Major Infiltrating Diseases Mimicking Sjögren’s Syndrome

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Sjögren’s syndrome (SS) is a systemic autoimmune disease that frequently presents with sicca symptoms of the main mucosa surfaces, can extend to systemic involvement (extraglandular manifestations) and may be complicated by the development of lymphoma. The already-difficult diagnostic process often becomes complicated by symptoms that might be confused with other disorders and causes.

The diagnosis of SS requires not only documentation of sicca symptoms but also objective evidence of dry eyes and dry mouth and analytical evidence of autoimmunity, as sicca syndrome has many causes. The most frequent cause of sicca symptoms is the use of drugs that have dryness as a side effect (mainly antihypertensive, antihistamine and antidepressant agents), especially in the elderly.

After the physician eliminates this factor, three main causes remain. First, SS may induce this symptomatology, and it should be remembered that SS should be considered as a diagnosis in patients with other autoimmune disease. Second, certain infections, mainly chronic viral infections, may induce lymphocytic infiltration of exocrine glands leading to a clinical picture often indistinguishable from that observed in SS patients. Third, some processes may mimic SS through a non-lymphocytic infiltration of the exocrine glands by granulomas.

Highlights from the 10th International Symposium on Sjögren’s Syndrome

by Alain Saraux, MD, PhD, Brest University Medical School, Co-Chairman of the Xth International Symposium on Sjögren’s Syndrome (Symposium Chairman: Pierre Youinou, MD, DSc)

More than 350 people attended the 10th International Symposium on Sjögren’s Syndrome (SS) in Brest, France held October 1-3, 2009. The growing interest and research activity in the field was reflected by the variety and depth of scientific presentations. More than 120 posters were presented and fruitful discussions occurred on the hottest topics during oral sessions and debates. Informal working groups devoted to practical issues in SS included sessions on ultrasonography (moderated by Athanasios Tzioufas, Sandrine Jousse-Joulin, Guido Valesini), refining criteria for SS (Troy Daniels, Manuel Ramos Casals, Anne Laure Fauchais), epigenetics (Steffen Gay, Yves Renaudineau, Quianjin Lu), and monitoring disease activity (Claudio Vitali, Simon Bowman, Xavier Mariette).
(sarcoïdosis, tuberculosis) or amyloid (amyloidosis) or malignant cells (hematological neoplasia). While we often recognize the difficulty in diagnosis created by major autoimmune diseases that mimic Sjögren’s, such as systemic lupus erythematosus and multiple sclerosis, this review focuses on a less frequently discussed topic: the main infiltrating diseases that mimic SS.

Several systemic diseases can mimic major symptoms and signs of SS through infiltration of the exocrine glands by an etiopathogenic mechanism different from that observed in primary SS. The three main groups of diseases mimicking SS are lymphocytic infiltrating processes (Mikulicz disease, graft-versus-host disease and lymphoma), granulomatous diseases (sarcoidosis) and metabolic diseases (amyloidosis, hypertriglyceridemia, hemochromatosis and diabetes).

### Diseases with Lymphocytic Infiltration

#### Mikulicz’s Disease

In 1888, Johann von Mikulicz reported a case with bilateral, painless symmetrical swelling of the lacrimal, parotid and submandibular glands. In 1927, Schaffer linked this case with underlying diseases such as sarcoidosis and lymphoma and named this clinical presentation Mikulicz’s syndrome in patients with underlying processes and Mikulicz’s disease (MD) in idiopathic cases. In 1953, Morgan and Castleman suggested that most cases reported as MD actually could be cases of SS. Since then, MD was considered a specific clinical presentation of primary SS.

Recent data, primarily from Japan, suggest that MD and SS are two different diseases with a clearly differentiated pattern of clinical expression. These data suggest that MD patients present with major lacrimal and salivary gland swelling and a paucity of other autoimmune features. The close association of MD with IgG4-related alterations suggests that it may be considered as an IgG4-related autoimmune disease. This novel group of diseases has recently been described by Kamisawa et al. and includes autoimmune pancreatitis, Riedel’s thyroiditis and tubulointerstitial nephritis. The lack of reported cases outside Japan suggests that this SS-like IgG4-related disease might be related to local genetic or environmental factors.

