/min) and SWSFR (0.56; 0.70 vs. 1.64 ml/min) compared to control subjects (p<0.001, Mann-Witney U-test; t-test). The pH values of saliva in patients with pSjS and dcSSc were lower with statistical significance compared to control subjects (6.0; 6.25 vs. 7.0) (p<0.001, Mann-Whitney U-test). The DMFT index of patients with dcSSc was higher (28.50) with statistical significance compared to control subjects (20.00) (p=0.01). The prevalnece of periodontitis was equal in patients with pSjS, dcSSc, and control subjects (p=0.384, λ2 test). Patients with pSjS and dcSSc had a statistically significant decreased interincisal distance compared to control subjects (4.38; 3.80 vs. 4.80) (p=0.003 and p<0.001, respectively; t-test).
Conclusions. Patients with pSjS and dcSSc show decreased UWSFR and SWSFR, pH values of saliva closer to an acidic medium, higher DMFT index, higher prevalence of periodontitis, decreased interincisal distance, i.e. poor oral and periodontal health. The results of our study indicate the importance of including various dental specialists (oral medicine specialist, periodontist) in the protocols of systemic autoimmune diseases such as pSjS and SSc.

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MULTI-SPECIALTY COLLABORATION IN DEVELOPMENT OF GUIDELINES FOR MANAGEMENT OF NEUROLOGICAL MANIFESTATIONS OF SJÖGREN'S DISEASE

Fox R.I.[2], Deboo A.[3], Hammitt K.M.*[1], Baker M.C.[4], Bloch D.[6], Danielides S.[5], De Sousa E.[7], Goodman B.[8], Mandel S.[9], Noaiseh G.[10], Pavlakis P.P.[11], Sarka G.[12], Varadhachary A.[13], Wallace D.J.[14], Makara M.[1], Scofield R.H.[15], Carsons S.E.[16], Carteron N.L.[17]

[1]Sjögren's Foundation, Reston, USA, [2]Scripps Medical Center, La Jolla, USA, [3]Temple Health, Philadelphia, USA, [4]Stanford Univeristy, Stanford, USA, [5]VCU Health, Richmond, USA, [6]Massachusetts General Hospital & Harvard University, Boston, USA, [7]Mercy , Moore, USA, [8]Mayo Clinic, Phoenix, USA, [9]Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, New York, USA, [10]University of Kansas, Kansas City, USA, [11]Hospital for Special Surgery, New York, USA, [12]University of California Los Angeles, Los Angeles, USA, [13]Washington University School of Medicine in St. Louis, Saint Louis, USA, [14]Cedar Sinai Medical Center, Beverly Hills, USA, [15]Oklahoma Medical Research Foundation, Oklahoma City, USA, [16]NYU Long Island School of Medicine, Mineola, USA, [17]University of California, San Francisco & Berkeley, San Francisco, USA

Background. Multi-specialty contribution is key to Sjögren's disease management. The Sjögren's Foundation in partnership with neurology and rheumatology Sjögren's experts is developing guidelines for management and treatment of peripheral nervous system (PNS) involvement in Sjögren's.
Methods. The Topic Review Group (TRG) consists of 6 rheumatologists, 7 neurologists, and 1 rheumatologist-neurologist, with 3 rheumatologists serving as Chairs of the Foundation guidelines initiative. Methodology was derived from the American College of Rheumatology, American Academy of Neurology, and American Society of Clinical Oncology. Clinical ques-

tions and parameters for included studies were delineated prior to the literature search. A minimum of two TRG members selected abstracts meeting the criteria and extracted data from articles. GRADE was utilized to rate quality of each study and strength of each recommendation. Recommendations developed by the TRG were reviewed and voted upon by a Consensus Expert Panel comprised of neurologists, rheumatologists, and Sjögren's patients or family members with experience in the health field. Recommendation finalization required a minimum of 75% agreement.

Results. Neuro-anatomic coverage includes motor, sensory and autonomic nerves with etiology including demyelinating, axonal and antibody-based pathologies. Total of 148 clinical questions covered cranial neuropathies; axonal or sensory motor or sensory neuropathies; small fiber neuropathies (length-dependent or non-length dependent); ataxic sensory neuropathies/large fiber ganglionopathies; mononeuritis multiplex/multiple mononeuropathies; and autonomic neuropathies. Workup and diagnosis were covered by 47 questions and treatment by 101. Literature search identified more than 2,000 abstracts, of which 139 were selected for article review for recommendation development and 58 met the pre-determined inclusion criteria for full data extraction. Recommendations were drafted based on response to the clinical questions.

Conclusions. The perspective of neurologists in addition to rheumatologists is key to development of effective clinical practice guidelines in PNS-Sjögren's. A multi-specialty effort identifies neurologists with an interest in Sjögren's; amplifies educational efforts as the guidelines are published and shared by professional organizations from different specialties; increases identification of Sjögren's in neurology patients; and ensures the inclusion of neurologists by rheumatologists in the optimal care of Sjögren's patients.

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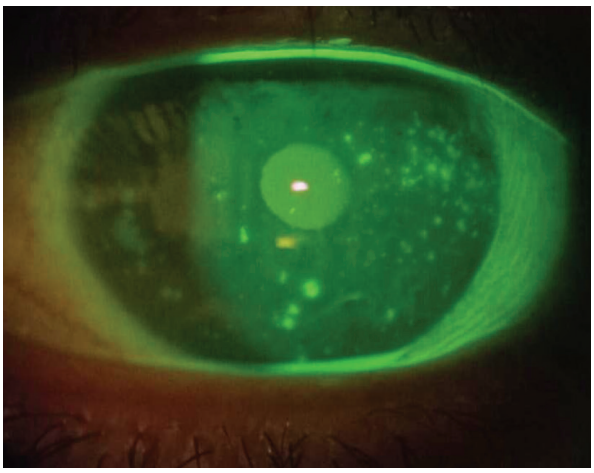
NEW INSIGHT INTO OCULAR SURFACE DYSFUNCTION IN SJÖGREN SYNDROME

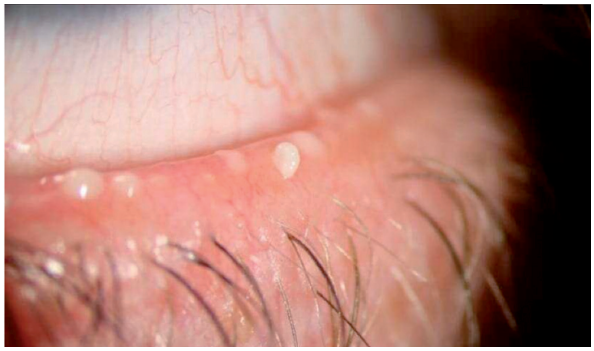
Moawad P., Hassanein D., Shamma R., El Zawahry O., Ragab G.*
Cairo University Hospital, Cairo, Egypt

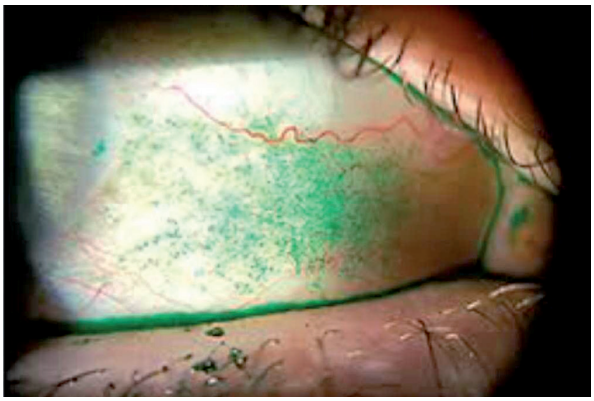
Introduction. Dry eye disease in Sjögren syndrome (SS) has been classically described as tear film aqueous deficient being expressed in terms of Schirmer test<5mm as a diagnostic criterion in ACR and AECG. Few reports mentioned the evaporative element in dry eyes of SS. In our study we performed comprehensive ocular surface evaluation including tear volume, ocular surface staining using two different scoring systems, meibomian gland function, lid margin abnormality score and also assessment of the response of these ocular surface parameters to two different topical immunomodulatory eye drops.

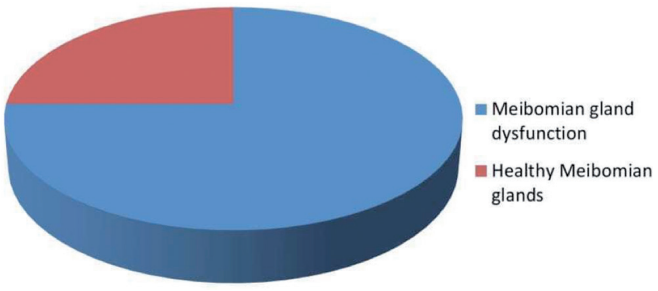
Methods. 60 Sjögren syndrome patients were enrolled in our study, ocular surface assessment was described in terms of ocular surface disease index questionnaire (OSDI), Schirmer I test, tear breakup time (TBUT)in seconds, SICCA staining score, Van Bijsterveld score, meibum quality score, meibum expressibility score, and lid abnormality score. Patients were divided into two groups: Group A was prescribed topical cyclosporine 0.05% bid and Group B tacrolimus 0.03% bid. All the above tests were performed to all patients enrolled in our study day 0 and 90 days after treatment.

Results. Among the 60 studied SS patients, mean age was 49.4±12.92 years, 45 patients were diagnosed as Meibomian gland dysfunction (MGD) according to the guidelines of the International Workshop on MGD. In group A baseline OSDI 63.1±18.65%, at day 90:31.41±19.04 %, *p*0.02in group B baseline OSDI 70.74±13.49%, at day 90 :32.51±20.35% *p*-0.02. In group A baseline Schirmer I test 5.93±5.79, at day90:8.10±7.50, *p*-value 0.01 in group B 6.77±5.66, at day 90: 8.10±7.50 *p*-value 0.02 at day 0 and 90 respectively. For TBUT 3.17±2.61s, 4.63±3.13s *p* 0.419, in group A, and in group B: 2.77±2.50, 3.70±3.12 0.374 *p* 0.02 at day 0 and 90 values respectively. Ocular surface staining, SICCA score was 6.03±3.09, 3.63±3.11 *p* 0.01 in group A, in group B7.20±2.59, 4.33±3.23, *p* 0.02 as day 0 and 90 values respectively. Van Bijsterveld score 5.50±2.60, 3.33±2.64 *p* 0.04 in group A and 6.37±2.54,4.40±3.19 *p* 0.03in group B as day 0 and 90 values respectively. Meibomian gland function evaluation was in terms of meibum quality score that was 2.87±0.82, 2.79±0.92 *p* 0.72 and2 .77±0.94, 2.77±0.91 p0.348 in group A and B as day 0 and 90 respectively. Meibum expressibility score was 3.83±0.15, 3.73±0.22 *p* 0.808 and 3.8±0.82, 3.80±0.81, *p* 0.706 in group A and B as day 0 and 90 respectively. Lid abnormality score was 2.20±0.81, 2.3±0.77 *p* 0.374 in group A and 2.37±0.93, 2.25±0.94, p0.407 in group B at day 0 and day 90 respectively.









Conclusions. The ocular surface dysfunction in Sjögren syndrome patients can be multifactorial, not only caused by aqueous deficiency. The ocular surface in our patients showed evidence of an additional evaporative element of dry eyes in the form of meibomian gland dysfunction and lid margin abnormality. Topical immunosuppressives significantly improved some ocular surface parameters as OSDI, Schirmer I and ocular surface staining score, with no significant effect on the second arm of the dry eye disease which is the lid margin abnormality and the meibomian gland function thus should be addressed separately to improve the overall ocular surface health of dry eyes of SS patients.

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CULTURAL ADAPTATION AND PRELIMINARY VALIDATION OF THE QUALISEX QUESTIONNAIRE FOR ITS USE IN PATIENTS WITH SJÖGREN'S SYNDROME

Villa M.*[1], Giardina F.[1], Gioia C.[1], Iannuccelli C.[1], Gattamelata A.[1], Colafrancesco S.[1], Mastromanno L.[1], Simoncelli E.[1], Conti F.[1], Di Franco M.[1], Curcio G.[2], Priori R.[3]

[1]Rheumatology Unit, Department of Clinical Internal, Anaesthesiologic and Cardiovascular Sciences, Sapienza University of Rome, Rome, Italy, [2]Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, L'Aquila, Italy, [3]Saint Camillus International University of Health Science, UniCamillus, Rome, Italy

Background. Even if a domain of health such as sexuality is important from the patient's perspective, this has been largely neglected in Sjögren's Syndrome (SS) and it is generally not considered neither in clinical trials nor in clinical practice.
Objectives. To adapt and preliminarily validate for women with primary SS (pSS) in Italy the Qualisex, a new a 10-question questionnaire originally created for French patients with rheumatoid arthritis.
Methods. Consecutive sexually active women with pSS (AECC criteria) with ≥18 years of age attending a dedicated SS clinic were enrolled. Sociodemographic variables were recorded, ESSDAI, SSDDI, ESSPRI and Hospital Anxiety and Depression Scale (HADS) calculated. The Italian version of the Qualisex was prepared according to existing guidelines. To assess the factorial structure of the questionnaire in Italian an Exploratory Factor Analysis (EFA) was carried out; the level of redundancy evaluated by means of intra-item correlation of the Qualisex questionnaire. As a measure of reliability, internal consistency was assessed through Cronbach's alpha coefficient. Face and content validity were assessed cross-sectionally by correlations with other disease aspects previously found associated to a reduced quality of sexual life in pSS such mood disorders, patient-reported symptoms, quality of the relationship.
Results. 40 patients were enrolled (median age 53; 45.2-57.2). The median Qualisex score was 4.65 (2.125-6.2). EFA showed that the model with a single factor appeared to be highly significant (Chi235=2943.10; $p<0.0000001$); Cronbach's alpha coefficient resulted to be 0.89 which indicates an adequate internal consistency. Age positively correlated with qualisex (Rho=0.39; $p=0.008$) as well as anxiety (HADS-A; Rho=0.38; $p=0.02$) and depression (HADS-D; Rho=0.47; $p=0.002$). The worst was the relationship considered, the higher the qualisex (Rho=0.55; $p<0.013$). A positive correlation with ESSPRI (Rho=0.43; $p=0.007$) was demonstrated, as well. No correlation was found between ESSDAI and the Qualisex.
Conclusions. to the best of our knowledge, we are the first to adapt and preliminarly validate the Qualisex to women with pSS in Italy. Even if other more general questionnaires have been previously used to evaluate sexual dysfunction in pSS, the availability of a specific, simple, valid and reliable tool to assess the quality of sexual life represents a nudge for considering a neglected domain of health and well-being. This tool, once validated in larger international cohorts, might be included in a more complete core outcome set.

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HEARING DYSFUNCTION IN SJÖGREN'S SYNDROME

Simoncelli E.*[1], Gattamelata A.[1], Giardina F.[1], Villa M.[1], Colafrancesco S.[1], Mastromanno L.[1], Izzo R.[1], Mancini P.[2], Portanova G.[2], Mariani L.[2], Atturo F.[3], Conti F.[1], Priori R.[4]

[1]Rheumatology Unit, Department of Clinical Internal, Anaesthesiologic and Cardiovascular Sciences, Sapienza University of Rome, Rome, Italy, [2]Department of Sense Organs, Sapienza University of Rome, Rome, Italy, [3]Otorhinolaryngology Unit, San Giovanni Addolorata Hospital, Roma, Rome, Italy, [4]Saint Camillus International University of Health Science, UniCamillus, Rome, Italy

Background. Hearing dysfunction, caused by the involvement of the vestibulocochlear nerve or by direct damage on inner ear structures has been described in patients with Sjögren's Syndrome (SS). Previous studies evaluating the prevalence and incidence of hearing dysfunction in SS showed conflicting results, therefore, to date, the exact prevalence has not been extensively evaluated.
Objectives. The aim of this study is to evaluate the prevalence of hearing involvement in patients with primary SS (pSS).
Materials and methods. Patients with pSS (AECC criteria) with ≥18 years of age attending a dedicated Sjögren's syndrome clinic were consecutively enrolled Auditory function was investigated by pure tone audiometry (PTA), It-Matrix test (Speech Reception Threshold in noise leading to 50% correct sentences-SRT) and the Hearing Handicap Inventory (HHI) during a baseline visit and at a follow up visit. A questionnaire of auto-evaluation of hearing loss impact on life was also administered to the patients.
Results. Twenty-five patients with pSS (24 females) were enrolled in the study. The median age was 56.2 years (IQR 49-64) The mean disease duration was 3.7 years, 8 were treated with hydroxychloroquine (HCQ) and 1 with methotrexate.
At baseline evaluation PTA revealed hearing loss in 17 patients (68%) with severity ranging from mild to severe. Fifteen patients (60%) presented mild hearing loss, 1(4%) moderate e 1 (4%) severe. The It-Matrix score ranged from -9.9 to 0.9 (median – 3.50). Median HHI score was 12.17 (min 0, max 68, SD 177.9). For Covid restrictions, a follow-up evaluation was available for 10 patients only. In these patients, a worsening of PTA and HHI was observed. Interestingly, the it-Matrix scores of patients with a stable disease showed an improvement.
Conclusions. These preliminary findings suggest that hearing involvement is common in patients with SS and that it progresses over time. If confirmed on larger cohorts, these data will be useful for physicians in counseling patients about their disease and, in case of suspicious symptoms, an early evaluation by an otolaryngologist may prevent delay in diagnosis and allow an appropriate diagnostic evaluation and therapeutic intervention.

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ADHERENCE TO THE MEDITERRANEAN DIET IN ITALIAN WOMEN WITH PRIMARY SJÖGREN'S SYNDROME

Mastromanno L.*[1], Izzo R.[1], Colafrancesco S.[1], Barbati C.[1], Buoncuore G.[1], Gattamelata A.[1], Giardina F.[1], Simoncelli E.[1], Villa M.[1], Conti F.[1], Priori R.[2]

[1]Rheumatology Unit, Department of Clinical Internal, Anaesthesiologic and Cardiovascular, Rome, Italy, [2]Saint Camillus International University of Health Science, UniCamillus, Rome, Italy

Objectives. The Mediterranean Diet (MD) has anti-inflammatory and immunomodulatory effects (1, 2) suggesting a protective role in rheumatic diseases. There is limited knowledge about the eating habits in patients with primary Sjögren Syndrome (pSS) living within the Mediterranean area (3). The aim of the study is to evaluate the adherence to the MD in Italian women with pSS and its correlation with the clinical, laboratory and histological data.
Methods. patients classified as pSS according to AECG criteria 2002 (4) who had undergone to minor salivary gland biopsy (MSG) during the previous twenty-four months were consecutively enrolled during follow-up visits. The adherence to the MD was assessed by the Med Diet (MDiet) (5) which includes eleven groups of foods; to each group is assigned a value ranging between 0 and 5 based on the frequency of monthly intake. The total score spans from 0 (poor adherence) to 55 (maximum adherence). Systemic disease activity was evaluated with the EULAR SS disease activity index (ESSDAI); EULAR SS patient-reported index (ESSPRI) was calculated as well. Focus score calculation was performed and the presence of germinal centres (GC) assessed in MSG. Multivariate statistical analysis was performed by R Studio Software.
Results. MDiet was administered to 73 female pSS outpatients [median age (±SD) 50.6 (±13.4)]. At the time of the study the mean BMI was 22.9 (±3.64 SD), the mean MDiet score was 33.4 (± 4.29 SD) (third quartile), the mean age was 50.6 (± 13.4 SD).
A significant association was found between MDiet and ESSPRI index ($p=0.028$), but not with the ESSDAI score (p = ns). No other significant correlations were detected, in particular the severity of MSG involvement, in terms of the presence and percentage of GC, is not correlated with MD adherence.
Conclusions. This preliminary study shows a moderate adherence similar to what previously reported in the general female population in Europe (32.5 ± 5 DS) (6). It is noteworthy that patients with a higher adherence to MD show a lower symptom burden as assessed by ESSPRI.

References

1. Schwingshackl: *Nutr Metab Cardiovasc Dis* 2014.
2. Mena: *Am J Clin Nutr* 2009.
3. Carubbi: *Clin Exp Rheumatol* 2021.
4. Vitali: *ARD* 2002.
5. Panagiotakos: *J Med Food* 2007.
6. Fallaize: *Nutrients* 2018.