#### Chronic Graft-Versus-Host Disease

A major complication of allogenic bone marrow transplantation (BMT) is graft-versus-host disease (GVHD), characterized principally by ocular involvement which produces a Sjögren’s-like syndrome. The first cases were reported in 1977. Recent studies have suggested that BMT may be a trigger for the development of SS in some patients with a specific genetic predisposition.

#### Lymphoma

Lymphoproliferation is a well-known SS feature, including that involved in sicca syndrome and parotid enlargement. This has led to pre-existing lymphoma being included as an exclusion criterion in SS classification criteria. However, some patients may present with sicca symptoms many years before the development of lymphoma but not have an established diagnosis of SS when the lymphoma is diagnosed. In these patients with an underlying, non-diagnosed primary SS, lymphoma could not be considered as pre-existing, and they may be diagnosed with primary SS.

### Granulomatous Diseases

Granulomatous infiltration of the exocrine glands may be caused by caseating granulomas induced by infections such as tuberculosis, syphilis or leprosy or by non-caseating granulomas, principally sarcoidosis. No cases of SS mimicked by tuberculosis or leprosy have been reported recently; in contrast, nearly 80 cases of an association between sarcoidosis and SS have been reported in the last 10 years. We have described two different types of association between sarcoidosis and SS (mimicry and coexistence). Analysis of well-documented cases shows the coexistence of the two diseases in more than half the patients, while in the remainder, sarcoidosis involving exocrine glands mimicked SS. A lip biopsy in patients with sarcoidosis may be useful not only as confirmatory evidence of sarcoid involvement but also to eliminate coexisting SS.

### Metabolic Diseases

#### Amyloidosis

Amyloidosis can mimic SS when amyloid infiltration involves the exocrine glands. Systemic amyloidosis presenting as a sicca syndrome has been reported in some cases. However, systemic amyloidosis has been reported to coexist with SS in only two cases. The association between SS and localized nodular amyloidosis has been reported in nearly 30 cases.

#### Dyslipidemia

Association between sicca features and lipid alterations first was reported in 1969 when Kaltreider and Talal described 5 patients with hyperlipoproteinemia and bilateral parotid enlargement. In 2000, Izumi et al analyzed the main clinical features of 24 patients with a sicca syndrome related to dyslipidemia, including 50 patients with primary SS as a control group. They found parotid gland swelling in all patients with hypertriglyceridemia but not in those with hypercholesterolemia, suggesting a close relationship between parotid gland swelling and high serum triglyceride levels.

Continued on page 10
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References:
Brief Summary – See package insert for full prescribing information.

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Cevimeline is characterized by an exaggeration of its parasympathetic effects. These may include headache, visual disturbances, tachycardia, sweating, parasympathetic-related symptoms, nausea, vomiting, diarrhea, pharyngitis, dysphagia, tachypnea, dyspnea, increased salivary and lacrimal gland secretions, conjunctivitis, urinary urgency, and polyuria. Cevimeline should be administered with caution to patients with a history of gastrointestinal disturbances, constipation, or asthma.

Cevimeline should be administered with caution to patients with a history of myasthenia gravis or gastrointestinal disturbances. Constipation, dyspepsia, or asthma. Cevimeline may cause exacerbation of symptoms in patients who are also known to be sensitive to these effects. Cevimeline may be expected to have adverse effects. Cevimeline may interfere with desensitization to adverse effects of drugs associated with it.

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The Role of Nailfold Capillaroscopy in the Diagnosis of Primary Sjögren’s Syndrome

by Maurizio Cutolo, MD, Full Professor of Rheumatology, Director, Research Laboratories and Academic Unit of Clinical Rheumatology, Director, Postgraduate Academic School of Rheumatology, Chairman, EULAR Standing Committee for Education and Training (ESCET) University of Genova Italy, Genova, Italy

Introduction

Nailfold capillaroscopy (NC) is a non-invasive method of assessing skin microvasculature and contributes to the differential diagnosis and prognosis of several autoimmune disorders and between primary and secondary Raynaud’s phenomenon (RP)\(^1\,^2\) (Figure 1). The most characteristic capillaroscopic pattern with prognostic value is the scleroderma pattern characterizing systemic sclerosis patients (SSc)\(^3\,^4\) (Figure 2).