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PHYSICAL ACTIVITY LEVEL IN PATIENTS WITH PRIMARY SJÖGREN'S SYNDROME

Miyamoto S.T.[1], Oliveira F.R.*[2], Valim V.[3], Machado K.L.L.[4], Serrano É.V.[4], Gianórdoli A.P.E.[4], Altoé L.B.[5], Noronha B.D.[5], Santos P.H.A.[5], Pedrini A.P.T.[5], Nicole N.R.S.[5], Mota J.C.[5], Rosa B.B.[6], Favarato L.F.[7], Alochio L.V.[7], Tomé W.A.[7]

[1]Departamento de Educação Integrada em Saúde, Universidade Federal do Espírito Santo, Vitória, Brazil, [2]Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo, Ribeirão Preto, Brazil, [3]Departamento de Clínica Médica and Hospital Universitário Cassiano Antônio Moraes, Universidade Federal do Espírito Santo, Vitória, Brazil, [4]Hospital Universitário Cassiano Antônio Moraes, Universidade Federal do Espírito Santo, Vitória, Brazil, [5]Graduação em Fisioterapia, Universidade Federal do Espírito Santo, Vitória, Brazil, [6]Graduação em Medicina, Universidade Federal do Espírito Santo, Vitória, Brazil, [7]Residência Médica em Reumatologia, Universidade Federal do Espírito Santo, Vitória, Brazil

Background. Sjögren's Syndrome (SS) is a chronic autoimmune inflammatory systemic disease with a slow and progressive evolution. The inflammatory process can affect any system, such as the musculoskeletal and cardiorespiratory systems, and can lead to a decline in physical function and psychosocial impairment, with the potential for worsening quality of life and functional capacity. When compared to healthy individuals, patients with primary Sjögren's syndrome (pSS) have low levels of physical activity.
Objectives. The aim of this study was to evaluate the level of physical activity and its association with quality of life, disease activity and disease symptoms in pSS patients in Brazil. Methods: This is a cross-sectional study. Physical activity level was assessed by the international physical activity questionnaire (IPAQ-SF), quality of life by EuroQOL (EQ-5D), disease activity by the Sjögren Syndrome Disease Activity Index (ESSDAI) and disease symptoms by the Sjögren's Syndrome Patient-Reported Index (ESSPRI).
Results. A total of 219 patients from two Brazilian research centers participated in the study. Only 36.5% of the patients were considered active and 68% reported performing some type of regular physical exercise with an average weekly frequency of 3.37 (±1.73) times. Pain was negatively correlated with all levels of physical activity intensity and quality of life.
Conclusions. Most patients had a low level of physical activity, despite reporting some type of regular physical exercise. Disease activity and symptoms were negatively associated with physical activity level.

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IMPACT OF SJÖGREN'S SYNDROME ON OCCUPATIONAL PERFORMANCE AND QUALITY OF LIFE

Cintra B.C.*, Marzola M.M., Carretta R.Y.D., Rocha E.M., Oliveira F.R.
Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto, Brazil

Objectives. In general, studies have described unfavorable labor outcomes and impaired social participation in patients with systemic autoimmune diseases. Our objective was to evaluate the impact of primary Sjögren's syndrome (pSS) on activities of daily living, quality of life, and occupational health, mainly focused on work, leisure, and social participation.
Patients and methods. Twenty pSS patients fulfilling the 2016 ACR/EULAR criteria were evaluated for symptoms, disease activity and damage indices (ESSDAI and SSDDI), impact on occupational performance, and quality of life, and were compared to 25 healthy volunteers matched for sex and age. Occupational instruments assessed the interference in actions performed in daily life. The Profile of Fatigue and Discomfort (PROFAD) questionnaire and EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) assessed additional subjective symptoms (fatigue, dryness, and pain). Functional impairment and humor disorders were measured using the Short Form Health Survey Questionnaire (SF-36) and the Hospital Anxiety and Depression Scale (HADS).
Results. Patients were predominantly female (95%), white (80%), and 30% were obese. The mean age was 44.3±10.1 years, and the mean disease duration was 4.5±4.2 years. Focus score ≥1 and anti-SSA/Ro were present in 85% of the pSS sample. The median of current ESSDAI was 2 (IQR 0-6) and the mean ESSPRI was 5.96±2.8. There were positive correlations between ESSPRI, anxiety and depression measured by HADS (r=0.56; p=0.009), and fatigue measured by PROFAD (r=0.78; p<0.0001). There was no association between symptoms and disease activity or damage. SS patients reported loss of physical ability, concentration, self-expression and house management skills compared to controls (p<0.05). Patients also experienced behavioral changes in social participation, mainly a reduction in work, leisure and physical activities, and friendship relations. Among pSS subjects, 75% were married, 35% were homemakers, and 55% were employed, as opposed to healthy volunteers (48%, 12%, and 72%, respectively). The quality of life in the pSS group was lower than controls in all domains of the SF-36 questionnaire (p<0.05).
Conclusions. Our results suggest that pSS patients have poorer quality of life and employment status, loss of competences and self-confidence, and social withdrawal when compared with healthy subjects. It appears independent of active disease (ESSDAI) or disease damage (SSDDI) and correlates with higher symptoms (ESSPRI, PROFAD, HADS) scores.

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ULTRA-HIGH FREQUENCY ULTRASONOGRAPHY OF LABIAL GLANDS IN PEDIATRIC SJÖGREN'S SYNDROME: A PRELIMINARY STUDY

Marrani E.*[1], Virgili C.[1], Fulvio G.[2], Izzetti R.[3], Dini V.[4], Oranges T.[5], Baldini C.[2], Simonini G.[1]

[1]Rheumatology Unit, Azienda Ospedaliero-Universitaria Meyer, Firenze, Italy, [2]Rheumatology Unit, Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy, [3]Dentistry and Oral surgery, Department of Surgical, Medical and Molecular Pathology and Critical Care Medicine, Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy, [4]Dermatology Unit, Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy, [5]Dermatology Unit, Azienda Ospedaliero-Universitaria Meyer, Firenze, Italy

Introduction. Sjögren's Syndrome (SS) is a chronic autoimmune disease, primarily affecting lacrimal and salivary glands. The 2016 American-European Consensus Group criteria are not validated in pediatric population. Therefore, the diagnosis of pediatric SS mostly relies on clinical suspect, resulting in a significant diagnostic delay. Recently, Ultra-High Frequency Ultrasound (UHFUS) of labial glands has been proposed as a diagnostic method in adults with suspected SS.
Objectives. The aim of the study is to evaluate the potential role of Ultra-High Frequency Ultrasound (UHFUS) of minor salivary glands for the diagnosis of Sjögren's Syndrome in a cohort of pediatric population.
Methods. Consecutive paediatric patients with suspected diagnosis of SS seen at AOU Meyer were evaluated with UHFUS. To be eligible patients should have received a clinical diagnosis of Sjögren's Syndrome before the age of 16 years, according to a combined set of clinical, serological, and instrumental findings. Clinical, radiological, and histopathological findings were retrospectively collected using a dedicated CRF. Intraoral UHFUS scan of the lip mucosa was performed with Vevo MD equipment, using a 70 MHz probe with a standardised protocol and the images were independently reviewed by two operators. LSG were assessed by using a four-grade semi-quantitative scoring system (0-3), similar to the OMERACT scoring system used for major salivary glands.
Results. Twelve patients with paediatric SS were included in the study (n = 12, 11 females; 10 Caucasian, 2 Asian), with a median age at the diagnosis of 14.1 years (range 7.75-17) and a median disease duration of 13.5 months (range 1-94). Eleven patients were ANA positive; Ro/SSA were positive in 6/12 while none tested positive for LLA/SSB. Minor salivary gland biopsy was performed in 9/12, showing inflammatory chronic sialadenitis in 8/12. Treatment with hydroxychloroquine was ongoing in 11/12. When applying UHFUS to this cohort of patients, all patients showed a UHFUS grade of ≥1 with 8/12 showing a mild glandular alteration (*i.e.* grade 1), 2/12 a moderate glandular alteration (*i.e.* grade 2) and finally 2/12 a severe glandular alteration (i.e. grade 3). A moderate intraglandular vascularization was seen in 9/12, with only 3/12 showing a mild intraglandular vascularization. Due to limited size of the sample, the relationship between histological findings, autoantibodies status and UHFUS grade could not be performed
Conclusions: Paediatric SS is a rare condition, and its prevalence is underestimated due to the lack of standardized diagnostic criteria and the subtle early clinical presentation. New approaches to a faster diagnosis are urgently needed in clinical practice. This preliminary pilot study seems to report UHFUS as feasibility technique to identify salivary gland alterations in children with a clinical suspect of SS. This technique might contribute to drive guided lip biopsy, thus reducing the rate of false negative. Further studies are currently in progress in our clinics to identify the exact role of UHFUS and its potential predictive role of the various patterns observed in pediatric SS.

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NEUROPSYCHIATRIC SJÖGREN SYNDROME: AN ATYPICAL MANIFESTATION OF ENCEPHALITIS A CASE REPORT

Navarrete Motta L.E.*, Ramirez J., Gutierrez J.M., Diaz M.C., Fernández Ávila D., Garcia Alfonso C., Bernal Macias S.
Pontificia Universidad Javeriana, Bogotá, Colombia

Sjögren syndrome (SS) is a systemic, inflammatory, chronic autoimmune disease that primarily affects exocrine glands, is characterized by a lymphocytic infiltration to lacrimal and salivary glands that lead to its atrophy, resulting in sicca symptoms like xeroderma, keratoconjunctivitis, xerostomia and dryness (1, 2). However, Sjögren syndrome is not only limited to glandular manifestations, the extraglandular or systemic manifestations are also common in this syndrome, it has been described that systemic manifestations may precede dry symptoms as the initial manifestation of Sjögren's syndrome (4). However the extra glandular or systemic manifestations which are less known, are even less considered when establishing the diagnosis, this occurs especially with the neurological manifestations.
We present a case report of a of a 29-year-old female patient that came to the emergency room with hemiparesis that progresses to global aphasia even though she was a young patient this case required thrombolysis.
When the patient was questioned there were several findings, which started to change the course of management and after extensive investigation the diagnosis of Sjögren was made, even NMDA auto antibodies were found.
The case exposed is a clear statement of the need to expand the knowledge about the extraglandular manifestations of the different autoimmune diseases.

Table I. Paraclinicos.

Perfil autoinmune	
Paraclínico	**Valor**
Hemograma	10/08/21 • *Leu: 3.600 RAN: 1.400*, RAL: 1.700, Hb: 12.1, VCM: 81, HCM: 28.3, RDW:13.3, Plaquetas: 252.000
ANAs	17/08/21 - ANA 1/2560 moteado
ENAS	10/08/21 • ANTI RNP 2.82 • ANTI SM 2.781 • ANTI DNA negativo • ANTI RO 132.9 • ANTI LA 50.93 17/08/21 • Anti B2GP IgG 1.38 negativo, IgM 4.27 negativo • Anticoagulante lúpico negativo, • Anticardiolipina o IgM 11.68 (negativo) o IgG 1.74 (negativo)
Otros exámenes	10/12/21 • Anti R-NMDA (positivo débil) positivo • Crioglobulinas negativas

Elaborada por los autores

Table II. Perfil infeccioso.

Exámenes infecciosos	
Screening infeccioso	- Acs HCV negativo - AgS HBV negativo - Anti core total HBV negativo - VIH negativo - VDRL no reactivo.

Elaborada por los autores

Poster 194 (withdrawn by authors - late withdrawal)

SHORT-TERM RESULTS OF A PULSED THERAPY WITH HYDROCORTISONE EYE DROPS TO TREAT MODERATE TO SEVERE DRY EYE IN PRIMARY SJÖGREN SYNDROME PATIENTS

Menchini M.*[1], Sartini F.[1], Baldini C.[2], Figus M.[1], Gabbriellini G.[1]
[1]Ophthalmology, Department of Surgical, Medical, Molecular Pathology and Critical Care Medicine, University of Pisa, Pisa, Italy, [2]Rheumatology Unit, University of Pisa, Pisa, Italy

Background. We investigated the safety and efficacy of short-term treatment with topical low-dose hydrocortisone sodium phosphate 0.335% (PFH) in patients with moderate to severe primary Sjögren syndrome (SS)-related dry eye disease (DED).
Methods. a retrospective single-centre interventional study.
All patients received PFH for six days with a pulsed posology: three times daily for 2 days, twice daily for 2 days, and once daily for 2 days. This scheme was repeated for 3 consecutive months and then alternated for three months. Data were collected at baseline, three months, and six months of follow-up.
Results. a total of 40 SS patients were enrolled. Conjunctival hyperaemia and corneal-conjunctival stain significantly improved ($p<0.001$). Ocular Surface Disease Index score reduced significantly between baseline and three months and between baseline and six months ($p<0.001$). The tear film osmolarity lowered significantly in each eye from baseline to 3 months and from baseline to 6 months ($p=0.002$ and $p=0.037$, respectively).
Comparing results at three and six months, the Ocular Surface Disease Index score ($p=1.000$), the frequency of lacrimal substitutes installation ($p=0.632$), and tear film osmolarity (right eye $p=0.518$, left eye $p=1.000$) did not change significantly. Intraocular pressure did not change during the study period.
Conclusions. PFH eye drops with a pulsed posology improve signs and symptoms, not affecting the intraocular pressure in SS-related DED. Therefore, this pulsed treatment is safe and efficacious.

Poster 195 (withdrawn by authors - late withdrawal)

PREVALENCE OF LIVER FIBROSIS ASSESSED BY TRANSIENT ELASTOGRAPHY IN PATIENTS WITH SJÖGREN'S SYNDROME

Androutsakos T.[1], Voulgaris T.[2], Bakasis A.[1], Koutsompina M.L.*[1], Chatzis L.[1], Argyropoulou O.[1], Pezoulas V..C[3], Fotiadis D.I.[3], Goules A.V.[1], Papatheodoridis G.[2], Tzioufas A.G.[1]
[1]National and Kapodistrian University of Athens, School of Medicine, Department of Pathophysiology, Athens, Greece, [2]National and Kapodistrian University of Athens, School of Medicine, Department of Gastroenterology, Athens, Greece, [3]University of Ioannina, Unit of Medical Technology and Intelligent Information Systems, Ioannina, Greece

Background. Liver involvement is common among patients with Sjögren's syndrome (SS) and can be attributed to many causes including primary biliary cholangitis, hepatitis C virus infection, non-alcoholic fatty liver disease (NAFLD) and drug. Especially, NAFLD which is high prevalent in the general population may also affect SS patients. Interestingly, shared underlying pathogenetic mechanisms of inflammation and apoptosis between NAFLD and SS, are closely linked to fibrogenesis. However, no studies have been conducted to explore the net effect of SS per se in liver fibrosis.
Objectives. To assess whether SS per se is associated with advanced liver fibrosis (LF).
Methods. This is a prospective study involving consecutive SS patients from the rheumatology outpatient clinic of the Department of Pathophysiology, "Laiko" General Hospital, Athens, Greece between June 1st and December 31st, 2021, who underwent transient elastography (TE) to assess LF and liver steatosis (LS). Liver stiffness was used as a measure of LF and controlled attenuation parameter for LS. The cut-offs for LF grading were as follows: F0-1: 2-7 kPa, F2: 7-10 kPa, F3: 10-14 kPa, and F4: >14 kPa. Clinically insignificant LF included F0-F1 stages and advanced LF the F2-F4 stages. The cut-offs for LS staging were as follows: S0-S1: 100-260 dB/m, S2: 260-290 dB/m, and S3: >290 dB/m. Similarly, low level LS included stages S0-S1 and high level of LS, the S2-S3 stages. As comparator group, individuals from the hepatology outpatient clinic with possible NAFLD/LS on ultrasonographic criteria (higher echogenicity than renal cortex and/or

splenic parenchyma) were recruited. All participants had negative work up for viral or alcoholic hepatitis, autoimmune liver diseases, transaminasemia or liver disease attributed to drug hepatotoxicity. Clinical, demographic and laboratory data were recorded at the time of TE for all participants, including confounders such as medical history of diabetes mellitus, hyperlipidemia and body mass index (BMI).

Results. In the current study, 52 SS patients (49 females, 94.2%) and 198 comparators (104 females, 52.5%) were finally recruited. The median disease duration (range) of SS patients was 8 (1-46) years. The median age (range) of SS and comparators was 62.5 (30-81) and 55 (19-86) years old, respectively. The comparators and SS group had similar prevalence of type 2 diabetes mellitus (T2DM) and hyperlipidemia and similar BMI. Patients with SS had less frequently high level of LS (27% vs 62%, $p<0.001$) and advanced LF [2 (3.8%) vs 34 (17.2%), $p=0.014$], than comparators. Univariable analysis of T2DM, hyperlipidemia, BMI, age, gender, steatosis, and disease status (SS or comparators) between individuals with insignificant and advanced LF revealed age, liver steatosis, BMI, and disease status as statistically significant features but only age was finally identified as independent risk factor in the multivariable analysis (Table I).

Conclusions. Sjögren's syndrome per se is not associated with advanced liver fibrosis.

Table I. Multivariable logistic regression analysis for risk factors associated with advanced liver fibrosis among patients with Sjogren's Syndrome and comparators.

Variables	Coefficient	Odds ratio	p-value	CI low	CI upper
Age	0.057	1.059	0.023	1.019	1.1
Body Mass Index	0.099	1.105	0.121	1.012	1.207
Presence of Sjögren's syndrome	-0.941	0.419	0.346	0.067	2.826
High liver steatosis	0.344	1.473	0.62	0.355	6.167

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UPDATE ON RADIOGRAPHIC EVIDENCE OF IMPLANT THERAPY IN SJÖGREN'S PATIENTS

Laing Gibbard L.P.*[1], Lee J.[2]
[1]University of Toronto, Faculty of Dentistry, Toronto, Canada; [2]University of Toronto, Faculty of Engineering Science, Toronto, Canada

Background. Sjögren's is a chronic, slowly progressive, poorly understood, multi-system, inflammatory autoimmune disease, primarily affecting the lacrimal and salivary glands. As a result of hyposalivation, the oral environment is severely affected leading to difficulty speaking, swallowing, tasting, eating, and chewing as well as to increased dental caries, tooth breakage, and tooth loss. With the success of dental implants as a modality to replace missing teeth, the knee-jerk reaction of dentists has frequently been to place implants to restore the dentition of Sjögren's patients. The limited evidence in the literature suggests that this is a viable option.

Methods. A retrospective study was performed using radiographs from implant treated Sjögren's patients whose implants had been in function for ≥ 2 years. Each of the Sjögren's implants was matched to 3 implants in non-Sjögren's control subjects based on age, gender, plant sites were digitized, and peri-implant bone level measurements were made using ImageJ software. Success of the implants was based solely on radiographic evidence as per previous criteria (bone loss <0.2 mm annually after the implant's first year of service).

Results. While the implant survival rate in Sjögren's patients after ≥2 years in function vs. those in control participants was similar [117/123 (95.1%) vs. 423/425 (99.5%)], the success rate was significantly different [70/123 (56.9%) vs. 406/425 (95.5%)] based on a criteria of bone loss <0.2 mm annually after the first year in function.

Conclusions. Sjögren's patients experienced more rapid bone resorption around their implants and a higher implant failure rate compared to the non-Sjögren's participants. Although the peri-implant bone loss was significantly greater in the Sjögren's patients, the prostheses nevertheless provided the patients with an aesthetic and functional solution to their tooth loss. Significance: While implant therapy is a viable option for Sjögren's patients, they must be informed prior to the initiation of implant therapy that there may be greater bone loss around the implants with the potential of loss of implants. Reasons for the rapid bone loss continue to be investigated.

PSS AND COVID-19 INFECTION

Poster 21

A SINGLE-CENTER COVID VACCINATION EXPERIENCE IN PATIENTS WITH SJÖGREN'S SYNDROME

Horvath I.F.*[1], Nagy B.[2], Barath S.[2], Orosz V.[1], Szanto A.[1]
[1]University of Debrecen, Faculty of Medicine, Division of Clinical Immunology, Debrecen, Hungary, [2]University of Debrecen, Institute of Laboratory Medicine, Debrecen, Hungary

Introduction. Vaccination against SARS-CoV2 is beneficial for patients with autoimmune disease. Therefore, we recommended basic immunization as soon as it has become available for our patients. We preferred mRNA-based vaccination based on the international recommendations. However, several patients received other types of vaccines at their own or their general practitioner's discretion. Based on the antibody levels against the SARS-CoV2 spike protein measured at the Institute of Laboratory Medicine of our university, we were able to draw initial conclusions about the effectiveness of vaccination regarding our primary Sjögren's syndrome patients.

Patients and methods. Antibodies to SARS-CoV2 spike protein were analyzed in the sera of 77 patients with primary Sjögren's syndrome after being vaccinated with two doses between 1st January and 30th April, 2021, at least 30 days after the second vaccination. Antibody responses were classified as high (above 250 U/ml), moderate (between 50 and 250 U/ml) and low (below 50 U/ml). Relying on the SPSS statistical program, we were seeking correlations between the serum levels and the EULAR Sjögren's syndrome disease activity index (ESSDAI) and the potential influence of the different immunosuppressive treatment modalities, respectively. For the statistical analysis, χ^2 tests were performed. Results: Pfizer vaccine was given to 58 patients, and the rest of our cohort received Moderna (2 patients), Sinopharm (10 patients), Astra Zeneca (6 patients) and Sputnik vaccine (1 patient). High antibody levels were found in 54 subjects (70.1%), moderate levels in 11 subjects (14.3%), and low levels in 12 subjects (15.6%). After having received the Pfizer vaccine, 86.2% had high, and only 5.2% had low antibody levels. One patient vaccinated with Moderna had high, while the other had low antibody level. The majority (55%) of those vaccinated with Astra Zeneca achieved high titers, and 17% were classified as low responders. After immunization with Sinopharm vaccine, 20% of the patients were classified into moderate response category, while the rest (80%) presented low antibody levels. We also measured low value in the serum of the patient that received the Sputnik vaccine. Serum levels of specific antibodies in patients not receiving any specific therapy (14 subjects) did not differ significantly from those treated with antimalarials (18 subjects), methotrexate (19 subjects), azathioprine (6 subjects), or low-dose steroids (20 subjects). Based on our results, the type of immunosuppressive treatment had less effect on the protection developed than the type of vaccination.

There was no significant correlation between Sjögren's syndrome disease activity and the degree of specific antibody response to the vaccine.

Conclusions. Our initial results suggest that the use of COVID vaccines is safe and effective for Sjögren's syndrome patients, regardless of the treatment used or of the ESSDAI.

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MODEL IMMUNIZATION WITH CORONAVIRUS-2 VACCINES INDUCE POTENT ANTIBODY RESPONSES BUT DOES NOT AGGRAVATE LYMPHOCYTE ABNORMALITIES IN PRIMARY SJÖGREN'S SYNDROME PATIENTS

Steinmetz T., De Wolff L., Terpstra J., Visser A., Bootsma H., Kroese F., Verstappen G.*
UMCG - Department of Rheumatology and Clinical Immunology, Groningen, Netherlands

Objectives. The peripheral lymphocyte compartment of patients with primary Sjögren's syndrome (pSS) differs strongly from healthy individuals. Whether this altered lymphocyte composition also abnormally changes during immune reactions, especially in the context of novel mRNA-vaccines, is unknown.

Methods. Peripheral blood samples from 26 pSS patients were compared to 6 healthy controls before Coronavirus-2 (CoV-2) vaccination (BNT162b2, ChAdOx1, mRNA-1273) and 7 days after secondary vaccination. Spike

1 (S1)-receptor binding domain (RBD)-neutralizing IgG antibodies were measured in serum samples. Within peripheral blood mononuclear cells (PBMC), lymphocytes were characterized using spectral flow cytometry and B and T cell subpopulations were phenotypically analyzed.
Results. Immunization induced CoV-2 specific serum antibodies in all pSS and healthy participants. When analyzing pSS and healthy individuals together, frequencies of circulating IgG+ RBD-binding antibody-secreting cells (ASC) and anti-CoV-2 serum titers correlated (r=0.42, p=0.022). Previously described alterations of peripheral B cells in pSS patients (like reduced memory B cells, increased naïve and transitional B cells and higher maturity of ASCs) remained stable during vaccination. Also the subset distribution of $CD4^+$ and $CD8^+$ T cells mainly stayed unchanged. However, $CD4^+CXCR5\text{-}PD\text{-}1^+$ T cells phenotypically mimicking peripheral helper TPH cells increased in pSS patients comparing pre- and post-vaccination (p=0.020), while circulating $CD4^+CXCR5^+PD\text{-}1^+$ follicular helper TFH cells declined (p=0.024).
Conclusions. An immune reaction induced by vaccination with the novel mRNA technology yields adequate antibody production and vaccine specific lymphocytes in pSS patients and controls. However, no major changes within the typical composition of lymphocyte subpopulations of pSS patients were observed despite small changes in TPH and TFH subsets.

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IMMUNOGENICITY AND SAFETY OF CHADOX1 NCOV-19 VACCINE IN PRIMARY SJÖGREN'S SYNDROME

Libardi Lira Machado K.L.[1], Oliveira Souza B.[1], Barbosa Beloni Lírio M.[1], Neves Burian A.P.[2], Gonçalves Rodrigues DeAguiar L.[1], Smith Sobral Vieira G.[1], Ribeiro Moulaz I.[1], Gomes M.D.P.[1], Tatiama Miyamoto S.[1], Vieira Serrano É.[1], Reis Neto E.[3], Teixeira-Carvalho A.[4], Valim V.*[1], Monticielo O.A.[3], De Souza V.A.[3], Ferreira G.A.[3], Inoue Sato E.[3], Xavier R.[3], Salviato Pillegi G.[3], Mill J.G.[1], Assis Martins-Filho O.[4]
[1]University Hospital of Federal University of Espírito Santo (HUCAM-UFES/EBSERH), Programa de Pós Graduação em Saúde Coletiva (PPGSC-UFES), Vitória, Brazil, [2]Centro de Referências de Imunobiológicos Especiais, Vitória, Brazil, [3]Core Group SAFER Study of the Brazilian Society of Rheumatology, São Paulo, Brazil, [4]Instituto Renè Rachou, Fundação Oswaldo Cruz, Belo Horizonte, Brazil

Introduction. There are few studies that evaluated the response to Covid-19 vaccines, in primary Sjögren's Syndrome (pSS) and none evaluated ChAdOx1 n-Cov19 (AstraZeneca/Fiocruz). The aim of this study was to evaluate the efficacy and safety of the ChAdOx1 n-Cov19, a viral vector vaccine, in pSS compared to healthy control (HC).
Methods. Patients with pSS >18 years, classified according to ACR/EULAR 2016 were included. Neutralizing antibodies against the Receptor Binding Domain - RBD portion of the Spike protein of SARS-CoV-2 (IgG-S) were measured by chemiluminescence (Abbott), before the first dose (D0) and 28 days after the second dose (D28*). The test is considered reactive if >50 AU/ml.
Results. Sixty pSS patients and 62 HC were recruited from a single center (HUCAM-UFES, Vitória, ES, Brazil). The HC group was homogeneous for sex (92% women) and younger than HC (47±11 vs. 39±13, p<0.05). In the pSS group, 45.2% were anti-Ro positive, mean ESSDAI was 3.2, 83.3% were using DMARD or immunosuppressant/biological therapy, 31.9% were in high immunosuppression. The frequency of mild adverse events (AE) was similar in both two groups. No serious AE, hospitalizations or death were reported. There was no difference between the PGA ("Patient's Global Assessment") after vaccination (4.5 vs.5, p=0.903).
Among seronegative individuals at baseline, the seroconversion rate (100% vs. 89%, p=0.02) was lower, and geometric mean titers (GeoMean IgG-S) was similar in pSS=696.9(CI95%237.6 -2,043) compared to HC=1,986(CI95%1,463-2,697; p=0.316). However, in those with high immunosuppression, the seroconversion (71%, p=0.001) and GeoMean titers were lower 229.4 (CI95%14.64-3,594, p=0.004). Patients in moderate to high disease activity (ESSDAI ≥5) showed lower seroconversion (60%, p=0.006) and Geomean titers 31.7 (CI95%0.06-15.4; p=0.004).
Conclusions. ChAdOX1 vaccine is safe and induced high GeoMean neutralizing antibodies titers and seroconversion rate in pSS patients similar to HC. Immunossuppression therapy and disease activity decreased the immune response to the vaccine.

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SARS-COV-2 INDUCES A SJÖGREN'S SYNDROME-LIKE PHENOTYPE

Shen Y.[1], Voigt A.[1], Goranova L.[1], Chiorini J.[2], Craft W.[1], Ostrov D.[1], Tuanyok A.[1], Nguyen C.*[1]
[1]University of Florida, Gainesville, USA, [2]National Institute of Dental and Craniofacial Research, Bethesda, USA

Sjögren's syndrome (SS) is a chronic and systemic autoimmune disease characterized by lymphocytic infiltration and the development of dry eyes and dry mouth due to the secretory dysfunction of the lacrimal and salivary glands. In recent years, infectious pathogens have been proved to be associated with SS, including Cytomegalovirus, Coxsackie, EBV, and lymphotropic virus-1 (HTLV-1). Studies suggest that infections caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may trigger an autoimmune response, as evidenced by increased autoantibodies in patients diagnosed with Coronavirus disease 2019 (COVID-19). To investigate the relationship between SARS-CoV-2 and SS, the study was performed by infecting humanized ACE2 mice with SARS-CoV-2. Mice infected with the virus showed a decreased saliva flow rate, elevated antinuclear antibodies (ANAs) and anti-SSB/La, and lymphocyte infiltration in the lacrimal and salivary glands. We detected the viral nucleocapsid protein in mice exocrine glands with significant apoptotic bodies by the acinar cells. Confirmed with clinical data, we also observed the elevation of SS-specific autoantibodies (ANA, anti-SSB/Ro52, and anti-SSA/La) and specific ANA patterns in sera from COVID-19 patients. One unique aspect of SS is the high degree of sexual dimorphism, with women being affected 10-20 times more than men. To determine whether COVID-19 patients exhibited an element of sexual dimorphism in the autoantibody response, we grouped the sera by sex. We found the male patients showed elevated anti-SSA/Ro52 compared to female patients (p=0.0029), and female patients had more diverse ANA patterns. Lastly, monoclonal antibodies isolated from recovered patients using single-cell antibody nanowells technology were shown to recognize the nuclear antigens. Overall, by observing SS-like phenotypes in mouse models and patients, our study confirms a direct pathogenic role of SARS-CoV-2 in SS.

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SARS-COV-2 INFECTION IN 898 PATIENTS WITH SJÖGREN'S SYNDROME: CHARACTERISTICS ASSOCIATED WITH POOR OUTCOMES

Flores-Chavez A.*[1], Yazdany J.[2], Kostov B.[4], Brito-Zerón P.[3], Romão V.C.[5], Armagan B.[6], Seror R.[7], Melchor Díaz S.[8], Carubbi F.[9], Priori R.[10], Valim V.[27], Lawson-Tovey S.[11], Hyrich K.[12], Strangfeld A.[13], Gossec L.[14], Carmona L.[15], Mateus E.F.[16], Schaefer M.[13], Hausmann J.S.[17], Liew J.W.[18], Gianfrancesco M.[19], Jacobsohn L.[19], Sirotich E.[20], Gore-Massey M.[21], Sufka P.[22], Bhana S.[23], Grainger R.[24], Wallace Z.[25], Ramos-Casals M.[1], Machado P.M.[26]
[1]Department of Autoimmune Diseases, ICMiD, Hospital Clínic, Barcelona, Spain, [2]Division of Rheumatology, University of California, San Francisco, USA, [3]Research and Innovation Group in Autoimmune Diseases, Millenium Balmes-Hospital CIMA Sanitas, Barcelona, Spain, [4]Primary Healthcare Transversal Research Group, IDIBAPS, Barcelona, Spain, [5]Rheumatology Department, Centro Hospitalar Universitário Lisboa Norte, Centro Académico de Medicina de Lisboa (CAML); Rheumatology Research Unit, Instituto de Medicina Molecular, Faculdade de Medicina, CAML, Lisboa, Portugal, [6]Hacettepe University Faculty of Medicine, Division of Rheumatology, Ankara, Turkey, [7]Rheumatologye Department, Université Paris-Sud, Paris, France, [8]Department of Rheumatology, Hospital 12 de Octubre, Madrid, Spain, [9]Internal Medicine and Nephrology Unit, University of L'Aquila, L'Aquila, Italy, [10]Sapienza Università di Roma, Roma, Italy, [11]University of Manchester, Manchester, UK, [12]Manchester University NHS Trust, Manchester, UK, [13]German Rheumatism Research Center (DRFZ Berlin), Epidemiology and Health Services Research, Berlin, Germany, [14]Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique, Paris, France, [15]Instituto de Salud Musculoesquelética, Madrid, Spain, [16]Portuguese League Against Rheumatic Diseases (LPCDR), Lisboa, Portugal, [17]Division of Rheumatology and Clinical Immunology, Harvard Medical School, Boston, USA, [18]Section of Rheumatology, Department of Medicine, Boston University School of Medicine, Boston, USA, [19]Division of Rheumatology, Department of Medicine, University of California, San Francisco, USA, [20]Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Canada, [21]Lupus Foundation of America, USA, [22]Healthpartners, St. Paul, MN, USA, [23]Pfizer, Inc, New York, USA, [24]Department of Medicine, University of Otago Wellington, New Zealand, [25]Clinical Epidemiology Program, Division of Rheumatology, Allergy, and Immunology, Massachusetts General Hospital, Harvard Medical School, Massachusetts, USA, [26]Centre for Rheumatology

and Department of Neuromuscular Diseases, University College London, London, UK, [27]University Hospital Cassiano Antônio Moraes (HUCAM-UFES/EBSERH), Federal University of Espírito Santo, Vitoria, Brazil

Objectives. To determine characteristics associated with a more severe COVID-19 outcome in people with Sjögren's disease (SJD).
Methods. People with SJD and COVID-19 reported to two international registries (Sjögren Big Data Consortium and COVID-19 Global Rheumatology Alliance) from March 2020 to October 2021 were included. An ordinal COVID-19 severity scale was defined: (1) not hospitalized, (2) hospitalized with no ventilation, (3) hospitalized requiring non-invasive ventilation, (4) hospitalized requiring invasive ventilation, and (5) death. Odds ratios (OR) were estimated using a multivariable ordinal logistic regression model adjusted for age, sex, comorbidities and anti-rheumatic medications included as covariates.
Results. A total of 898 people with SJD were included (825 (91.8%) women, mean age SARS-CoV-2 infection diagnosis: 55.5 years), including 652 patients with primary SJD and 246 with other associated systemic rheumatic diseases. 33.9% were hospitalized, 14.5% required ventilation, and 4.3% died. In the multivariable model, older age (OR 1.03, 95% CI 1.02 to 1.05), male sex (OR 1.81, 95% CI 1.10 to 2.92), two or more comorbidities (OR 2.99, 95% CI 1.92 to 4.67; vs none), baseline therapy with corticosteroids (OR 2.04, 95% CI 1.20 to 3.46), immunosuppressive agents (OR 2.09, 95% CI 1.30 to 3.38) and B-cell depleting agents (OR 5.38, 95% CI 2.77 to 10.47) were associated with worse outcomes (reference for all medications: hydroxychloroquine only).
Conclusions. More severe COVID-19 outcomes in individuals with Sjögren's are largely driven by demographic factors and baseline comorbidities. Patients using immunosuppressants, especially rituximab, also experienced more severe outcomes.

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SAFETY AND EFFICACY OF SARS-COV-2 VACCINATION IN 1237 PATIENTS WITH PRIMARY SJÖGREN SYNDROME

Inanc N.*[1], Kostov B.[2], Priori R.[3], Flores-Chavez A.[7], Carubbi F.[4], Szántó A.[5], Valim V.[8], Bootsma H.[6], Praprotnik S.[9], Trevisani V.F.M.[19], Hernández-Molina G.[10], Hofauer B.[11], Pasoto S.G.[12], Dupla M.L.[13], Bartoloni Bocci E.[14], Rischmueller M.[15], Devauchelle-Pensec V.[16], Abacar K.Y.[1], Giardina F.[3], Alunno A.[4], Horváth I.F.[5], De Wolff L.[6], Caldas L.[19], Retamozo S.[17], Ramos-Casals M.[7], Brito-Zerón P.[18]

[1]Marmara University, School of Medicine, Division of Rheumatology, Istanbul, Turkey, [2]Primary Care Centre Les Corts, Consorci d'Atenció Primària de Salut Barcelona Esquerra (CAPSBE), Barcelona, Spain, [3]Department of Internal Medicine and Medical Specialties, Rheumatology Clinic, Sapienza University of Rome, Italy; Saint Camillus International University of Health Science, UniCamillus, Rome, Italy, [4]Internal Medicine and Nephrology Unit, Department of Life, Health and Environmental Sciences, University of L'Aquila, and Department of Medicine, ASL 1 Avezzano-Sulmona-L'Aquila, L'Aquila, Italy, [5]University of Debrecen, Debrecen, Hungary, [6]University Medical Center Groningen, Groningen, Netherlands, [7]Department of Autoimmune Diseases, ICMiD, Hospital Clínic, Barcelona, Spain, [8]Federal University of Espírito Santo, Vitoria, Brazil, [9]University Clinical Center, Ljubljana, Slovenia, [10]Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Vasco de Quiroga, Mexico, [11]University Hospital Klinikum rechts der Isar, Münich, Germany, [12]Disciplina de Reumatologia, Laboratório de Autoimunidade (DLC + LIM17), Hospital das Clínicas da Faculdade de Medicina da USP (HCFMUSP), R. Dr. Ovídio Pires de Campos, 225 - Cerqueira César, Sao Paolo, Brazil, [13]Department of Internal Medicine, Hospital Universitari Joan XXIII, Tarragona, Spain, [14]University of Perugia, Perugia, Italy, [15]The Queen Elizabeth Hospital, Adelaide, Austria, [16]Cavale Blanche-University Hospital, Brest, France, [17]Grup de Recerca Consolidat en la Síndrome de Sjögren (GRESS), Agència de Gestió d'Ajuts Universitaris i de Recerca (AGAUR), Generalitat de Catalunya, Barcelona, Spain, [18]Department of Medicine, University of Barcelona, Barcelona, Spain, [19]Federal University of São Paulo, São Paulo, Brazil

Objectives. To investigate the safety and efficacy of SARS-Cov-2 vaccination in a large international cohort of patients with primary Sjögren syndrome due to scarcity of data in this population.
Methods. By the first week of May 2021, all Big Data Sjögren Consortium centers had been contacted and asked for Registry patients to be included in the study if they had received at least one dose of any SARS-CoV-2 vaccine. The in-charge physician asked patients about local and systemic reactogenicity, using a pre-defined electronic questionnaire to collect epidemiologic data, COVID 19 vaccination data, and COVID 19 vaccination side effects. Adverse events were defined as those reported by the patient at the site of injection within 7 days from vaccination (reactogenicity) as local adverse events, systemic symptoms as systemic side effects, and post-vaccination AEs of special interest related to SS as SS flares.
Results. The vaccination data of 1237 patients (1170 women, with a mean age at diagnosis of primary SjS of 50.5 13.2) were received. A total of 835 patients (67 percent) reported any adverse event, including local (53 percent) and systemic (50 percent) AEs. Subjective symptoms (63%) were the most common local AEs, followed by objective signs at the injection site (16%) and general symptoms were the most commonly reported systemic AEs (46 percent), followed by musculoskeletal (25 percent), gastrointestinal (9 percent), cardiopulmonary (3 percent), and neurological (2 percent). People under 60 years old had a higher risk of developing AE after vaccination (OR 2.48, CI 95 1.89-3.27 percent), as did those with low systemic SS activity (OR 1.62, CI 95 1.22-2.15) and those who received mRNA vaccines, according to a multivariate analysis (OR 1.57, CI 95 percent 1.12-2.18). The risk of developing systemic AEs was also higher in women (OR 2.85, CI 95 percent 1.60-5.2346), White people (OR 1.73, CI 95 1.14-2.65), and those who received a deficient vaccination regimen (OR 1.78, CI 95 1.12-2.88 percent). In addition to 141 (11%) patients who reported a significant worsening/exacerbation of their pre-vaccination sicca symptoms as a result of post-vaccination SS flares, 15 (1.2%) patients (13 women, mean age at vaccination 41.9 years) reported active involvement in the glandular (n=8), articular (n=7), cutaneous (n=6), pulmonary (n=2), and peripheral nervous system (n=1) domains as post-vaccination systemic flare. All side effects and flares subsided within 1-3 weeks, with no lasting effects or deaths. In terms of vaccination efficacy, breakthrough SARS-CoV-2 infection was confirmed after vaccination in three (0.24 percent) patients, all of whom recovered completely, and positive anti-SARS-Cov-2 antibodies were detected in approximately 95 percent of vaccinated SjS patients, according to data available.
Conclusions. SARS-CoV-2 vaccination in patients with primary SjS, like other vaccines with adequate response and no safety signals, raised no concerns about the vaccine's efficacy or safety.

EVOLVING TOPICS IN pSS THERAPY

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IN SJÖGREN SYNDROME SALIVARY GLANDS BARICITINIB DOWNREGULATES INFLAMMATION VIA A DOUBLE EFFECT ON EPITHELIAL CELLS AND INFLAMMATORY INFILTRATES

Colafrancesco S.*[1], Barbati C.[1], Giardina F.[1], Buoncore G.[1], Izzo R.[1], Gattamelata A.[1], Spinelli F.R.[1], Scarpa S.[1], Fusconi M.[1], Merelli I.[2], Cavalli G.[3], Alessandri C.[1], Priori R.[1], Conti F.[1]

[1]Sapienza University, Rome, Italy, [2]Italian National Research Council (CNR), Milan, Italy, [3]IRCCS San Raffaele Scientific Institute and Vita-Salute San Raffaele University, Milan, Italy

Objectives. In the pathogenesis of primary Sjögren Syndrome (pSS), salivary gland (SG) epithelial cells (SGECs) participate in the inflammatory process via activation of autophagy and expression of activation molecules (1). Most of the currently available drugs for pSS primarily target lymphocytes infiltrating SGs with limited effects on the epithelial cell component. We hypothesize that treatment with baricitinib dampens SG inflammation in pSS by reducing SGEC autophagy and activation in addition to exerting anti-inflammatory effects on immune cells.

Methods. SGECs were isolated from pSS minor SG biopsies and evaluated by flow-cytometry, immunoblotting (WB), and immunofluorescence (IF) to assess autophagy (LC3IIB, p62, LC3B+/LAMP1+ staining), apoptosis (annexin V/PI, Bcl-2) and activation (ICAM-1) following treatment with baricitinib. Single-cell analysis was performed to evaluate pSS minor SG transcriptome following treatment with baricitinib.