Primary Sjögren’s syndrome (pSS) often is associated with vascular features such as RP (in 10–30% of pSS cases) and vasculitis.\(^5\) Microvascular abnormalities assessed by NC range from non-specific to more specific or scleroderma-like findings (SSc-like)\(^6\,^7\) (Figure 3). In contrast with specific NC patterns found in SSc and dermatomyositis (DM), no specific NC pattern can be defined for pSS.\(^9\,^10\) However, several important studies have explored the role of nailfold capillaroscopy in pSS, and their findings could influence the way clinicians monitor pSS patients.

Nailfold capillaroscopy and autoantibodies in Sjögren’s

In a study of 22 patients with pSS and 30 with systemic lupus erythematosus (SLE), similar and non-specific findings were observed in both sets of patients, including a slight increase in capillary diameter and tortuosity.\(^11\) While this study did not correlate the presence of specific autoantibodies with NC pattern, other studies have done so with interesting results and provided information on NC as it relates to anticientromere antibodies, SS-A/Ro and SS-B/La autoantibodies, and anti-endothelial cell antibodies.

Tektonidou et al analyzed patients by NC and antinuclear antibodies array and included 40 pSS patients (16 with and 14 without RP and 10 with anticientromere antibodies and RP), 40 normal controls and 20 SSc patients.\(^12\) The authors observed altered NC with non-specific findings in approximately half of the patients and SSc-like findings in 10 (25%) patients, eight of whom had anticientromere antibodies. The non-specific findings observed in pSS were comprised mainly of tortuous and crossed capillaries and moderate visibility of the sub-papillary venous plexus.

In a more recent study by Capobianco et al, investigators correlated clinical and serological findings for 61 pSS patients and performed standardized NC assessment.\(^13\) This study found a lower prevalence of non-specific NC abnormalities (29.5%) and SSc-like pattern (11.5%). The difference in results from the previous study might be due, at least in part, to the lower number of patients with anticientromere antibodies in this sample (only one case). Also in contrast with the Tektonidou study, different rates of prevalence of non-specific characteristics compared to normal controls were not observed.
Among several capillaroscopic parameters tested by Capobianco, a significantly higher vascular deletion score occurred in pSS patients than in controls. The number of capillary hemorrhages and megacapillaries also tended to be higher in pSS patients. These results parallel those found by Tektonidou in which a reduction in capillary density and higher prevalence of hemorrhages were observed in the group of patients with RP.

The Capobianco study confirmed previous studies which found an association between the existence of anti-SSA/Ro and anti-SSB/La antibodies and a higher frequency of systemic manifestations of pSS, especially vasculitis. While no direct association between these autoantibodies and NC findings was detected in the Capobianco study, patients with systemic manifestations presented higher vascular deletion scores regardless of the existence of an SSc-like pattern. Therefore, the observation of the SSc-like pattern suggests that some patients with pSS might suffer from a type of microangiopathy similar to the one occurring in SSc and/or could identify some patients with overlapping syndromes with SSc spectrum diseases such as Mixed Connective Tissue Disease (MCTD).

**Nailfold capillaroscopy and anti-endothelial cell antibodies in Sjögren’s**

A recent study investigated possible links between NC findings and serological parameters of endothelial damage. These links include anti-endothelial cell antibodies (AECAs), which have been designated as having a possible pathogenetic role in autoimmune diseases, have been detected in 25–30% of pSS and appear more frequently in those patients with RP. The study looked for NC abnormalities and AECAs in a group of 66 consecutive pSS patients diagnosed according to the American–European Criteria. Classical morphological markers of microvascular damage were evaluated, including the number of capillaries per square millimeter, alterations in the capillary length, morphology (tortuous, ramified/bushy capillaries) and distribution, and presence of megacapillaries, hemorrhages and flux abnormalities. A semi-quantitative rating scale was adopted to score these changes according to previous studies.

- score 0 = no changes
- 1 = few (less than 4 alterations)
- 2 = some (between 4 and 6 alterations)
- 3 = frequent (more than 6 alterations per linear millimeter)

The mean score for each subject was obtained analyzing all fingers. Twenty-six (39.4%) of the 66 SS patients presented with RP, and an NC score of 1 was found in 33 cases (50%). Antinuclear antibodies were found in 55 patients (83.3%), anti-SSA/Ro antibodies in 47 (71.2%) and anti-SSB/La in 35 (53%) subjects. Sixteen (24.2%) patients had AECAs. RP was present in 8 (50%) AECA-positive patients and in 17 (34%) patients without these autoantibodies. The presence of ANA inversely correlated with the presence of AECAs (56 vs 92%) (P < 0.003). An NC score of 1 was found in 13 (81.2%) AECA-positive patients (Figure 1) and 20 (40%) AECA-negative patients (P < 0.008). No association was found concerning other clinical, capillaroscopic or laboratory features.