Results. In SGECs, a baricitinib induced downregulation of autophagy was detected by WB and flow cytometry (n=8) (decreased LC3IIB, increased p62) and confirmed by IF (n=3) [reduction in autophagolysosomes (LC3B+/LAMP1+ staining)]; increase in apoptosis (increased annexin V/PI, decreased Bcl2) and decrease in activation (decreased ICAM-1) were detected too. Single-cell analysis on minor SG (n=1) confirmed a baricitinib induced dampening of autophagy and activation and revealed both reparative and immune suppressive effects (Figure).

Conclusions. *In vitro* treatment with baricitinb exerts both restorative effects on pSS SGECs homeostasis and activation and anti-inflammatory properties on immune cells infiltrating SGs. These data indicate that baricitinib might have incremental therapeutic potential compared to agents exclusively targeting immune cells in pSS.

Reference

1. Colafrancesco S *et al*.: Maladaptive autophagy in the pathogenesis of autoimmune epithelitis in Sjögren's syndrome. *Arthritis Rheumatol* 2022; 4(4): 654-64.

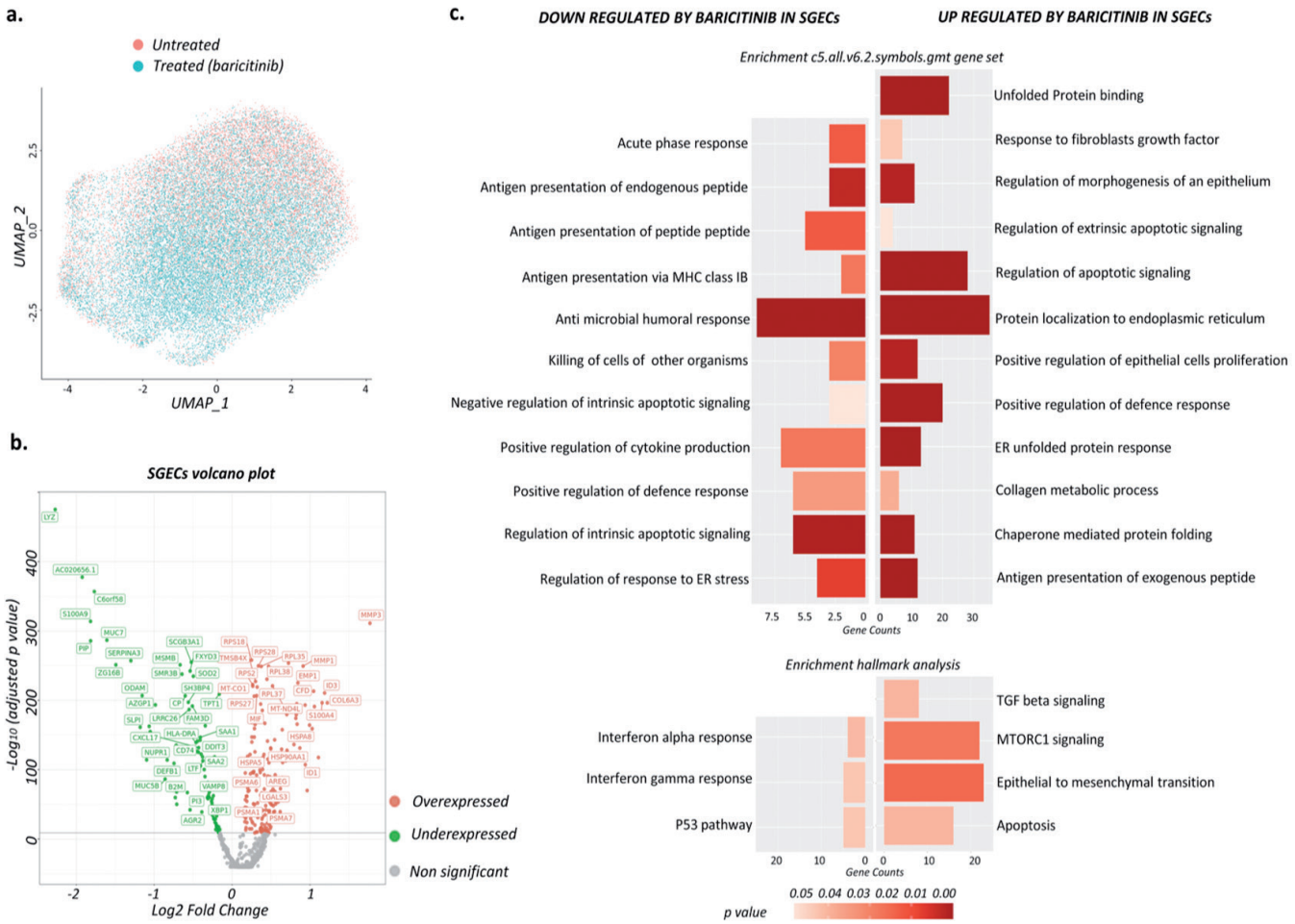

Figure. UMAP (Uniform Manifold Approximation and Projection) representation of baricitinib induced changes on global SG cells' population (**a**). Volcano plot indicating top significantly down (green dots) and up (red dots) regulated genes in SGECs following treatment with baricitinib with labels indicating most relevant pathogenic genes (**b**). Most relevant down (left panel) and up (right panel) regulated pathways by baricitinib in SGECs (enrichment "c5.allv6.2.symbols.gmt gene set" analysis in the top panel, enrichment "hallmark" analysis in the bottom panel) (**c**).

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METFORMIN IMPROVES OBJECTIVE MEASURES OF DRY EYES AND FOCUS SCORE IN SJÖGREN'S DISEASE: A RETROSPECTIVE OBSERVATIONAL STUDY

Rasmussen A.*[1], Scofield R.H.[2], Grundahl K.[1], Radfar L.[3], Lessard C.J.[1], Farris A.D.[2]

[1]Genes and Human Disease Program, Oklahoma Medical Research Foundation, Oklahoma City, USA, [2]Arthritis and Clinical Immunology Program, Oklahoma Medical Research Foundation, Oklahoma City, USA, [3]Department of Oral Diagnostics, College of Dentistry, University of Oklahoma Health Sciences Center, Oklahoma City, USA

Introduction. Metformin (dimethyl biguanide, Met) is a widely used, first-line antidiabetic drug with AMPK-dependent anti-inflammatory and immunomodulatory effects. In vitro studies and human trials in SLE and multiple sclerosis have shown that Met associates with reduced Th17 cells, IL-17, IL-1beta, IL-6, IFN-gamma, and TNF-alpha, while restoring or increasing regulatory T-cells (Treg). Sjögren's Disease (SjD) is a systemic autoimmune disorder characterized by autoantibody production and lymphocytic infiltration of the exocrine glands. In SjD, T cells participate in target organ inflammation and promote B cell activation; it has been proposed that an imbalance between pro-inflammatory Th17 and Tfh cells and their regulatory counterparts, Treg and Tfr cells, is a key component of pathogenesis. A study of an SjD mouse model treated with Met showed improved salivary gland function and re-establishment of the T cell equilibrium. Based on this premise, we reviewed the potential impact of Met on SjD in a large cohort.
Methods. The clinical and serologic features of patients meeting the ACR-EULAR classification criteria for SjD in the OMRF SjD cohort were retrospectively reviewed. Cases were defined as SjD diabetic patients treated with Met (SjD-Met) at the time of evaluation (n=31). The comparison groups were 1) SjD non-diabetic, not on Met matched by age, sex, and race 1:4 to the cases (SjD-match, n=124); 2) SjD diabetic patients not treated with Met (SjD-DM-notMet, n=59); 3) All diabetic SjD, irrespective of treatment (SJD-DM, n=84); and 4) All non-diabetic SjD in the cohort (SjD-nonDM, n=375).
Results. 459 participants that met SjD classification had sufficient data for analysis. No significant differences in sociodemographic features were observed across groups. SjD-Met subjects had lower rates of (+) Schirmer's and OSS than SjD-match (OR 0.40, p=0.028; and OR 0.24, p=0.004, respectively). Interestingly, while no differences were observed in salivary flow, SjD-Met also showed significantly lower focus scores on salivary gland biopsy than SjD-match (1.88+-1.32 vs. 3.26+-2.91, p=0.0002).
This pattern persisted when SjD-Met was compared to SjD-DM-notMet but the effects disappear when comparing all diabetics to non-diabetics so this seems directly associated with Met. The differences that could be attributed to diabetes, since they were observed when comparing all diabetics (irrespective of treatment) to non-diabetics, were lower salivary flow volumes and higher ESR in SjD-DM. No differences were identified in disease activity, autoantibodies, complement, or immunoglobulin levels. Limited ESSPRI data precluded drawing conclusions despite a consistent trend toward lower ESSPRI scores in the SjD-Met group.
Conclusions. Our retrospective study shows that SjD patients receiving Met have lower rates of abnormal ocular tests (Schirmer's and OSS) and less extensive focal lymphocytic infiltration of the minor salivary glands (Focus Score) than their counterparts not on Met. These results justify the design of prospective, randomized, double-blind control trials of Met, an accessible and safe drug for SjD, a disease with great unmet therapeutic needs.

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SAFETY AND TOLERABILITY OF NIPOCALIMAB ADMINISTERED AT DIFFERENT RATES OF INTRAVENOUS INFUSION IN HEALTHY ADULTS: A PHASE 1 PLACEBO-CONTROLLED SINGLE-DOSE STUDY

Leu J.H.[1], Vermeulen A.[2], Zazzetti F.*[3], Ling L.E.[4]

[1]Janssen Research and Development, LLC, Spring House, USA, [2]Janssen Research and Development, a division of Janssen Pharmaceutica NV, Beerse, Belgium, [3]Janssen Medical Affairs Global Services, LLC, Buenos Aires, Argentina, [4]Janssen Research and Development, LLC, Cambridge, USA

Objectives. Primary Sjögren's Syndrome (pSS) is a chronic, progressive autoimmune disease characterized by abnormally high immunoglobulin G (IgG) levels. Standard of care treatments sometimes offer symptom relief but there is a need for options that alter the disease course. Nipocalimab, which is in clinical development for the treatment of pSS, targets the IgG binding site on neonatal Fc receptor (FcRn) to reduce serum levels of total and pathogenic IgG. The objective of this study was to assess the safety and tolerability of single doses of nipocalimab administered at different IV infusion rates in healthy adults to support the potential use of shortened infusions in future studies.
Methods. The trial was a single dose, sequential, randomized, double-blind, placebo-controlled, escalating dose and infusion rate study. Eligible participants were males or females aged 18-55 years with no clinically significant medical or physical conditions. Participants were randomized to 1 of 5 cohorts (n=8 per cohort [6 nipocalimab, 2 placebo]) to receive nipocalimab 30 mg/kg IV infused over 60, 30, 15 or 7.5 min (0.5, 1, 2, or 4 mg/kg/min), nipocalimab 60 mg/kg IV infused over 15 min (4 mg/kg/min) or matching placebo. Escalation to the next dose level was permitted following review by a safety monitoring committee. Safety was assessed by the frequency and nature of treatment-emergent adverse events (TEAEs), as well as abnormalities in laboratory assessments and vital signs. Pharmacokinetics of nipocalimab were also assessed.
Results. A total of 40 participants (70% female, 93% white) received study drug and were included in the safety analysis; 39 completed the study. A total of 12 participants (40%) experienced TEAEs across all nipocalimab dosing cohorts and 1 (10%) participant experienced TEAEs following administration of placebo. The most frequently reported TEAE was headache, reported by 6 participants with nipocalimab and 1 participant with placebo. Nausea was reported by 3 participants receiving nipocalimab. Grade 2 injection site reactions were reported by 2 participants but were considered unrelated to the investigational agent. None of the TEAEs were severe, and no participants discontinued treatment due to TEAEs; there were no serious adverse events or deaths. Only 4 participants experienced AEs that occurred within 24 hours after the infusion that were considered related to the study drug. Lower rates of nipocalimab infusion were associated with fewer TEAEs, while participants receiving 4 mg/kg/min (as either 30 mg/kg infused over 7.5 min or 60 mg/kg infused over 15 min) reported more TEAEs (Table).
Conclusions. Single doses of nipocalimab, when administered at doses up to 60 mg/kg and infusion rates up to 4 mg/kg/min were safe and well-tolerated in healthy adults. The frequency of reported TEAEs was lower in participants receiving IV nipocalimab at rates of 1 or 2 mg/kg/min, providing a target infusion rate for current and future studies.

Table. TEAEs by dosing cohort (safety population).

	Nipocalimab						
TEAEs, n (%)	30 mg/kg (60 min; 0.5 mg/kg/min)	30 mg/kg (30 min; 1 mg/kg/min)	30 mg/kg (15 min; 2 mg/kg/min)	30 mg/kg (7.5 min; 4 mg/kg/min)	60 mg/kg (15 min; 4 mg/kg/min)	Total	Placebo
Participants dosed	6 (100)	6 (100)	6 (100)	6 (100)	6 (100)	30 (100)	10 (100)
Participants with TEAEs	3 (50)	1 (17)	2 (33)	3 (50)	3 (50)	12 (40)	1 (10)
Most frequent TEAEs							
Headache	1 (17)	1 (17)	0	2 (33)	2 (33)	6 (20)	1 (10)
Nausea	0	0	0	1 (17)	2 (33)	3 (10)	0
Vomiting	0	0	0	0	2 (33)	2 (7)	0
Back pain	0	0	1 (17)	0	1 (17)	2 (7)	0
Nasal congestion	0	0	0	2 (33)	0	2 (7)	0
Rhinorrhea	0	0	0	2 (33)	0	2 (7)	0
Pruritis	0	0	0	1 (17)	1 (17)	2 (7)	0
Rash	0	0	0	1 (17)	1 (17)	2 (7)	0

TEAE, treatment-emergent adverse event.

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DESIGN OF A PHASE 2, MULTICENTER, RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND STUDY TO ASSESS THE EFFICACY AND SAFETY OF NIPOCALIMAB, AN FCRN ANTAGONIST, IN ADULTS WITH PRIMARY SJÖGREN'S SYNDROME

Hubbard J.*[1], Campbell K.[1], Sivils K.[1], Hoffman R.W.[1], Lo K.H.[1], Leu J.H.[1], Liva S.G.[1], Zuraw Q.[1], Stevens A.M.[1], Berhanu A.[1], Scofield R.H.[4], Seror R.[2], Wallace D.J.[3]

[1]Janssen Research & Development, LLC, Spring House, USA, [2]Department of Rheumatology, Université Paris-Saclay, INSERM U1184: Centre for Immunology of Viral Infections and Autoimmune Diseases, Assistance Publique-Hôpitaux de Paris, Hôpital Bicêtre, Le Kremlin Bicêtre, Paris, France, [3]Division of Rheumatology, Cedars-Sinai Medical Center, David Geffen School of Medicine, UCLA, Los Angeles, USA, [4]Arthritis & Clinical Immunology Program, Oklahoma Medical Research Foundation, Dept of Medicine, University of Oklahoma Health Sciences Center, Medical & Research Services, Oklahoma City Dept of Veterans Affairs Medical Center, Oklahoma City, USA

Objectives. Dysregulated humoral immunity is a hallmark of primary Sjögren's Syndrome (pSS). This dysregulation involves aberrant B-lymphocyte activity resulting in abnormally high immunoglobulin G (IgG) levels and the production of pathogenic autoantibodies, particularly those reactive with Ro/La ribonuclear complexes. pSS can affect almost any organ system, and current evidence-based therapies only offer some symptom relief, but no treatment has been shown to alter the disease course. Nipocalimab is a high-affinity, fully human monoclonal antibody that reduces circulating IgG levels by selectively blocking the interactions of IgG, including pathogenic pSS autoantibodies, with the neonatal Fc receptor (FcRn). Nipocalimab has previously induced rapid, safe, and durable serum IgG reductions in healthy volunteers (NCT02828046) and in autoantibody-driven myasthenia gravis in adults (NCT03896295), suggesting that nipocalimab may treat a broad range of autoimmune disorders associated with autoantibodies, immune complexes and B-lymphocyte hyperactivity, including pSS. The goal of this study is to evaluate the efficacy and safety of nipocalimab in pSS patients.

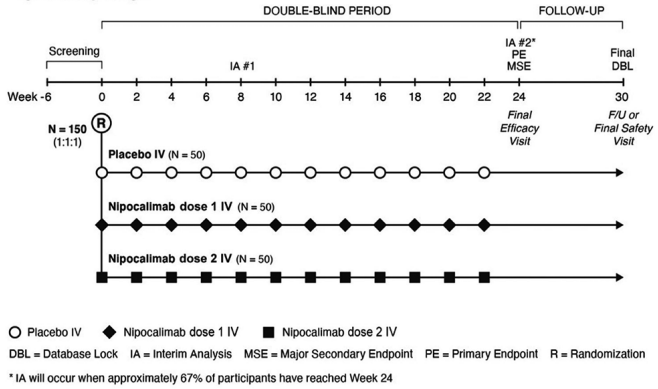
Methods. This is a phase 2, multicenter, randomized, placebo-controlled, double-blind study (NCT04968912) enrolling adults with moderately-to-severely active pSS. The study consists of a ≤6-week screening period, 24-week double-blind treatment period, and a 6-week follow-up period (Figure).

Participants are randomized 1:1:1 to treatment every 2 weeks with intravenous nipocalimab dose 1, nipocalimab dose 2, or placebo, through Week 22. All participants may receive protocol-permitted background standard of care, such as immunomodulators, antimalarial drugs, or glucocorticoids.

Results. The primary efficacy endpoint is change from baseline in Clinical European League Against Rheumatism Sjögren's Syndrome Disease Activity Index (clinESSDAI) score at Week 24. Major secondary efficacy endpoints assessed at Week 24 are change in EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI); improvement in disease activity (clinESSDAI/ESSDAI); and response to treatment according to the Composite of Relevant Endpoints for Sjögren's Syndrome (CRESS) (See Table for others). Safety endpoints include adverse events (AEs), abnormal vital signs and laboratory parameters.

Conclusions. This ongoing phase 2 study evaluates the safety and efficacy of nipocalimab in patients with moderately-to-severely active pSS, testing multiple clinical outcome measures.

Figure. Study design.



○ Placebo IV ◆ Nipocalimab dose 1 IV ■ Nipocalimab dose 2 IV

DBL = Database Lock IA = Interim Analysis MSE = Major Secondary Endpoint PE = Primary Endpoint R = Randomization

* IA will occur when approximately 67% of participants have reached Week 24

Table. Other Secondary and Exploratory Endpoints

Sjögren's Syndrome Responder Index (SSRI) response
Pharmacokinetics
Anti-drug and neutralizing antibodies
Reduction in disease-associated biomarkers including total serum IgG, autoantibodies, rheumatoid factor, inflammatory markers

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IANALUMAB (VAY736) SAFETY AND EFFICACY IN PATIENTS WITH SJÖGREN'S SYNDROME: 52 WEEK RESULTS FROM A RANDOMIZED, PLACEBO-CONTROLLED, PHASE 2B DOSE-RANGING TRIAL

Dörner T.*[1], Bowman S.J.[2], Fox R.[3], Mariette X.[4], Papas A.[5], Grader-Beck T.[6], Fisher B.A.[2], Barcelos F.[7], De Vita S.[8], Schulze-Koops H.[9], Moots R.J.[10], Junge G.[11], Woznicki J.[12], Sopala M.[11], Luo W.[12], Hueber W.[11]

[1]Department Medicine/Rheumatology and Clinical Immunology Charite Universitätsmedizin, Berlin, Germany, [2]Department of Rheumatology, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK, [3]Scripps Memorial Hospital and Research Institute, California, USA, [4]Université Paris-Saclay, Paris, France, [5]Division of Oral Medicine, Tufts School of Dental Medicine, Massachusetts, USA, [6]Division of Rheumatology, Johns Hopkins School of Medicine, Baltimore, USA, [7]Instituto Português de Reumatologia, Lisbon, Portugal, [8]Division of Rheumatology, DAME, University Hospital of Udine, Udine, Italy, [9]Division of Rheumatology and Clinical Immunology, Ludwig- Maximilians-University of Munich, Munich, Germany, [10]Academic Rheumatology Department, Aintree University Hospital, Liverpool, UK, [11]Novartis Pharma AG, Basel, Switzerland, [12]Novartis Pharmaceuticals Corporation, East Hanover, USA

Background. Sjögren's syndrome (SS) is an autoimmune disease affecting excretory glands and characterized by B-cell hyperactivity. Ianalumab (VAY736) is a human monoclonal antibody to B-cell activating factor receptor, engineered for direct ADCC-mediated B-cell depletion. A Phase 2b study evaluated three dose levels of Ianalumab (VAY736) vs placebo (PBO) in EULAR Sjögren's syndrome (SS) Disease Activity Index (ESSDAI) change from baseline (CHB) and other secondary endpoints. Primary results at Week (Wk) 24 were reported previously and showed statistically significant and clinically relevant dose-response1. Here we report 52 wks safety and exploratory efficacy from extended blinded treatment period 2 (TP2).

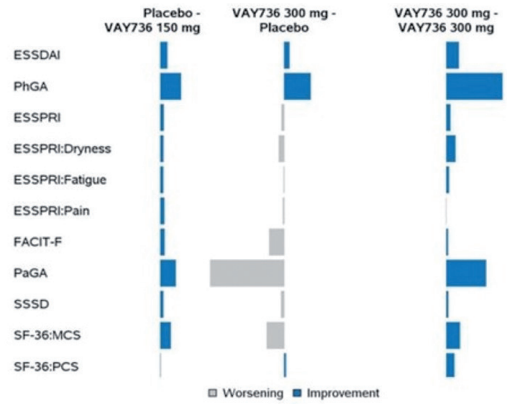
Methods. 190 patients were randomized equally to sc VAY736 (5/50/300 mg) or PBO every 4 Wks (q4w) in a blinded manner. Eligible patients fulfilled American European Consensus Group (AECG) criteria, were anti-Ro/SSA+, had ESSDAI ≥6 and EULAR SS Patient Reported Index (ESSPRI) ≥5. At Wk 24, PBO-treated patients were switched to VAY736 150 mg, and patients on 300 mg were re-randomized to continue 300 mg or PBO for 28 Wks in TP2. Patients were followed post-treatment for ≥20 Wks. Safety was assessed for all periods. Due to lack of PBO-control in TP2, descriptive efficacy analysis was performed for all efficacy endpoints.

Results. Overall, there was no dose dependency of treatment-emergent adverse events (TEAEs) except for injection-site reactions, which were mostly mild-to-moderate in severity. Lymphopenia and neutropenia were mostly grade (G)1 and G2, and none G4. Most common TEAEs were infections

Table. Key Safety Data (all study periods up to Week 52)†.

n (EAIR)[1]	5 mg 24 Wks (N=47)	50 mg 24 Wks (N=47)	150 mg 28 Wks* (N=47)	Any 300 mg (N=47)
Any AE	**43 (517.5)**	**43 (423.3)**	**44 (621.0)**	**45 (544.6)**
Any SAE	**3 (5.9)**	**5 (10.7)**	**8 (19.9)**	**8 (13.6)**
Infections and infestations (SOC)[2]	**33 (154.1)**	**31 (119.2)**	**34 (162.0)**	**38 (127.7)**
Nasopharyngitis[3]	7 [15.5]	4 [8.5]	9 [22.1]	9 [16.5]
Upper respiratory tract infections[3]	6 [12.8]	8 [17.8]	5 [11.6]	8 [13.6]
Bronchitis[3]	3 [6.2]	3 [6.2]	4 [9.5]	4 [6.6]
Tracheobronchitis[3]	1 [2.0]	0 [0.0]	0 [0.0]	3 [5.0]
Pneumonia[3]	1 [2.0]	0 [0.0]	1 [2.2]	2 [3.3]
Blood & Lymphatic Disorders (SOC)[2]	**8 (18.0)**	**9 (20.8)**	**6 (14.3)**	**9 (16.8)**
Lymphopenia[3]	4 [8.4]	4 [8.6]	3 [6.8]	2 [3.3]
Neutropenia[3]	5 [10.7]	1 [2.1]	2 [4.5]	4 [6.9]
Injection site reaction[3]	**4 (8.3)**	**9 (21.4)**	**17 (52.7)**	**27 (90.8)**

†Includes all safety data from TP1, TP2 and post-treatment follow-up; cut-off 06-Feb-2020
*150 mg also includes placebo-controlled patients who were switched to VAY736 150 mg at Week 24
[1]EAIR, incidence rate per 100 subject years. For patient with an event, exposure time is censored at time of first event
[2]Number of patients with at least one AE in SOC
[3]PT, preferred term
AE, adverse event; SAE, serious adverse event; SOC, system organ class; Wks, weeks.



ESSAI, EULAR Sjögren's Syndrome Disease Activity Index; ESSPRI, EULAR Sjögren's Syndrome Patient Reported Index; EULAR, European League Against Rheumatism; FACIT-F, Functional Assessment of Chronic Illness Therapy Fatigue; MCS, Mental component Summary; PaGa, Patient Global assessment; PCS, Physical Component Summary; PhGA, Physician Global Assessment; SF, Short Form; SSSD, Sjögren's Syndrome Symptom Diary

Figure. Summary of efficacy data at Week 52 (Treatment period from Wk 24 to Wk 52).

and infestations in exposure-adjusted analysis of incidence rates. Nasopharyngitis and upper respiratory tract infections were most common TEAEs, with no dose response (Table). At Wk 52, efficacy was sustained for patients who continued 300 mg in TP2 (ESSDAI, ESSPRI, Patient's (PaGA) and Physician's Global Assessments (PhGA) CHB: –9.06, –1.91, –22.03, and –35.80, respectively). Efficacy was partially lost for 300 mg patients who switched to PBO at Wk 24 (Figure). Slight improvement was noted for PBO patients who switched to 150 mg. Stimulated whole salivary flow at Wk 24 was improved for 300 mg (PBO-adjusted CHB 0.20 ml/min; p=0·037); at last measurement at Wk 48, further improvement was observed in 300 mg group that continued treatment (0.45 ml/min CHB) vs group switched to PBO (0.22 ml/min CHB).

Conclusions. Ianalumab 300 mg was well tolerated through 52 Wks. Exploratory efficacy measures showed that continued dosing of 300 mg sc q4w provided sustained clinical benefit.

Reference

1. Bowman *et al.*: *Lancet* 2022; 399(10320): 161-71.

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DYNAMICS OF US-CHANGES IN THE STRUCTURE OF SALIVARY GLANDS WITH CYCLOPHOSPHAMIDE THERAPY DURING ONE YEAR IN PATIENTS WITH PRIMARY SJÖGREN'S SYNDROME

Khvan Y.*[1], Torgashina A.[1], Chaltsev B.[1], Vasiliev V.[2]
[1]*V.A. Nasonova Research Institute of Rheumatology, Moscow, Russian Federation,* [2]*MEDSI, Moscow, Russian Federation*

Background. In the international scientific community there has been active discussion about the role of salivary glands ultrasonography (SGUS) and ultrasound scores for diagnosis of Sjögren's syndrome and evaluating effectiveness of different methods of therapy in dynamics.

Objectives. to evaluate dynamic ultrasound changes in the structure of the salivary glands of patients with primary Sjögren's syndrome (pSS) after treatment with cyclophosphamide (CYC).

Methods. We observed 13 patients (all women) with the mean age 54.0±11.0 years (minimum 32, maximum 75). They received intravenous cyclophosphamide during one year, the average cumulative dose was 5000 mg [3600; 6000]. A standard premedication was an intravenous methylprednisolone 250,0 mg. 10 patients of 13 took low doses of oral glucocorticoids (4 mg each or every other day). All patients underwent standard examination for the diagnosis of pSS (stomatological, ophthalmological, immunological), and SGUS was performed using GE LOGIQ 9 on the two parotid and two submandibular glands. Ultrasound images were evaluated with the OMERACT SGUS scoring system (SGUS SS) from grades 0 to 3. Statistical analyses (Wilcoxon matched pairs test $p<0.05$) were performed using STATISTICA version 12.

Results. Characteristics of patients at the beginning of observation are presented in Table I.

All patients had sialectasia on sialography and inhomogeneity structure in SGUS. SGUS SS grade 3 was determined in 12 patients and SGUS SS grade 1 - in 1 patient, SGUS SS grade 0 and 2 were not detected. We found significant changes (p=0.04) in the structure of salivary glands (Fig. 1) in 5 patients. The SGUS SS grade 3 decreased to grade 1 after CYC. At the beginning of the observation, 4 of 5 patients had globular sialectasia on sialography and 1 patient - punctate sialectasia. We found a significant decrease (p=0.003) in the average size of hypoechoic areas after treatment in all patients in the group.

Conclusions. We compared the US-parameters of salivary glands in patients with pSS before and after CYC treatment and showed that some changes of the structure of salivary glands occurred during the treatment. Visualization using ultrasound with OMERACT SGUS SS index can be used for dynamic assessment of these changes.

Table I.

N patient	Duration of disease *	ANA > 1:320	RF > 30 IU/ml	Anti-SSA/Ro **	Anti-SSB/La ***	Sialectasia ****	SSFT *****	Stimulated Schirmer's test <10 mm/5 min	TBUT <10 seconds	Ocular staining ******
1	11	+	+	-	-	+	+	-	-	+
2	4	+	-	+	-	+	+	+	-	+
3	0,1	+	-	+	+	+	-	-	-	-
4	11	+	-	+	+	+	-	+	+	+
5	5	+	+	+	-	+	+	+	+	+
6	7	+	+	+	+	+	+	-	+	+
7	6	+	-	+	-	+	+	-	+	-
8	1	+	+	+	+	+	+	-	+	+
9	5	+	-	+	-	+	+	+	+	+
10	2	+	-	+	-	+	-	+	+	-
11	9	+	+	+	+	+	+	+	+	+
12	8	+	-	+	-	+	+	+	+	+
13	0,1	+	+	+	-	+	+	-	+	-

Footnotes: * - duration of disease from the first symptoms of dry mouth and/or eyes (years) RF - rheumatoid factor, ** Anti-SSA/Ro positive (>25 IU/ml), *** Anti-SSB/La positive (>25 IU/ml), **** sialectasia on parotid sialography, ***** SSFT - Stimulated saliva flow test < 2.5 ml/5 min, TBUT - tear breakup time, ****** ocular staining fluorescein/lissamine green, «+» positive, «-» negative

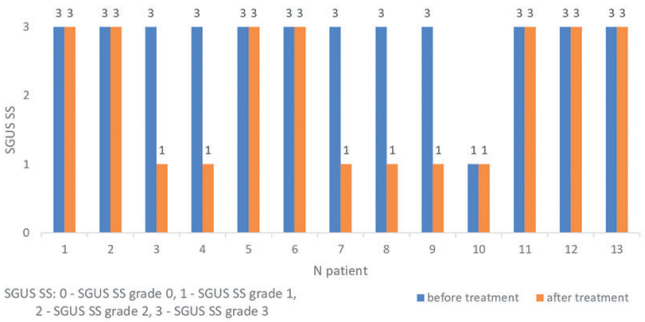

Fig. 1. Comparison of SGUS SS before and after CYC therapy.

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USE OF PLATELET RICH PLASMA (PRP) IN TREATMENT OF DRY EYE SYNDROME IN THE PATIENTS WITH SJÖGREN SYNDROME: PRELIMINARY RESULTS

Capacci A.*[1], Rubortone P.[1], Alvernini S.[1,2], D'Agostino M.A.[1,2]
[1]*Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy,* [2]*Università Cattolica del Sacro Cuore, Roma, Italy*

Introduction. Xeroftalmia and xerostomia are the hinge symptoms of Sjögren Syndrome and often they negatively influence patients' quality of life. The eyewashes use based on Platelet Rich Plasma (PRP) has been applicate in the treatment of the xeroftalmia, both primitive and secondary.

Objectives. To evaluate the effect of subconjunctival injections and PRP based eyewashes on the ocular dryness (subjective and objective) in patients suffering of primary Sjögren syndrome (pSS).

Materials and methods. 6 pSS patients (6 females, age at the beginning 48.2±9.7 years) have been recruited in the study. All patients were reaching the criteria for pSS diagnosis; for each patient clinical and immunological data have been recorded. Patients with Schirmer Test value, in at least an eye, inferior to 10 mm after 5 minutes, and suffering from severe dryness calculated by OSDI score (between 33 and 100, severe condition of dry eye)

in spite of therapies with tear substitutes were selected. The OSDI (Ocular Surface Index) is a questionnaire for the evaluation of the subjective ocular dryness. Selected patients have been addressed to treatment with PRP. The PRP is constituted by human plasma enriched with plaques by means of the utilisation of a special kit, therefore each patient has been subjected to a blood drawing, from which PRP has been extracted. Of this, a part has been injected in subconjunctival seat; from remained one, an eyewash has been extracted that the patients have assumed 6 times in the day up to exhaustion (about 5 days) during which another topic therapy was not used. The patients have been valued to the basal time and after ten days of the procedure; besides follow-up visits each three months are scheduled. To each evaluation Schirmer Test data and OSDI have been checked.

Results. Each patient had severe xeroftalmy, evaluated by Schirmer Test (right Eye: 3.33±2.66; left eye: 6.83±6.5) and index OSDI (59.71±20.72). All the patients had Schirmer Test values, in at least an eye, lesser than 10 mm after 5 minutes. The analized cohort had homogeneous clinical characteristics (presence of xerostomy and absence of inflammatory indexes, hypergammaglobulinemia, arthritis and linfoadenomegaly). After one week (T1), OSDI values were significantly more reduced compared to the basal time (38.89±15.12; p=0.028). The Schirmer Test values were not significative different to the follow-up visit compared to the basal one. No patients presented pre- and post-procedural complications, neither related infectious events. At 3 months follow up after first treatment (T2) no statistically significant difference in OD/OS Schirmer test values and OSDI score compared to the basal time were observed.

Conclusions. The use of PRP in dry eye syndrome in patients with Sjögren syndrome seems to be effective in alleviating symptoms and improving patients' life quality. Is need further follow-up to confirm data, to value effect also on the objective tests and to evaluate necessity of repeating treatment.

References

1. Shiboski SC: *Arthritis Care Res* 2012; 64(4): 475-87.
2. Alio J: *Ophtalmic Research* 2017; 39: 124-29.

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EARLY CHANGES IN FREE LIGHT CHAINS TO PREDICT ESSDAI, ESSPRI AND CRESS AND STAR OUTCOMES UPON LEFLUNOMIDE/HYDROXYCHLOROQUINE COMBINATION THERAPY

Hamkour S.*[1], Bogers C.[1], Redegeld F.[2], Leavis H.[1], Van Roon J.[1]
[1]UMC Utrecht, Utrecht, Netherlands, [2]University of Utrecht, Utrecht, Netherlands

Background. B-cell hyperreactivity is a hallmark feature of primary Sjögren's syndrome (pSS). In a recent trial Leflunomide (LEF) and hydroxychloroquine (HCQ) combination therapy was shown to effectively decrease B-cell hyperreactivity in patients with primary Sjögren's syndrome measured by serum IgG levels. κ and λ free light chains (FLCs) have a shorter halftime than serum IgG and subsequently were shown to better capture (changes in) disease activity in immune-mediated diseases. Our objective was to assess whether κ and λ free light chains can serve as biomarkers to (better) monitor and predict treatment response than serum IgG.

Methods. In the 21 patients treated with LEF/HCQ and 8 patients treated with placebo, blood was drawn at baseline, 8, 16 and 24 weeks. κ and λ FLCs were measured by ELISA to assess the ability to monitor treatment response. In addition the correlation of baseline levels with clinical response (as captured by clinESSDAI, ESSPRI and UWS as well as CRESS and STAR scores) were assessed. ROC analysis was used to determine the capacity of baseline values and early changes (after 8 weeks of treatment) in κ and λ FLCs to predict treatment response after 24 weeks.

Results. Treatment with LEF/HCQ showed a significant reduction of κ and λ FLCs (at 24 weeks both $p<0.0001$) as compared to placebo (κ $p=0.6875$, λ $p=0.153$). κ and λ FLCs significantly and more rapidly decreased (with 22% and 26% respectively at 8 weeks), as compared to in serum IgG levels (10% decrease at 8 weeks). Baseline κ and λ FLCs or serum IgG did not significantly correlate with clinical improvement as measure by clinESSDAI or UWS after 24 weeks, but did show significant correlations with changes in ESSPRI (κ r=0.46, $p=0.03$, λ r=0.41, $p=0.06$), whereas changes in κ and λ FLCs at 24 weeks significantly correlated with changes in ESSDAI at 24 weeks (κ r=0.53, $p=0.003$, and λ r 0.53 and $p=0.003$). Early (8 weeks) decreases in κ and λ FLCs serum levels correlated with decreases in clinical ESSDAI (κ r=0.53, $p=0.003$, and λ r=0.71 and $p=<0.0001$) and ESSPRI scores (κ r=0.50, $p=0.007$, and λ r=0.62 and $p=0.0005$) after 24 weeks. Early changes in κ and λ FLCs predicted ESSDAI treatment response (AUC =0.788 and 0.838, respectively), performing better than early changes in serum IgG levels (AUC=0.626). In follow up of association with ESSDAI and ESSPRI, we furthermore demonstrated excellent performance of early total FLC levels (week 8) and clinical endpoints defined by CRESS and STAR (AUC 0.939).

Conclusions. Our data indicate that κ and λ FLCs are better biomarker for disease monitoring than serum IgG levels. Early changes in free light chains might help to predict ESSDAI and ESSPRI, as well as CRESS and STAR outcomes upon leflunomide/hydroxychloroquine combination therapy.

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QUALITY OF LIFE IN PATIENTS WITH SJÖGREN'S DISEASE TAKING SIALAGOGUES

Sankar V.*[1], Pagni S.[1], Singh M.[1], Hammitt K.M.[2], Makara M.[2], Papas A.[1]
[1]Tufts University School of Dental Medicine, Boston, USA, [2]Sjogren's Foundation, Reston, USA

Background. Sjögren's disease (SjD) is a chronic autoimmune condition that presents clinically with oral and ocular dryness, pain, fatigue, anxiety, and depression. It is well known that health related quality of life (HRQoL) has been reported to be diminished in SjD patients. It has been proposed that improvement in symptom burden has the potential in improvement of HRQoL. We examine the effects of treatment with sialagogues on HRQoL compared with those not taking sialagogues.

Methods. In 2016, the Sjögren's Foundation, in collaboration with The Harris Poll®, conducted a survey via postal mail to adult Sjögren's patients in their member database. In the deidentified data set, we compared the participants who regularly take and/or those who took sialagogues in the past to those who did not take/use sialagogues and assessed for differences in HRQoL issues. The study was approved by the Western Institutional Review Board (20160808#14329711).

Results. Responses were received from 2,962 Sjögren's patients (96% female, mean age 65 years, and 93% Caucasian). Respondents taking sialagogues (currently or in the past) did not differ in their ability to cope with SjD, care for children, be impacted in job/career, attend and perform at school, or have a sex life compared to those who were or have not taken sialagogues (p values ranged between $p=0.90$-0.11).

Those taking sialagogues compared to those who did not had significant differences in their ability to complete items such as remembering details at home or work, concentrating on tasks, ability to multitask, need for diet alterations, desire for additional treatments and were less likely to feel that living with Sjogren's makes every day a challenge (p values ranged from $p<0.002$- 0.001). Items such as relationships, mood, ability to participate in hobbies, independence, ability to drive or travel revealed inconsistencies.

Conclusions. More information is needed to determine the effect of sialagogues on HRQoL in patients with SjD. It is unclear if the need for sialagogues is what drives the lower quality of life or if quality of life is improved after taking sialagogues.

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INTERFERON ASSOCIATED PROTEINS FOR MONITORING AND PREDICTION OF CLINICAL RESPONSE TO LEFLUNOMIDE/HYDROXYCHLOROQUINE COMBINATION THERAPY DEFINED BY COMPOSITE ENDPOINTS (PRELIMINARY) STAR AND CRESS

Bogers C.*[1], Hamkour S.[1], Blokland S.[1], Versnel M.A.[2], Leavis H.[1], Van Roon J.[1]
[1]UMC Utrecht, Utrecht, Netherlands, [2]Erasmus MC, Rotterdam, Netherlands

Background. The type I interferon (IFN) pathway is associated with B cell hyperactivity and clinical disease activity in primary Sjogren's syndrome (pSS). Combination therapy with Leflunomide (LEF) and Hydroxychloquine (HCQ) has recently been demonstrated as clinically effective treatment in pSS in a small randomized placebo-controlled trial1. LEF/HCQ was shown to target the IFN- pathway based on RNA signatures, but in particular IFN-associated proteins correlating with several clinical parameters. Recently, new composite clinical endpoints were proposed to assess treatment efficacy in pSS.

Objectives. To assess the performance of IFN-associated proteins in predicting and monitoring treatment response, as defined by composite endpoints preliminary STAR (pSTAR) and CRESS.
Methods. In 29 pSS patients serum IgG, CXCL10 and Galectin-9 levels and whole blood MxA concentrations were measured at baseline and after 8 and 24 weeks (clinical endpoint) of treatment with either LEF/HCQ (n=21) or placebo (n=8). Differences between responders and non-responders were assessed and ROC analysis was used to determine the capacity of changes in biomarkers at 8 and 24 weeks to predict and monitor treatment response according to pSTAR and CRESS at week 24.
Results. pSTAR and CRESS scores equally defined responders and non responders, with an overall response rate of 57.6% (12/21) in verum treated patients as compared to none of the patients treated with placebo (0/8). IFN-associated proteins Galectin-9 and CXCL10 at baseline significantly correlated with CRESS and STAR scores (both r>0.600, $p<0.05$) at the clinical endpoint. ROC analyses demonstrated good prediction of baseline Galectin-9 and CXCL10 (AUC 0.815 and 0.824, respectively) as compared to sIgG and MxA (AUC 0.750 and 0.699, respectively). All IFN-associated proteins robustly decreased upon treatment and were significantly correlated to absolute changes in CRESS and pSTAR scores (all $p<0.01$) after 24 weeks. Interestingly, early changes (at 8 weeks) in Galectin-9 and MxA showed improved prediction of clinical response (AUC both 0.899).
Conclusions. Our data indicate that IFN-associated proteins offer potential to monitor and predict clinical efficacy upon LEF/HCQ combination therapy as defined by new composite clinical endpoints. Given the association of IFN associated proteins such Galectin-9, CXCL10 and MxA with disease activity in pSS this suggests that these are promising biomarkers for prediction and monitoring of treatment responses in pSS.