Even though a peculiar NC pattern does not characterize pSS patients, the study showed that an NC score of 1 was detectable in 50% of cases and is more frequent in AECA-positive patients compared to those without these autoantibodies (P < 0.008). Although not significant, this group of patients also had more frequent RP compared to those without AECAs (50 vs 34%), as shown in previous studies and meaning that they may act with a mediated mechanism resulting in an increased vascular reactivity.

A high prevalence of AECAs has been frequently associated with the presence of vascular lesions and with disease activity in autoimmune diseases. However, it is difficult to define the role of pSS in the occurrence of AECAs, whose endothelial antigenic targets are still unknown. The pathogenetic role of AECAs in the development of vascular injury remains controversial; however, the interesting association of these NC findings with the presence of AECAs suggests that these autoantibodies might be involved in endothelial damage in pSS.

**How to Perform a Nailfold Exam**

Skin capillaries are generally observed through an incident light microscope or videocapillaroscopic microscope. While nailfold capillaroscopic microscopy can be performed by a series of instruments including an ophthalmoscope, a dermatoscope and a stereomicroscope, videocapillaroscopic analysis is the most sophisticated tool for investigating microvasculature and detecting blood flow at the microvessel level. Handheld videocapillaroscopic devices are also available and less expensive.

Morphological evaluation of skin capillaries is generally performed at the nailfold because it is easily accessible and the major axis of the capillaries is parallel to the skin surface. Each subject must remain in the test room for a minimum of 15 minutes before the nailfold analysis and the room temperature maintained at 20–22°C. Usually at least 8 fingers should be examined (excluding the thumbs). Fingers affected by recent local trauma are not analyzed.

The most accurate morphological assessments are commonly performed on the fourth and fifth fingers, because of the greater transparency of the skin on these fingers. Generally, to detect early capillaroscopic changes, the following parameters are considered: presence of enlarged and giant capillaries, microhemorrhages, loss of capillaries, edema, amified/bushy capillaries (angiogenesis) and disorganization of the vascular array.
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†Some patients may require twice-daily use for optimal results.
‡Multicenter, 2-visit, 4-week, single-arm study conducted in moderate to severe Dry Eye patients who had previously been using ATs (N=528). Results are based on 418 patients who completed the study.
"Clinician’s Corner" Continued from page 13 ▼

In conclusion, the simultaneous presence of AECAs and more frequent NC abnormalities might suggest the hypothesis that these two parameters can help in evaluating the expression of vasculopathy in SS.

Nailfold capillaryscopy and Laser Doppler imaging in Sjögren’s

Laser Doppler imaging (LDI) is a relatively new method for measuring the microcirculation of cutaneous perfusion. Recently, capillary morphology and microcirculation among patients with pSS and PM/DM were investigated by NC and Laser Doppler imaging (LDI). Thirty patients with pSS, 30 with PM/DM, 30 with primary RP and 30 healthy volunteers were included in the study.

NC most often detected a vascularity in pSS patients and a vascularity and capillary morphology changes among PM/DM patients. With LDI, the mean steady-state cutaneous perfusion was 1.49 perfusion units (PU) at the fingertips in RP patients. The corresponding values were 1.48 PU in pSS, 1.19 PU in PM/DM, and 2.2 PU in controls. The differences were significant between each autoimmune group compared to the control group (p<0.02, p<0.001, and p<0.001, respectively).

Both investigative tools can be useful in the detection of secondary RP associated with pSS or in distinguishing whether the reduced blood flow is due to primary/systemic autoimmune diseases.