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EFFECTS OF SIALAGOGUES TREATMENT IN SJÖGREN'S DISEASE PATIENTS

Khoury Z.*[1], Pagni S.[1], Sankar V.[1], Singh M.[1], Makara M.[2], Hammitt K.[2], Papas A.[1]
[1]Tufts University School of Dental Medicine Department of Oral Medicine, Boston, USA, [2]The Sjogren's Foundation, Reston, USA

Background. Sjögren's disease is a chronic, autoimmune condition that is more prevalent in women (typically perimenopausal or postmenopausal) with 9:1 female to male ratio. Approximately 2-4 million Americans are estimated to have Sjögren's disease. In Sjögren's disease, lymphocytes invade the salivary and lacrimal glands causing destruction in the acinar cells, leading to dry mouth and dry eyes. Lymphocytes also commonly invade the joints and cause musculoskeletal issues. Some patients can have systemic organs involvement and develop kidney failure, liver failure, or interstitial lung disease, and 5% of patients are at risk of developing non-Hodgkin's lymphoma.
Objectives. The aim of our study is to collect information from the 2016 Sjögren's Foundation "Living with Sjögren's" survey related to patients who used sialagogues and compare them to those who did not for oral complication and dryness.
Methods. In 2016, the Sjögren's Foundation, in collaboration with The Harris Poll®, conducted a survey via postal mail to adult Sjögren's patients in their member database. The Study was approved by the Western Institutional Review Board (IRB) (WIRB 20160808#14329711) and participants provided written informed consent. The survey received responses from 2,962 diagnosed Sjögren's participants (96% female, mean age 65 years, and 93% Caucasian). The Sjögren's foundation provided us with a deidentified version of the survey results for analysis in addition to written permission to use the data. We compared the participants who regularly took sialagogues to those who did not for dental treatment cost, dry mouth, and yeast infection. Additionally demographic data was analyzed to assure groups are comparable.
Results. At the time of the survey, 85% of respondents stated that they experience oral dryness on a daily basis, 35.59% of patients used sialagogues, 35.09% used saliva substitutes, and 63.45% used oral comfort agents (gels, rinses, sprays). Sixty-one percent of patients reported having tooth decay during the prior year with a mean cost of $2030.14 on dental care. There is a statistically significant difference in level of oral dryness between those who were currently using a sialagogue and those who were not using a sialagogue ($p<0.001$). Additionally, differences in money spent on healthcare appointments ($p<0.045$), parotid swelling ($p=0.008$) and in frequency of "yeast infection in mouth" between those who currently take a sialagogue and those who do not ($p<0.001$) were found.
Conclusions. Treatment with Sialagogues improves dry mouth symptoms in Sjögren's patients compared to patients who have never used them, which makes their regular usage important as it will aid in the reduction of their oral infections.

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PATIENT SATISFACTION AND IMPACT OF SALIVARY FLOW ON EFFECTIVENESS OF XEROSTOMIA PRODUCTS: PATIENT CENTERED APPROACH FOR THE MANAGEMENT OF XEROSTOMIA

Brennan M.*[1], Purdie J.[1], Stephens C.[1], Taylor Y.[1], Hammit K.M.[2], Napenas J.[1], Noll J.[1]
[1]Atrium Health's Carolinas Medical Center, Charlotte, USA, [2]Sjogren's Foundation, Reston, USA

Objectives. To determine the types of products used to treat dry mouth and their perceived effectiveness, the relationship between salivary function and xerostomia symptoms, and whether salivary function predicts response to management strategies.
Study design. Cross-sectional study of 87 patients with dry mouth and documented unstimulated (UWS) and stimulated (SWS) whole salivary flow rates. Participants completed a questionnaire assessing dry mouth complaints and symptoms and effectiveness of specific dry mouth products.
Results. Mean (SD) age was 61.7 (12.9) years including 78 (90%) females. 47 (54%) participants had Sjögren's disease. Oral dryness symptoms (0-10 scale) rated highest with a mean (SD) of 7.2 (2.17); other symptoms scored from 3.4-5.1. Lower levels of UWS and SWS were associated with worse dry mouth and difficulty speaking while lower levels of SWS flow alone were associated with greater difficulty swallowing and decline in taste. More than half of participants (55%, n=48) reported using ≥4 dry mouth products. Participants with normal SWS flow had significantly better responses to lozenges and prescription products.
Conclusions. Patients with dry mouth and normal stimulated flow (i.e., residual salivary capacity) respond better to stimulatory products (parasympathomimetic and lozenges). These findings point to the potential of utilizing baseline tests to provide a more targeted approach based on presenting subjective and objective findings of oral dryness. From our current study we believe the assessment of salivary flow levels may be a useful guide for more targeted recommendations of dry mouth products.

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PERSONALIZED MEDICINE IN TREATING SJÖGREN'S SYNDROME BY TARGETING AUTOANTIGENIC EPITOPES AND HLA-DRB1*0301 ALLELE INTERACTION

Gupta S.*, Nguyen C.
University of Florida, Gainesville, USA

Background. Sjögren's syndrome (SjS) is characterized by lymphocytic infiltration and the dysfunction of the salivary and lacrimal glands. The adaptive autoimmune response is driven by activating the effector helper T cells, where autoantigen presentation occurs by human leukocyte antigen (HLA) class II molecules on antigen-presenting cells. Genome-wide association studies indicate a strong correlation between risk HLAs and SjS. The HLA-DRB1*0301 allele has one of the most influential associations with primary SjS, having the highest odds ratio and occurrence across different ethnic groups. The goals of the study were to determine the pathogenic effect of antigenic epitopes of signature SjS autoantigens and identify small molecule drugs blocking DRB1*0301 to prevent the onset of SjS in NOD-DR3 mice.
Methods. Autoantigenic epitopes binding to HLA-DRB1*0301 were mapped using structural modeling tools such as Immune Epitope Database and Analysis Resource IEDB, AutoDock Vina, and COOT. To determine the pathogenicity of the autoantigenic epitopes, transgenic humanized DR3 mice were injected with the predicted peptides, and disease profiling was conducted. Lastly, using structural modeling, in-vitro screening, and in-vivo

experiments, small molecule drugs were screened to identify potential inhibitors of HLA-DR3.
Results. Specific peptide epitopes with effective binding to Ro60, Ro 52, La, muscarinic receptor (M3R), and alpha-fodrin autoantigens were identified. Several autoantigenic peptides elicited SjS-like phenotypes (loss of saliva secretion, presence of autoantibodies, exocrine gland inflammation) in the NOD-DR3 mice. Lastly, small molecule drugs with strong HLA-DRB1*0301 binders suppressed SjS-like phenotypes in immunization-induced SjS NOD-DR3 mice.
Conclusions. This study identified and confirmed autoantigenic epitopes that can recapitulate SjS. More important, it discovered small molecules that can interfere with T cell response and prevent the development of SjS. The study sheds light on the pathogenic nature of the autoantigens and provides a personalized therapeutic approach to treating SjS.

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LEFLUNOMIDE / HYDROXYCHLOROQUINE COMBINATION THERAPY TARGETS TYPE I IFN-ASSOCIATED PROTEINS IN PATIENTS WITH SJÖGREN'S SYNDROME THAT ALLOW PREDICTION AND MONITORING OF CLINICAL RESPONSE

Hamkour S.*[1], Van Der Heijden E.[1], Pinheiro Lopes A.[1], Blokland S.[1], Bekker C.[1], Van Helden-Meeuwsen C.G.[2], Versnel M.A.[2], Kruize A.[1], Timothy R.[1], Hillen M.[1], Van Roon J.[1]
[1]UMC Utrecht, Utrecht, Netherlands, [2]Erasmus MC, Rotterdam, Netherlands

Background. A recent clinical trial showed clinical efficacy for combination therapy with leflunomide (LEF) and hydroxychloroquine (HCQ) in patients with primary Sjögren's syndrome (RepurpSS-I). We assessed whether LEF/HCQ therapy targets type I IFN-associated responses and studied the potential of RNA and protein interferon (IFN)-signature associated biomarkers to predict and monitor treatment.
Methods. In the 21 patients treated with LEF/HCQ and 8 patients treated with placebo, blood was drawn at baseline, 8, 16 and 24 weeks. IFN-scores were quantified in circulating immune cells and whole blood. IFN-scores were quantified based on the expression of MX1, IFIT3, IFI44, IFI44L, and Ly6E using material from 13 (PBMC) and 23 (WB) healthy donors for comparison. MxA protein levels were measured in whole blood, and levels of CXCL10 and Galectin-9 were quantified in serum. Of the 21 patients in the treatment group, based on ESSDAI scores (≥3 ESSDAI points) 11 were defined as responders. Differences between responders and non-responders were assessed using Mann-Whitney U-tests and ROC analysis was used to determine the capacity of baseline values and early changes (after 8 weeks of treatment) in biomarkers to predict treatment response at the clinical endpoint.
Results. IFN-signature RNA and protein biomarkers, all but PBMC IFN signatures (p=0.051) decreased after 24 weeks of LEF/HCQ treatment. RNA based IFN signatures did not correlate with clinical activity and did not predict response to treatment. Baseline Galectin-9 levels significantly correlated with clinical activity at the endpoint (r=0.467, p=0.032) and predicted response with good accuracy (AUC 0.809). Decreases in circulating MxA, CXCL10 and Galectin-9 proteins were associated with clinical response (r=0.556, r=0.447 and r=0.692, all at least p<0.05). Interestingly, early changes in serum Galectin-9 best predicted clinical response at 24 weeks (AUC 0.90), as compared to serum IgG (AUC 0.66) and MxA (AUC 0.66).
Conclusions. Our data indicate that LEF/HCQ combination therapy targets type-I IFN activity and is associated with strongly decreased B cell hyperactivity. IFN-associated protein Galectin-9 is a promising biomarker for treatment prediction and monitoring in pSS patients treated with LEF/HCQ. Given its significant association with disease activity Galectin-9 may serve as general biomarker for treatment monitoring and prediction.

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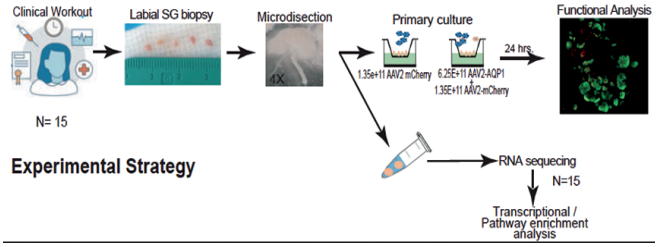
AQP1 GENE THERAPY CORRECTS FLUID SECRETION DEFICITS IN SJÖGREN'S DISEASE

Perez P.[1], Warner B.[1], Ji Y.[1], Afione S.[1], Pranzatelli T.[1], Beach M.[1], Khavandgar Z.[1], Grisius M.[1], Pelayo E.[1], Baer A.[2], Chiorini J.*[1]
[1]NIH, Bethesda, USA, [2]Johns Hopkins, Baltimore, USA

Sjögren's disease is a complex systemic autoimmune disease with variable clinical presentation. The most common symptoms are dry mouth and dry eyes resulting from salivary and lacrimal gland dysfunction. Preclinical studies in mouse models of Sjögren's disease suggest that expression of the AQP1 gene in the salivary glands can restore gland secretory activity.
As several mechanisms have been proposed to explain reduced salivary gland activity in patients, we aimed to test the application of AQP1 gene therapy in patients' salivary gland biopsy tissues. Primary short-term cultures of lobules from labial LSGs showed good viability, stimulated water release for up to 48 hours, and were permissive to transduction with an AAV2 vector encoding AQP1.
Our experimental results show that AQP1 expression in the lobules can induce a statistically significant increase in fluid movement in most samples; recovery of fluid movement was up to 80% of the levels observed in lobules from healthy donors. Transcriptomic analysis of participants' biopsies indicated that response was inversely associated with a mesenchymal gene expression pattern and histological analysis confirmed a higher level of fibrosis in the patients' sample.
These findings suggest that AAV2-AQP1 expression can increase fluid movement in human tissue and highlights fibrosis and associated loss of glandular parenchyma as a limiting factor.



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RITUXIMAB PREVENTS WORSENING OF B-CELL DRIVEN SALIVARY GLAND INFLAMMATION AND EXCRETORY FUNCTION IN PRIMARY SJÖGREN'S SYNDROME: RESULTS FROM THE TRACTISS TRIAL

Pontarini E.*[1], Chowdhury F.[1], Sciacca E.[1], Grigoriadou S.[1], Emery P.[2], Ng W.F.[3], Sutcliffe N.[4], Rivellese F.[1], Tappuni A.[4], Lucchesi D.[1], Seror R.[5], Mariette X.[5], Porcher R.[6], De Wolff L.[7], Arends S.[7], Bootsma H.[7], Lewis M.[1], Pitzalis C.[1], Bowman S.J.[8], Bombardieri M.[1]
[1]Experimental Medicine and Rheumatology, William Harvey Research Institute, Queen Mary University of London, London, UK, [2]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Chapel Allerton Hospital, Leeds, UK, [3]Translational and Clinical Research Institute, Newcastle University, Newcastle-upon-Tyne, UK, [4]Royal London Hospital, Bart's Health NHS Trust, London, UK, [5]Rheumatology, Assistance Publique-Hôpitaux de Paris (AP-HP), Hôpitaux Universitaires Paris-Sud-Hôpital Bicêtre, Le Kremlin-Bicêtre, Paris, France, [6]Centre d'Epidémiologie Clinique, INSERM U1153, Faculté de Médecine, Université Paris Descartes, Paris, France, [7]Department of Rheumatology and Clinical Immunology, University Medical Center Groningen, University of Groningen, Groningen, Netherlands, [8]Rheumatology Department, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK

Objectives. To study the transcriptomic and histological features of sequential salivary gland (SG) biopsies from primary Sjogren's Syndrome patients (pSS) treated with rituximab (RTX) or placebo and identify mechanisms of response/resistance to B-cell depletion.
Methods. pSS patients enrolled in the TRACTISS trial (n=133) were randomised to receive two RTX cycles or placebo at baseline and week 24. 29 patients consented for sequential SG biopsies at 0, 16 and 48 weeks. SGs underwent histological and RNA sequencing analyses to identify biomark-

ers predictive of treatment response defined using ESSDAI and newly developed CRESS and STAR composite score criteria.
Results. SGs from placebo-treated patients, compared to RTX, showed worsening of SG inflammation, highlighted by the increment of B-cell density, aggregate size, and a higher prevalence of ectopic germinal centres at 48 weeks. No differences in focus score, total T-cell and plasma cell infiltration was observed between RTX and placebo. RTX significantly downregulated key genes involved in immune-cell recruitment and lymphoid organization including CXCL13, IL21 and IL21-receptor. Deconvolution of SG mRNA data indicated that RTX inhibits the accumulation of class-switched memory-B-cells at 48 weeks. Pathway analyses showed a downregulation of leukocyte migration, antigen presentation, and T-cell co-stimulation pathways. Patients classified as RTX-responders according to the CRESS and, to a lesser extent, STAR criteria had a significantly lower increase of SG B-cell infiltration over time and showed a significant improvement in unstimulated whole salivary flow associated with transcriptional evidence of SG epithelial metabolic restoration in CRESS responders.
Conclusions. We highlighted mechanisms through which treatment with RTX in pSS inhibits the progression of B-cell driven SG inflammation and preserves SG excretory function.

EVOLVING TOPICS IN HEALTH POLICIES

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HOW RARE IS PRIMARY SJÖGREN SYNDROME?

Chevet B.*[1], Chiche L.[2], Devauchelle-Pensec V.[1], Cornec D.[1]
[1]UMR 1227 Lymphocytes B et Auto-Immunité, Univ Brest, Inserm, CHU de Brest, Brest, France, [2]Internal medicine division and clinical research, European Hospital of Marseille, Marseille, France

While several criteria for diagnosis have been used for epidemiological studies about primary Sjögren Syndrome (pSS), it remains unclear if pSS is an orphan disease.
Among 11 analyses retrieved from 9 population-based studies, 8 show a prevalence lower than the orphan disease threshold (50/100 000 inhabitants). In two meta-analyses, prevalence is 39 to 43 per 100 000 inhabitants. There is no difference among prevalence in studies using or not classification criteria. ACR/EULAR 2016 criteria have not been used yet. Women are 6 to 9-fold more involved than men in pSS, and incidence for diagnosis is at the highest between 60 and 70 years old. Although Asian people are the most likely to present pSS, Whites are also more likely than Blacks or Hispanics.
Collectively, pSS shall be now considered as an orphan disease, with important implications for clinicians, for development of new therapies and for national health programs.

EVOLVING TOPICS IN COOPERATIVE RESEARCH

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A DIAGNOSTIC ALGORITHM FOR EVALUATING CHILDHOOD SJÖGREN'S DISEASE

Stern S.M.*[4], Basiaga M.L.[1], Cha S.[2], Thatayatikom A.[3], Treemarcki E.B.[4], Randell R.[5], Dizon B.L.[6], Diilanni J.[7], Tiger S.[7], Orrock J.E.[8], Appenzeller S.[9], Edens C.[10], Lieberman S.M.[11]
[1]Mayo Clinic, Rochester, USA, [2]University of Florida, Gainesville, USA, [3]AdventHealth Medical Group, Orlando, USA, [4]University of Utah School of Medicine, Salt Lake City, USA, [5]Duke University School of Medicine, Durham, USA, [6]National Institute of Arthritis and Musculoskeletal Diseases, Bethesda, USA, [7]Childhood Arthritis and Rheumatology Research Alliance (CARRA), Broomall, USA, [8]The University of Texas at Austin Dell Medical School, Austin, USA, [9]University of Campinas, Campinas, Brazil, [10]The University of Chicago Medicine, Chicago, USA, [11]University of Iowa Carver College of Medicine, Iowa City, USA

Background/Objectives. There are no widely accepted diagnostic or classification criteria for childhood Sjögren's disease (cSjD). Few children meet the 2016 ACR/EULAR classification criteria, and many lacked sufficient testing to meet criteria. To address the urgent need for consensus, the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Sjogren's Workgroup created a clinical diagnostic algorithm for cSjD. This study evaluates the accuracy of the diagnostic algorithm using an international cohort of patients with clinician diagnosed cSjD.
Methods. The diagnostic algorithm was developed per expert opinion from the CARRA and International Childhood Sjögren Disease Workgroup and has four distinct clinical pathways: Parotitis (P), Systemic/Neurologic Manifestations (SN), Sicca symptoms (SIC) and Incidental Salivary or lacrimal Gland Inflammation on Imaging (INC). The validation cohort was an international cohort of 300 cSjD cases, which includes extensive demographic and clinical information. De-identified clinical data from the cSjD cohort was analyzed using R statistical software to evaluate the individual patient's disease status from the diagnostic algorithm. The results of the algorithm were categorized into a binary outcome. A response of Sjögren's disease (SjD) and probable SjD was classified as "positive" for SjD and all other responses were classified as "negative" for SjD. Each pathway was evaluated separately, and then the results were aggregated. The sensitivity was calculated for each pathway. The proportion of patients who had adequate data to complete the pathway was calculated. The data was reviewed to identify the frequency of the missing components needed to complete the algorithm.
Results. The cSjD cohort (n=300) is 83% female with a mean age of diagnosis 12 (9,15) years. Due to missing data, the sensitivity of participants in the cohort able to complete algorithm was low (25% of the aggregated pathways (AGG), 25% P, 6% SN, 6% SIC, and 15% INC). When the data was limited to participants with complete data to complete a pathway of the algorithm (n=100), the sensitivity increased to 75% AGG, 77% P, 50% SN, SIC 73%, and INC 68%. The proportion of patients without information for each component as follows: parotid biopsy (98%), ocular or oral screen (91%), minor salivary gland biopsy (65%), salivary gland ultrasound (65%) and positive SSA or SSB (2%).
Conclusions. The sensitivity of the algorithm was limited by the lack of completion of diagnostic studies commonly performed in adults with SjD. The P and SIC arms of the algorithm had the highest sensitivities. The SN arm was the least sensitive arm possibly due to the inhomogeneous and rare presentations of cSjD. Invasive and difficult testing (parotid biopsy, ocular or oral screen, and minor salivary gland biopsy) were the least likely to be completed. This algorithm has good sensitivity in the setting of complete data, suggesting it is an appropriate diagnostic algorithm for cSjD until more sensitive, pediatric-specific criteria can be developed.

Table. Proportion of children diagnosed with Sjogren's disease correctly identified using proposed diagnostic algorithm.

	Sensitivity with complete data (%)	Sensitivity out of entire dataset (%)
Aggregated Diagnosis	75	25
Parotitis	77.3	25
Systemic_Neurologic	50	6.3
SICCA	73.1	6.3
Incidental	67.7	15.3

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KEY FEATURES AT DIAGNOSIS OF PRIMARY SJÖGREN SYNDROME IN 15,652 PATIENTS: 2022 SJÖGREN BIG DATA PROJECT

Flores-Chavez A.*[5], Horváth F.I.[18], Li X.[19], Rasmussen A.[20], Ng F.[1], Dong X.[21], Priori R.[22], Olsson P.[23], Baldini C.[24], Seror R.[25], Bootsma H.[2], Armagan B.[26], Gottenberg J.[6], Kruize A.[27], Hernandez-Molina G.[28], Paprovnik S.[7], Danda D.[29], Özkiziltas B.[8], Inanc N.[30], Sebastian A.[9], Bartoloni Bocci E.[31], Quartuccio L.[32], Romão V.C.[33], Rischmueller M.[34], Suzuki Y.[35], Kwok S.[36], Kvarnstrom M.[37], Solans R.[38], Pasoto S.G.[39], Galisteo C.[40], Sene D.[41], Moça Trevisani V.[42], Isenberg D.[43], Hofauer B.[10], Shimizu T.[44], Nordmark G.[45], Valim V.[46], Jurcut C.[4], Carubbi F.[47], Gonzalez Garcia A.[48], Retamozo S.[5], Devauchelle-Pensec V.[11], Melchor Díaz S.[12], Gheita T.A.[3], Brito-Zerón P.[13], López-Dupla M.[49], Fonseca-Aizpuru E.[50], Sánchez-Berná I.[51], Morel J.[14], Giacomelli R.[52], Atzeni F.[15], Consani S.[16], Vazquez M.[17], Akasbi M.[53]

[1]The United Kingdom Primary Sjögren's Syndrome Registry, UK, [2]University Medical Center Groningen, Netherlands, [3]Department of Rheumatology, Faculty of Medicine, Cairo University, Egypt, [4]Internal Medicine, Central University Emergency Military Hospital, Bucharest, Romania, [5]Sjögren Syndrome Research Group, GRESS-AGAUR, Barcelona, Spain, [6]Department of Rheumatology, Strasbourg University Hospital, Université de Strasbourg, CNRS, Strasbourg, France, [7]University Clinical Center, Ljubljana, Slovenia, [8]Department of Internal Medicine, Gazi University Faculty of Medicine, Turkey, Turkey, [9]Department of Rheumatology and Internal Medicine, Wroclaw Medical Hospital , Poland, [10]University Hospital Klinikum Rechts der Isar, Germany, [11]Cavale Blanche-University Hospital, Brest, France, [12]Department of Rheumatology, Hospital 12 de Octubre, Madrid, Spain, [13]Research and Innovation Group in Autoimmune Diseases, Millenium Balmes-Hospital CIMA Sanitas, Barcelona, Spain, [14]Montpellier Hospital, Montpellier, France, [15]Rheumatology Unit, University of Messina and Milan, Milan, Italy, [16]Servicio Medicina Interna y de Enfermedades Autoinmunes. Hospital Maciel. Universidad de la República, Montevideo, Uruguay, [17]Department of Rheumatology of the Hospital de Clínicas de San Lorenzo, Paraguay, [18]University of Debrecen, Debrecen, Hungary, [19]Department of Rheumatology and Immunology, the First Affiliated Hospital of USTC, University of Science and Technology of China, Hefei, Anhui, China, [20]Oklahoma Medical Research Foundation, Genes and Human Disease Research Program, USA, USA, [21]Department of Rheumatology, Peking Union Medical College Hospital, Beijing, China, [22]Rheumatology Clinic, Sapienza University of Rome, Rome, Italy, [23]Lund University, Malmö, Sweden, [24]Rheumatology Clinic of Pisa, Pisa, Italy, [25]Rheumatologye Department, Université Paris-Saclay, Paris, France, [26]Hacettepe University Faculty of Medicine, Division of Rheumatology, Ankara, Turkey, [27]University Medical Center Utrecht (UMCU), Utrecht, Netherlands, [28]Rheumatology Department, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Ciudad de Mexico, Mexico, [29]Medical College and Hospital, Tamil Nadu, India, [30]Marmara University, School of Medicine, Istanbul, Turkey, [31]University of Perugia, Perugia, Italy, [32]University Hospital Santa Maria della Misericordia, Undine, Italy, [33]Rheumatology Department, Centro Hospitalar Universitário Lisboa Norte, Centro Académico de Medicina de Lisboa (CAML); Rheumatology Research Unit, Instituto de Medicina Molecular, Faculdade de Medicina, CAML, Lisbon, Portugal, [34]The Queen Elizabeth Hospital, Adelaide, Australia, [35]Kanazawa University Graduate School of Medicine, Kanazawa, Japan, [36]Seoul St. Mary's Hospital, College of Medicine, South Korea, Korea, Republic of, [37]Karolinska Institutet Stockholm, Sweden, [38]Department of Internal Medicine, Hospital Vall Hebron, Barcelona, Spain, [39]Rheumatology Division, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [40]Department of Rheumatology, Hospital Parc Tauli, Barcelona, Spain, [41]Hôpital Lariboisière, Paris, France, [42]Divison of Health Based Evidence, Federal University of São Paulo, São Paulo, Brazil, [43]University College of London, London, UK, [44]Department of Immunology and Rheumatology, Unit of Advanced Preventive Medical Sciences, Division of Advanced Preventive Medical Sciences, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, [45]Uppsala University, Uppsala, Sweden, [46]University Hospital Cassiano Antônio Moraes (HUCAM-UFES/EBSERH), Federal University of Espírito Santo, Vitoria, Brazil, [47]Internal Medicine and Nephrology Unit, Department of Life, Health and Environmental Sciences, University of L'Aquila, and Department of Medicine, ASL 1 Avezzano-Sulmona, L'Aquila, Italy, [48]Department of Internal Medicine Hospital Ramón y Cajal, Madrid, Spain, [49]Department of Internal Medicine, Hospital Universitari Joan XXIII, Tarragona, Spain, [50]Unidad de Autoinmunes, del Hospital Universitario de Cabueñes, Gijón, Asturias, Spain, [51]Department of Internal Medicine Hospital Rey Juan Carlos de Móstoles, Madrid, Spain, [52]Clinical Unit of Rheumatology and Clinical Immunology, University of Rome Campus Biomedico (former L'Aquila), L'Aquila, Italy, [53]Department of Internal Medicine Hospital Infanta Leonor, Madrid, Spain

Objectives. To obtain a "high-definition" picture of the main features of primary Sjögren syndrome (SjS) at diagnosis following a worldwide data-sharing cooperative merging of international clinical SjS databases.

Methods. The Big Data Project Consortium is an international, multicentre registry created in 2014. As a first step, baseline clinical information from leading centers on clinical research in SjS of the 5 continents was collected. The centers share a harmonized data architecture and conducted cooperative online efforts in order to refine collected data under the coordination of big data statistical team. Inclusion criteria were the fulfilment of the 2002/2016 classification criteria.

Patients. By May 2022 the participant centres had included 15652 valid patients from 26 countries, including 10283 (65.8%) patients from Europe, 3185 (20.3%) from Asia, 1890 (12.1%) from America, 214 (1.4%) from Australia and 80 (0.5%) from Africa. Ethnicity categories were defined following the FDA classification (White 74%, Asian 15%, Hispanic 5%, Black 1%, Others/mixed 5%). The cohort included 14644 (93.6%) women and 1008 (6.4%) men (female:male ratio 15:1), with a mean age at diagnosis of primary SjS of 52.09 years (range 5-97 years). Glandular involvement consisted of dry mouth (92%) and dry eye (91%); diagnostic tests included abnormal ocular test (84%), abnormal oral diagnostic tests (salivary flows, parotid scintigraphy) (79%), and positive minor salivary biopsy defined as a focus score >1 (82%). The key immunological markers detected at diagnosis included antinuclear antibodies (82%), anti-Ro/SSA antibodies (75%), anti-La/SSB antibodies (43%), rheumatoid factor (46%), low C4 complement levels (13%), low C3 complement levels (13%), and serum cryoglobulins (8%).

Conclusions. The Sjögren Big Data Project has achieved to multiplied by 8 the largest number of patients ever included in an international SjS registry, and by 10 the largest number of patients included in Nationwide multicentric cohorts. A major achievement of the project has been the bidirectional communication between the data scientists and the clinicians, an essential feature for reaching reliable clinical conclusions from Big Data studies.

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CD4+ CYTOTOXIC T LYMPHOCYTES (CTL) ARE PRESENT IN SJÖGREN'S DISEASE MINOR SALIVARY GLANDS AND ASSOCIATE WITH MARKERS OF EPITHELIAL CELL DAMAGE NEAR INFILTRATES

Joachims M.[1], Li C.[1], Rusbuldt J.[2], Fowler B.[1], Rasmussen A.[1], Grundahl K.[1], Scofield R.H.[1], Sivils K.L.[2], Lessard C.J.[1], Farris A.D.*[1]

[1]Oklahoma Medical Research Foundation, Oklahoma City, USA, [2]The Janssen Pharmaceutical Companies of Johnson & Johnson, Spring House, USA

Introduction. CD4+ T cells dominate focal lymphocytic infiltrates in Sjögren's disease (SjD), but their differentiation states have remained unclear. Here, we used single cell (sc)RNAseq to discover CD4+ T cell states and spatial proteomics to confirm the findings.

Methods. CD4+CD45RA– memory T cells were singly sorted from minor salivary gland biopsies of individuals meeting the 2016 ACR/EULAR criteria for SjD (n=6) and subjected to scRNAseq using SmartSeq2. Transcripts aligning to the genome with HISAT2 and expressed in >10% of cells were used for dimensionality reduction. Data from the first 10 principal components were visualized with UMAP. Gene set enrichment analysis (GSEA) was used to identify the clusters. Differentially expressed (DE) transcripts between clusters were assessed by MAST using genes expressed in >1% of cells. FFPE tissue sections from an independent set of SjD cases (n=49) and symptomatic individuals with no objective signs of SjD (n=15) were subjected to Nanostring spatial proteomic analysis, with regions of interest (ROI) segmented on CD45 or pan cytokeratin (PanCK) fluorescent signals. Data normalized to ROI area were used to evaluate relationships between proteins using Pearson's correlations.

Results. Half of single cell cDNAs passed quality control (QC) and underwent library preparation and sequencing with PE150 reads. Of 402 sequenced cells, 385 passed QC (<30% mitochondrial reads, avg expression>3). Clusters (CL) corresponded to central memory T helper (CL0), quiescent (CL1), activated CD4+ cytotoxic T lymphocyte (CTL) (CL2), early activated/stressed (CL3), and regulatory/T follicular helper (CL4) cells. CL0 and CL2 were enriched for CD4+ CTL precursor and effector signatures, respectively, by GSEA. Within Nanostring ROIs containing lymphocytic foci, GZMA and GZMB showed stronger correlative relationships with CD3 (r=0.724, p<0.0001; r=0.640, p<0.0001) compared to CD56 (r=0.462, p<0.0001; r=0.449, p<0.0001) in SjD cases. GZMA and GZMB were more strongly correlated with CD4 (r=0.711, p<0.0001; r=0.512, p<0.0001) than CD8 (r=0.523, p<0.0001, r=0.221, p=0.003) in SjD cases. Correlations between CD4 and GZMA (r=0.432, p=0.004) or GZMB (r=0.185, p=ns) were weaker or absent in non-SS control ROIs containing lymphocytic clusters. CD4 in the CD45 segment of SjD cases correlated with markers of epithelial to mesenchymal cell transition (FAP-α) and tissue damage (CD95/Fas, PARP, BIM, p53, GZMA, GZMB) in the PanCK segment of matched ROIs, while similar relationships with CD8 were absent or weak.

Conclusions. Activated CD4+ CTL are present in minor salivary glands of SjD cases, and proteomic markers of cytotoxicity associate with CD3 and CD4 in regions containing focal infiltrates. GZMA, GZMB, and CD4 protein levels in $CD45^+$ cells correlate with markers of tissue damage in epithelial cells near lymphocytic infiltrates, implicating $CD4^+$ CTL in glandular pathology of SjD.

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PERSONALITY TRAITS CORRELATE WITH DISEASE ACTIVITY IN PRIMARY SJÖGREN'S SYNDROME

Módis L.*[1], Aradi Z.[2], Horváth I.F.[2], Szántó A.[2], Bugán A.[1]
[1]University of Debrecen, Faculty of Medicine, Department of Behavioral Sciences, Debrecen, Hungary, [2]University of Debrecen, Faculty of Medicine, Department of Internal Medicine, Division of Clinical Immunology, Debrecen, Hungary

Interactions between chronic diseases and personality have been recognized in health psychology. Personality changes associated to primary Sjögren's syndrome (pSS) are also revealed. However, correlations between personality traits typical for pSS and disease activity are not yet examined.
The goal of this study is to establish such psychobiological interactions. In the sample of 84 participants (mean age: 59.96; 95.24% women) disease activity was registered by the outpatient clinic of the Department C of Internal Medicine, University of Debrecen, using the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) and the EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI). The personality traits of the patients were assessed by the 7-factor Temperament and Character Inventory Revised version (TCI-R). Sociodemographic data was also recorded. The statistical analysis happened through spearman correlation and linear regression. Disease duration correlated with many factors and subscales of the TCI-R, among which negative correlation with the Persistence factor (PS) (r=-0.31; p=0.004) and its Perfectionism subscale (r=-0.31; p=0.004) was the most pronounced. The Harm avoidance factor (HA) and its Fatigability subscale (ha4) showed significant correlation with self-reported fatigue (HA: r=0.37; p<0.001; ha4: r=0.52; p<0.001), self-reported pain (HA: r=0.26; p=0.016; ha4: r=0.42; p<0.001) and ESSPRI score (HA: r=0.37; p=0.002; ha4: r=0.49; p<0.001). Regarding the biological parameters, ESSDAI component complement C3 correlated significantly with the Spiritual acceptance subscale of the Spiritual transcendence factor (r=-0.3; p=0.006). ESSPRI score was significant predictor for different personality traits separately, with HA explaining most of the variance (R2=0.27).
Based on our results gained in small population it is likely that personality traits correlate with both self-reported and biological disease activity scores in pSS. The TCI-R has neurobiological foundation; hence the results might indicate central nervous system alterations in pSS. HA turned out as the most sensitive factor to disease activity, which may indicate neural alterations in the serotonergic system, since HA is suggested to be related to it. Further investigations are needed to investigate the central nervous system in pSS (*e.g.*, neuroradiology) to prove these alterations and to help to build a complex psychobiological image of pSS.

MISCELLANEOUS

Poster 8

WORLD SJÖGREN'S DAY 2021: A 3-AXIS CAMPAIGN ABOUT FATIGUE

Grosjean A.*, Stone L., Vieira A., Koelewijn-Tukker J., Bouillot C., Antonopoulou K., Oosterbaan M.
Sjögren Europe, Bienne, Switzerland

Fatigue. Fatigue is one of the most prevalent and disabling patient reported symptoms of Sjögren's. Fatigue in Sjögren's clearly differs from ordinary tiredness. It as an ever-present, fluctuating, and nonrelievable lack of vitality being beyond one's own control. Not everyone experiences it in the same way, but fatigue is undeniably a permanent part of patients' lives. It is a debilitating symptom which is associated with reduced health-related quality of life.
World Sjögren's Day. Every 23 July is World Sjögren's Day (WSD). For WSD 2021, Sjögren Europe (SE) decided to focus on fatigue, with the hope to bring forth a topic often misinterpreted and poorly addressed. To contribute to increase awareness and acknowledgment of fatigue as a major factor in Sjögren's and promote a growing knowledge that Sjögren's is a systemic disease, various activities and informative material related to fatigue were presented in honour of WSD 2021.
The campaign was disseminated over a month, culminating with WSD and it was posted on a dedicated webpage on SE website www.sjogreneurope.org/wsd, on social media and in a newsletter. It was also disseminated by our members and other patients' communities.
A 3-axis campaign about fatigue. The campaign was organised in 3 axes, to present fatigue from 3 perspectives:
1. the medical perspective
A webinar about fatigue was organised with a rheumatologist from UK specialised in Sjögren's, in order to better understand fatigue.
2. the psychological perspective
A self-help booklet on targeting chronic fatigue in Sjögren's was published, written by a Dutch psychologist involved in the development of treatment programs and international guidelines for the treatment of fatigue and pain in RMDs.
3. the patient perspective
The core of the campaign is to express the different ways in which fatigue manifests itself, as experienced by patients. The article by Teri Rumpf, a Sjögren's patient, "15 types of Sjögren's fatigue", first written for the Sjögren's Foundation blog, was shared in a visual campaign available in 13 languages.
One type of fatigue per day was shared with an expressive picture, the pictorial name of the fatigue and a short sentence summarizing the fatigue. The complete description was shared in addition.
These publications aim to help patients feel understood and validated in their experience, and to put into words what they live and feel.
Results. The campaign had a great impact and a lot of visibility. It won the first prize at the Best Practice Fair Award during the EULAR PARE conference 2021.
In July 2021, just on Sjögren Europe Facebook page, it had more than 50'000 views. The visits on our website more than doubled to reach 500 visits a day.
This campaign allowed many patients to feel less alone in the face of fatigue as it made visible the invisible and initiated a rich dialogue. We noticed an increased presence of young people and men which is probably due to their representation in the photos.
The involvement and contribution of our member organisations was critical to the success of our campaign. They made the campaign their own, allowing patients to unite for WSD.

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(withdrawn by authors)

Poster 15

(withdrawn by authors)

Poster 16

(withdrawn by authors)

Poster 17

(withdrawn by authors)

Poster 49

IMPACT OF NEUROLOGICAL COMPLICATIONS ON QUALITY OF LIFE IN SJÖGREN'S

Church J.E.*, Makara M., Hammitt K.M.
Sjögren's Foundation, Reston, USA

Background. Sjögren's is a serious and systemic autoimmune disease that affects the entire body, including the nervous system. This analysis aimed to better understand the occurrence of neurological disease manifestations and their impact on QoL in a Sjögren's population.
Methods. A QoL survey was administered online by The Harris Poll between Oct. 13, 2021, and Nov. 8, 2021. The survey was available to all Sjögren's patients based in the U.S. aged ≥18 years. Questions were related to all aspects of Sjögren's, including neurology. Data was analyzed in Microsoft Excel and RStudio.
Results. A total of 3,622 eligible survey responses were received and 83% of respondents reported having been diagnosed with ≥1 nervous-system related condition. The most common diagnoses in this area were anxiety/depression (50%), brain fog (47%) and neuropathy (45%). When asked about symptoms experienced during the prior year, a majority of respondents reported experiencing brain fog (80%), trouble sleeping (73%), anxiety (66%), forgetfulness (64%), neuropathy (64%) and headache (56%). For each of these symptoms, a majority of respondents stated a major or moderate (negative) impact on their life (range, 58%-88%). When asked to choose a single symptom with the greatest negative impact, 5 of the top 10 reported symptoms were related to the nervous system, and, cumulatively, nervous system-related symptoms accounted for 24% of the total response in this area. The presence of related neurological conditions was associated to a decline in factors related to QoL. Notable differences were seen in the negative impact experienced when performing activities of daily living (range: 1, OR =2.26; 5+, OR=17.78), the ability to exercise (range: 1, OR=2.04; ≥5, OR=13.34), the ability to participate in social activities (range: 1, OR=2.35; ≥5, OR=12.77), the ability to be independent (range: 1, OR=1.96; ≥5, OR=12.25) and overall mood (range: 1, OR=2.08; ≥5, OR=11.46). Respondents with neurological conditions were more likely to state that they did not feel they were living a fulfilling life compared to those without (range: 1, OR 1.67; ≥5, 6.88) Respondents stated that new therapies to address nervous-system related symptoms were critical for addressing sleep problems (77%), brain fog and forgetfulness (77%), neuropathy (68%), impaired coordination (58%) and dizziness / POTS (55%).
Conclusions. Neurological disease manifestations frequently occur in Sjögren's patients and have a major impact on QoL. Patients commonly experienced brain fog, sleep problems, anxiety, depression and neuropathy. As a group, neurological symptoms represent some of the most bothersome experienced by Sjögren's patients. Because of its multifactorial nature, fatigue was not included in this analysis, though it remains one of the biggest issues for Sjögren's patients.
The presence of multiple neurological conditions was associated to worsening QoL in a variety of factors, including the ability to exercise and overall mood. Better recognition, management and treatment options are needed to help improve patient QoL.