Conclusion

In conclusion, the microcirculation in pSS patients as evaluated morphologically (NC) or functionally (LDI) is generally altered but without a specific pattern. However, the presence of a NC SSc-like pattern in pSS patients could identify some patients with overlapping syndromes within the SSc spectrum of diseases, such as MCTD. Therefore, patients with RP must always be analyzed by NC, and if they present clinical and/or laboratory markers for pSS, they should be followed by regular NC in order to detect possible overlapping syndromes. ▼

References:

Continued on page 14 ▼
SSF Partners with Professional Organizations to Support Student Fellowships in Sjögren’s

The Sjögren’s Syndrome Foundation for the first time is partnering with professional organizations to award fellowships to students who propose scientific or clinical projects in Sjögren’s. This latest expansion of the SSF Student Fellowship program was made possible once again with support from the Bannon Humphery Foundation which shares the SSF goal of furthering the education of students in Sjögren’s and increasing awareness of Sjögren’s and the SSF among students and their mentors.

Awards in 2010 will be made through the American College of Rheumatology (ACR) REF Preceptorship Program, the American Association for Dental Research (AADR), and the Contact Lens Association of Ophthalmologists Education and Research Foundation (CLAO ERF). The ACR program is geared toward medical or graduate students in rheumatology; the CLAO program toward those working on an advanced degree and who may be ophthalmologists, optometrists, technicians, nurses, optometry students, ophthalmology residents and fellows or medical students.

2010 deadlines for applications vary according to the individual organization’s schedule. Check the SSF website at www.sjogrens.org/research for more information and links to each organization’s web page on the SSF Student Fellowships.

We Need Your Support For Sjögren’s Research!

The Sjögren’s Syndrome Foundation is proud of our highly respected Sjögren’s Research Program. We have, for the past six years, increased our funding for Sjögren’s research every Spring. This year, we are hoping to continue that tradition by offering nearly $300,000 in research grants to promising Sjögren’s projects, but we need your help. Funding is in need to ensure that we reach that goal.

Each year, the Foundation staff and research volunteers work diligently to attract talented and dedicated scientists to our research program. We foster relationships with top researchers in the field of Sjögren’s, as well as autoimmune diseases, in hopes they will consider conducting Sjögren’s research.

While we have made great progress, we need your help this year to ensure we can fund more research projects than last year. In 2009, we turned away sixteen promising projects due to lack of funding, and 2010 is shaping up to be the same ratio. Every project that is turned away means one less chance for a breakthrough in our fight against Sjögren’s syndrome.

Our goal is to increase our research program this year once again but we need your help. We hope you will consider making a donation to the SSF Research Program so that we can ensure more research is done for Sjögren’s.

To make your donation, contact the Foundation directly by calling 800-475-6473.

On behalf of Sjögren’s patients, thank you for believing in the Sjögren’s Research Program! With your support, we will uncover potential therapies for patients as well as unlock the mystery of Sjögren’s and find an overall cure.
Salivary gland biopsies obtained from two patients with hypertriglyceridemia revealed extensive lipid infiltration of the glandular lobules which was confirmed by MRI. Conversely, the salivary gland of a patient with hypercholesterolemia alone showed a less extensive lipid infiltration, mainly in the interlobular connective tissue. Lipid infiltration was rarely observed in salivary glands from patients with primary SS.

**Diabetes mellitus**

SS and diabetes mellitus (DM) are linked by both experimental (the non-obese diabetic or NOD mouse is a murine model of diabetes that develops an exocrine disease similar to human SS) and clinical studies (a high frequency of sicca syndrome in patients with diabetes). Clinical studies have found sicca features in a substantial percentage of patients with DM (20-55%), suggesting that DM should be considered an important cause of sicca syndrome in elderly patients. However, it should be kept in mind that sicca symptoms may have other causes apart from DM itself, such as aging-related factors or the coexistence of SS.

**Hemochromatosis**

Four cases of hemochromatosis involving salivary glands were reported in the 1980s. These patients presented with sicca features, and one had a submandibular salivary gland enlargement. No recent reports have been published on this association.

**Conclusion**

Early studies classified patients with SS as either primary or secondary according to its association with other processes. Secondary causes of SS principally included other systemic autoimmune diseases but also organ-specific autoimmune diseases, infections, neoplasia or metabolic diseases. These definitions have remained in use for the last 30 years and are still widely accepted. However, advances in the epidemiology and etiopathogenesis of SS in recent years suggest that these definitions should be questioned.

The main causes of mimicry seem to be processes involving the exocrine glands (sarcoidosis, lymphoma, systemic amyloidosis, hypertriglyceridemia, hemochromatosis, GVHD and MD), although, in some patients, some of these processes (sarcoidosis, amyloidosis and lymphoma) may coexist with SS as associated diseases (overlapping situation). Finally, we anticipate growing interest in the role of metabolic alterations in the etiopathogenesis of primary SS in forthcoming years.