Poster 50

PERCEPTIONS, BEHAVIORS AND EXPERIENCES RELATED TO COVID-19 AND THE COVID-19 VACCINE: A SURVEY OF U.S.-BASED SJÖGREN'S PATIENTS

Makara M.*, Church J.E., Hammitt K.M.
Sjögren's Foundation, Reston, USA

Background. Information specific to Sjögren's patients and their experience with COVID-19 and COVID-19 vaccination have been relatively limited. To help address these gaps, the Sjögren's Foundation created a survey for its members and U.S.-based Sjogren's patients to gain insight into their perceptions, behaviors and experiences related to COVID-19 and the COVID-19 vaccine.
Methods. The Sjögren's Foundation created and launched a nine-question patient survey on COVID-19 and COVID-19 vaccination on March 11, 2021. The survey has remained open since. The survey was hosted on SurveyMonkey, an online survey platform, and shared with adult Sjögren's patients aged ≥ 18 and living in the United States who were members of the Sjögren's Foundation. Responses were collected anonymously through the online platform and summary data for the group as a whole has been analyzed on an ongoing basis.
Results. A total of 593 responses to the survey were received as of May 4, 2022. The majority of respondents have not had COVID-19 (95%). In those self-reporting that they had been diagnosed with COVID-19 (n=35), 80% reported experiencing only mild-to-moderate symptoms. Combined, 72% of respondents had received a first dose of the COVID-19 vaccine (Pfizer, 36%; Moderna 34%; Johnson & Johnson, 2%). Within this group, 64% reported that they either did not experience any reactions or symptoms or experienced only mild events. Additionally, in those who experienced a reaction or symptom after receiving the first dose of the vaccine (n=264), 78% stated the experience lasted 48 hours or less. Combined, 49% had received a second dose of the COVID-19 vaccine (Pfizer, 26%; Moderna, 23%). Similar to the first dose of the COVID-19 vaccine, most respondents either did not experience any reactions or symptoms or experienced only mild events (59%). Events experienced after the second dose subsided in 48 hours or less in the majority of respondents (72%). In total, 12% of respondents stated that they were not willing to get the vaccine.
Conclusions. The majority of patients with Sjögren's responding to the survey have not had COVID-19 and were willing to be vaccinated. In those who have had COVID-19, Sjögren's patients reported that symptoms were mostly mild to moderate and lasted less than 48 hours. Similarly, most Sjögren's patients responding to the survey experienced only mild reactions or symptoms that subsided after 48 hours when receiving the first and second dose of the COVID-19 vaccine.
It is important to note that this survey was launched early in the vaccine rollout, and those stating that they had not received a first or second dose of the vaccine or stated that they did not plan to get the vaccine, may not have done so or felt that way due to availability, eligibility and information available at the time. The majority of responses were received between March and May of 2021.

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UNMET NEEDS IN RESEARCH, HOW PATIENTS CAN COLLABORATE: THE EXAMPLE OF NECESSITY

Bouillot C.*[1], Hammitt K.M.[2], Hjertviksten Lindland A.[3], Oosterbaan M.[4], Pincemin M.[1], Stone L.[5]
[1]Association Française du Gougerot-Sjögren, Paris, France, [2]Sjögren's Foundation, Reston, USA, [3]NRF Sjøgrens Syndrom, Oslo, Norway, [4]Nationale Vereniging Sjögrenpatiënten, Maarssen, Netherlands, [5]British Sjögren's Syndrome Association, Birmingham, UK

Background. NeceSSity stands for "New Clinical Endpoints in primary Sjögren's Syndrome: an Interventional Trial based on stratifYing patients". International consortium involving 25 partners (20 academics, 4 pharma and 1 patient association) funded by the Innovative Medicines Initiative (IMI2), this public-private partnership between EU and EFPIA specifically requested the involvement of Sjögren's patients.
Objectives. To determine realistically the role patients should play and elucidate their added value in such a project.
Methods. A patient association has been included from the beginning of the project (even before submission) as partner and is involved in 6 out of 10 Working Packages (WPs).

Results. Patients were involved in the conception and design of the study. In particular, they established a Patient Advisory Group (PAG). The PAG participated in the creation of the website and the design of lay versions in several languages, reviewed and adapted protocol and consent forms, largely contributed to the creation of STAR, the new primary endpoint assessment score, and participated in dissemination and communication. Patients have an active advocacy role in this project. As the voice of a large Sjögren's community with sometimes major disparities in care, the PAG has been active in participating in the different meetings and supporting and promoting the project to the general public and Health Authorities. As a culmination of the first phase, 20 patients provided valuable input, particularly during the development of STAR, to ensure that the validated clinical endpoints are relevant for patients, raising issues that had not been considered fully, if at all. The opinions expressed by patients during the Delphi Survey contributed substantially to this evaluation tool, taking into account the patient's feelings, which are often poorly evaluated or ignored. This future "gold standard", which will be presented to the EMA and FDA, could not have been developed without the participation of patients. In addition, patients were invited to test a webapp that will serve as an evaluation tool throughout the clinical trial. The feedback from the PAG will contribute to the success of this patient-reported outcome tool and has helped to correct issues to ensure its success during the clinical trial.
Conclusions. Patient involvement in research is now widely accepted and the benefits are clear. The authorities now frequently require validation by patients. It is quite possible to work in harmony, bearing in mind the constraints and specificities of each stakeholder, in particular that patient participation is voluntary and that their health might not allow them to react immediately. Clinicians, researchers and patients have complementary skills and perspectives which, when shared, will strengthen the project.

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AN EMPIRICAL LINGUISTIC ANALYSIS OF THE TERMS USED FOR THE DISEASE DESCRIBED BY HENRIK SJÖGREN

Yarowsky D.[1], Mackey A.[2], Turner B.[1], Blanck J.[1], Hammitt K.[3], Ramos-Casals M.[4], Baer A.*[1]
[1]Johns Hopkins University, Baltimore, USA, [2]Georgetown University, Washington, USA, [3]Sjogren's Foundation, Reston, USA, [4]University of Barcelona, Barcelona, Spain

Objectives. While most commonly known as Sjögren's Syndrome, many different terminologies, spellings, and nomenclatures are in use in English and other languages for the disease described by Henrik Sjögren. The U.S. Sjögren's Foundation has advocated the adoption of the term Sjögren's Disease rather than Sjögren's Syndrome due to patients' concerns that "syndrome" can imply that the illness is a collection of nuisance symptoms as opposed to a potentially serious and distinct systemic autoimmune disease. We performed an empirical analysis of terminology applied to this disease in a wide range of global publications in order to inform a Delphi process on Sjögren's nomenclature in the medical community.
Methods. The corpora of literature used for the analyses included over 34,000 unique medical citations and abstracts, taken from: a) Articles (1992-2022) identified from 5 medical literature databases using 15 search terms, and controlled vocabulary terms for "Sjoegren's Syndrome" or "Sjoegren Syndrome" depending on the database, and b) Scanned books contained in the Google Books n-gram database (1980-2018). The analyses utilized linguistically normalized N-gram techniques to enumerate usage of selected search phrases, both in aggregate and as a trend over time.
Results. Twenty-three unique synonyms for Sjögren's syndrome are listed. The term "Sjögren's Syndrome" (including spelling and possessive variants) was used 97.8% and Sjögren's Disease only 1% of the time in English. The synonyms "Gougerot-Sjögren's" and "Autoimmune Exocrinopathy" were used only 0.8% and 0.4% of the time respectively. Geographical differences were present for Gougerot-Sjögren's, being used for example 19% of the time in the French "Revue de Medicine Interne." The use of Gougerot-Sjögren's increased from 0.6% to 1% and that of "Autoimmune exocrinopathy" (and its variants) decreased from 1.0% to 0.2% over the last 25 years. Sjögren's was used with the possessive apostrophe 's' in 72.6% of 82,901 citations, in contrast to the non-possessive forms, Sjögren (26.6%) and Sjögrens (0.8%). Over time, there has been a trend away from the possessive usage of Sjögren's (and other spelling variants) and towards the non-possessive usage Sjögren. The relative usage of "Secondary Sjögrens" and "Overlap Syndrome" was 80.4% vs 19.6% in 1998-2002, and narrowed to 55.5% vs. 44.5% in 2018-2022.
Conclusions. "Sjögren's syndrome" is overwhelmingly the predominant usage worldwide. Alternative names, primarily confined to "Sjögren's Disease" "Gougerot-Sjögren" and "Autoimmune Exocrinopathy," do not come anywhere close in usage. The possessive form of Sjögren's has been used predominantly, but there has been an increase in usage of the non-possessive form over the past 25 years. "Secondary" Sjögren('s) has been predominantly used relative to "Associated Sjögren('s)" but the use of "Overlap Syndrome" to mean the same thing has increased steadily and is likely to surpass the frequency of "Secondary" Sjögren('s) in the next 2-3 years.
These data support clear empirical statements about the usage of terms applied to Sjögren's in the effort to reach international consensus on disease nomenclature.

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(withdrawn by authors)

Poster 144

RECIPROCAL IMPACT OF FIBROMYALGIA ON DISEASE CHARACTERISTICS AND PHYSICAL AND PSYCOLOGICAL DOMAINS IN SJÖGREN SYNDROME: CROSS SECTIONAL OBSERVATIONAL STUDY

Capacci A.*[1], Rubortone P.[1], Alivernini S.[1,2], D''Agostino M.A.[1,2]
[1]Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy, [2]Università Cattolica del Sacro Cuore, Rome, Italy

Background. Sjögren Syndrome (SS) is an autoimmune exocrinopathy, resulting mainly in ocular and oral dryness, with approximately half of patients displaying symptoms from different organ systems, further adding to the heterogeneous clinical phenotype of the disease. Fatigue and pain are common systemic symptoms in patients with primary SS and fibromyalgia is a frequent condition associated with chronic diseases.
Objectives. The aim of the study was to evaluate the impact of concomitant fibromyalgia in patients with Sjogren Syndrome in terms of clinical features and disease activity.
Methods. 50 patients with Sjogren Syndrome were enrolled in the study (100% female, age: 53.7±13.2 years and disease duration: 8.7±5.3 years), 25(50.0%) with concomitant fibromyalgia (SS/Fibro-group) and 25(50.0%) without (SS-group). 36 patients with primary fibromyalgia (Fibro-group) were included as control group. At study entry, demographic, educational, life-style and clinical parameters were recorded for each patient. SS was diagnosed according to the American College of Rheumatology (ACR) classification criteria (1) and fibromyalgia was diagnosed according to criteria for fibromyalgia defined by ACR (2). Moreover, each patient with fibromyalgia, with and without concomitant SS, was asked to fill a self-reported questionnaire to assess the impact of Fibromyalgia on multiple physical and psycological domains (Italian-FIQR).
Results. Stratifying the study cohorts based on the demographic and life-style characteristics, no significant differences were found comparing SS-group, Fibro-group and SS/Fibro-group. However, considering the different organ involvement, SS/Fibro-group were more likely reporting arthralgia symptoms (100.0%) than SS-group (76.0% p=0.02), despite similar clinical evidence of arthritis-synovitis among the two groups (12.0% in both groups respectively, p=1.00). Moreover, SS/Fibro-group showed significantly lower ESSDAI score (2.8±1.7) and higher ESSPRI score (7.0±0.9) compared to SS-group (ESSDAI: 7.5±3.7 p<0.001 and ESSPRI: 5.2±1.4, p<0.001 respectively). Finally, analyzing the differential distribution of individual scores of physical and psycological domains of the Italian-FIQR Questionnaire, SS/Fibro-group did not differ compared to Fibro-group (p>0.05 for all the 21 questions included).
Conclusions. SS is affected by concomitant fibromyalgia in terms of subjective-dependent parameters (i.e. joint complaints) however the concomitant SS does not affect the impact of fibromyalgia on physical and psycological domains, even if disease activity is higher in SS patients without fibromyalgia.

References
1. Shiboski SC *et al.*: *Arthritis Care Res* 2012.
2. Wolf F. *et al.*: *Arthritis Rheum* 1990.

Poster 177

(withdrawn by authors)

Poster 181

DIAGNOSTIC UTILITY OF A SECOND MINOR SALIVARY GLAND BIOPSY IN PATIENTS WITH SUSPECTED SJÖGREN'S SYNDROME: A RETROSPECTIVE COHORT STUDY

Carvajal Alegria G.*[1], Depinoy T.[1], Devauchelle-Pensec V.[1], Jousse-Joulin S.[1], Marhadour T.[1], Guellec D.[1], Marcorelles P.[1], Pers J.O.[2], Saraux A.[1], Cornec D.[2]
[1]CHRU de Brest, Brest, France, [2]LBAI UMR1227 INSERM - Université de Bretagne Occidentale, Brest, France

Objectives. To determine whether repeated minor salivary gland biopsy (MSGB) has a clinical diagnostic utility in patients with suspicion of Sjögren's syndrome (SS).
Methods. Clinical, biological, pathological data and physician's diagnosis after each MSGB from patients with suspected primary or secondary SS who had benefited from 2 MSGB at Brest University Hospital between January 1, 1990 and January 14, 2015, were retrospectively collected. We compared the characteristics of patients with and without first positive MSGB, concordance between the MSGB, and analyzed the modifications of diagnosis after the second MSGB.
Results: Ninety-three patients were included, first MSGB was positive for 23 and negative for 70. Patients with first positive MSGB had more often renal involvement (p=0.03) and hypergammaglobulinemia (p=0.01), anti-SSA antibodies (p=0.03) and positive second biopsy with focus score ≥1 or Chisholm >2 (p<0.01). The mean time between the 2 MSGB was 5.7±4.3 years. The concordance between the results of the 2 biopsies was low (κ=0.345). MSGB influenced diagnostic's change in 10 cases where the second MSGB was always guided by new specific clinical manifestations.
Conclusions. We observed a low concordance between 2 MSGB in patients with suspected pSS in our study. Despite this variability, performing a second MSGB changed the initial diagnosis in only a minority of the patients and was particularly useful when clinical manifestations had deeply evolved.

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SJÖGREN'S AND NON-SJÖGREN SICCA IN TIMES OF CORONA

Baert-Jansen A.*, Koelewijn-Tukker J., Visser-Noordegraaf M.
Nationale Vereniging Sjögrenpatiënten, Maarssen, Netherlands

Background. The National Sjögren's Patient Association (NVSP), the only Sjögren's patient association in the Netherlands, was founded on 10 December 1986 and currently has 2150 members. Our goals are to represent the interests of our members and to provide patients and their families with information.
Objectives. The NVSP receives questions through several channels from patients with Sjögren's and non-Sjögren sicca. They are worried about the consequences of the restrictions on daily life and work and what corona can do to their disease.
Methods. An attempt was made to get a picture of what the patients think by means of a survey. The results of the survey can lead to recommendations. In this way, their concerns can be addressed and the continuity of care among the many care providers with whom a Sjögren's patient comes into contact can be guaranteed also during the corona pandemic.
Results. A total of 95 patients completed the survey in the period from 26 May to 20 July 2020, between the first and second lockdown. *Concerns about corona in relation to daily life and work*: 73% of respondents adjusted their daily activities during the pandemic due to government guidelines and the fear of getting corona. Hobbies outside the home and voluntary work have been drastically reduced. Working at home increased because employers did not consider it wise to come to work. *Continuity of healthcare*: A quarter of the participants think that healthcare has changed a lot to very much (Fig. 1). Relatively many appointments with GPs, dentists, oral hygienists, ophthalmologists and physiotherapists were cancelled, rescheduled or postponed compared to the other disciplines. The GP was virtually unavailable by phone.
Concerned more than others: Corona contributes to uncertainty in Sjögren's patients for several reasons. It is not clear in which case the condition leads to a higher risk of corona and what it means for work.
Conclusions. *Concerns about corona in relation to daily life and work*: people have started to work more inside than outside, both in business and in private. *Continuity of healthcare*: due to the sudden pandemic, many decisions were made about the patient and not with the patient. Even though many appointments continued, albeit in a different way, the patients were very satisfied with this. Alternatives to maintain face-to-face contact with patients (such as video calling) were not sufficiently explored. *Concerned more than others*: 66% indicated that they consider themselves vulnerable to corona because they have Sjögren's disease (Fig. 2), or take immunosuppressive medication, or because the specialist indicates that they are in a high-risk group. Several of the above factors may apply to a patient.

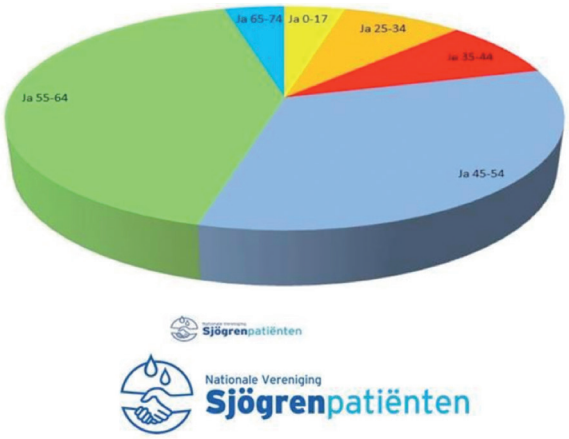

Fig. 1. Has healthcare changed (N=24).

Fig. 2. Vulnerable to Corona (N=95).

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PATIENT ASSOCIATION IN TIMES OF CORONA: WHEN FACE-TO-FACE CONTACT IS NO LONGER POSSIBLE, WHAT NEXT?

Abma A., Baert-Jansen A., Koelewijn-Tukker J.*, Oosterbaan M., Pors V.
Nationale Vereniging Sjögrenpatiënten, Maarssen, Netherlands

Background. The National Sjögren's Patient Association (NVSP), the only Sjögren's patient association in the Netherlands, was founded on 10 December 1986 and currently has 2150 members. Our goals are: to provide patients and their families with information; to represent the interests of our members with health insurers and medical practitioners; to organise contact with fellow sufferers; to combat misunderstandings; to promote the disease through the website www.nvsp.nl (Fig. 1), the quarterly magazine and other social media; to inform general practitioners and specialists about the symptoms and complaints; to stimulate and participate in scientific research into the cause and treatment of the disease.
Objectives. How does the NVSP maintain contact with its members and other interested parties in corona time.
Methods. Going from live to digital.
Results. Newsletter 'Het Kleine Ogenblikje': in order to inform our members more quickly of current developments, we have published, in addition to the quarterly magazine Ogenblikje (Fig. 2), Het Kleine Ogenblikje (Fig. 3). This newsletter is distributed digitally.
Webcasts and digital contact with fellow sufferers: Before corona, we held meetings in 8 regions across the Netherlands to meet and share information from healthcare professionals. During corona, we held monthly meetings for fellow sufferers via Zoom. Spread throughout the year, healthcare professionals discussed various medical topics via live webcast (Fig. 4). Members could also ask the health professional questions during the webcast. All webcasts can be viewed for those interested via YouTube on the NVSP page.
Talk show 'Talk about Sjögren's: In 2020, the talk show (Fig. 5) entitled 'Talk about Sjögren' was established for the first time because organising the annual contact day live (approximately 400 visitors) was not justified. The talk show broadcasts (in 2020 and 2021) were recorded in advance and at various locations. Patients, medical specialists and researchers have cooperated in the recordings. On the day of the planned national contact day the talk shows were broadcasted, and these shows can also be seen on the NVSP YouTube channel (2020 https://www.youtube.com/watch?v=aBUIVElNRXw) and 2021 https://www.youtube.com/watch?v=Pg1vzVDdsCc). Sjögren Europe provided subtitles in several languages for the 2020 broadcast.
Conclusions. We have been able to make the most of the digital highway and its opportunities. The work of the NVSP has not stood still despite corona and the lockdowns. We have been able to reach our members and our members have been able to reach us. This has enabled us to share new developments and thus maintain contact.
Even though we were able to reach many more people digitally, and the huge number of viewers for the various broadcasts surprised us, we missed live contact with our members due to corona.

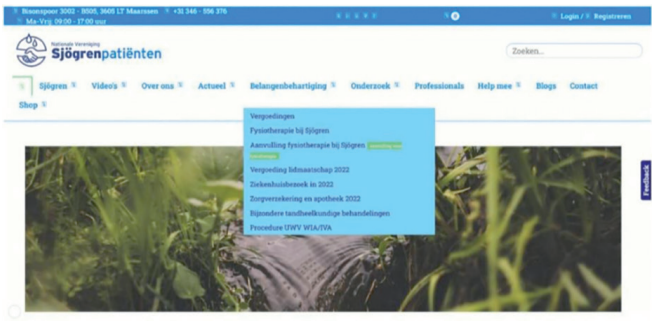

Fig. 1. website: www.nvsp.nl.

Fig. 2. Quarterly Magazine 'Ogenblikje'

Fig. 3. Newsletter 'Het Kleine Ogenblikje'

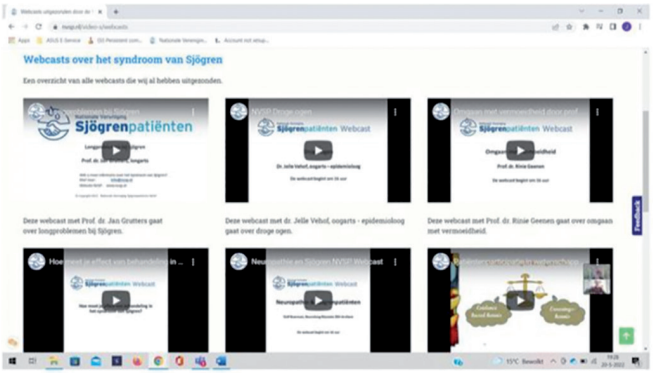

Fig. 4. Webcasts.

Fig. 5. Talk show.

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