**Recommended References**


**Epigenetics**

For the first time, epigenetics became a major topic for discussion and research reports. Epigenetics reflects both genetic and environmental processes that affect T cells and B cells as well. The main epigenetic modifications associated with autoimmune diseases concern histone modifications, DNA methylations and miRNAs, all of which could potentially be important as cellular activation markers or effectors on target cells.

Further study in this field could lead to the discovery of new diagnostic or prognostic markers for SS. The international epigenetic autoimmune group, “Brest Epigenetic Task Force,” has been set up to establish gold standards in the field and launch collaborative studies. The group has scheduled a meeting in Ljubljana, Slovenia during the 7th Autoimmunity Congress in May 2010.

**The Role of BAFF**

Fabienne Mackay updated the audience on B cell-activating factor (BAFF) in autoimmunity. Overproduction of BAFF in transgenic (Tg) mice triggers autoimmune disorders similar to...
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SS, possibly the result of abnormal self-reactive B cell survival. Prior studies demonstrated that excess BAFF only mildly affected B cell immune tolerance, could not prevent deletion of high affinity self-reactive B cells but could rescue some low affinity self-reactive B cells, specifically marginal zone (MZ) B cells. As germinal center formation and antibody affinity maturation are not essential for disease in these mice, the real implication of low affinity autoreactive B cells in driving the disease remains unclear. Indirect and direct effects of BAFF on T cell activation and expansion of the effector T cell compartment in BAFF Tg mice may contribute to nephritis in these animals. Surprisingly, however, BAFF Tg mice lacking T cells also develop the same autoimmune disease as the original BAFF Tg mice.

Overall, this work reveals that autoimmunity in BAFF Tg mice is the result of an abnormal innate B cell response involving the combined effects of excess BAFF and TLR signaling. However, many commercially-available ELISAs designed to assess this cytokine are defective since BAFF presents as an incredibly heterogeneous molecule. BAFF is also surprisingly pro-apoptotic in certain circumstances. The use of BAFF antagonists at the moment for treatment in primary SS (pSS) could therefore be hampered by the above limitations.

Ultrasonography

An informal working group discussed a novel scoring system for ultrasonography of the salivary glands in Sjögren’s syndrome. Sandrine Jousse-Joulin described the utility of the technology for this indication. Sensitivity of ultrasonography in the diagnosis of pSS ranged from 50-70% and specificity from 70-90%. The parotid and submandibular glands were most commonly evaluated using imaging pictures and dynamic studies. Salivary gland length, volume, margins, hypoechoic areas and parenchymal heterogeneity were routinely assessed. Athanasios Tzioufas proposed the elaboration of an objective grading system including all possible parameters/images in SS and subsequent validation in multicenter studies.

Mikulicz’s Disease

Mikulicz’s disease (MD) long has been considered a manifestation of Sjögren’s. However, new data from Japan suggest it may be a different disease with overlapping clinical features. Recently, it has been considered an IgG(4)-related disorder. Hiroki Takahashi presented data comparing IgG(4)-related disorders including MD to SS. A study was undertaken to investigate patients with MD and IgG(4)-related disorders registered in Japan and set up provisional criteria for the new clinical entity, IgG(4)-positive multiorgan lymphoproliferative syndrome (IgG(4)+MOLPS).

The incidence of xerostomia, dry eyes, arthralgias and rheumatoid factor and antinuclear antibodies (anti-SSA/ Ro and anti-SSB/La) was significantly lower in patients with IgG(4)+MOLPS than in those with typical SS. Allergic rhinitis and autoimmune pancreatitis were significantly more frequent, and total IgG, IgG(2), IgG(4) and IgE levels were significantly increased in IgG(4)+MOLPS. Histological specimens from patients with IgG(4)+MOLPS revealed marked IgG(4)+ plasma cell infiltration. Many patients with IgG(4)+MOLPS had lymphocytic follicle formation, but lymphoepithelial lesions were rare. Few IgG(4)+ cells were seen in the tissue of patients with typical SS. Thirty-eight patients with IgG(4)+MOLPS treated with glucocorticoids showed marked clinical improvement.

Despite similarities in involved organs, considerable clinical and pathological differences existed between IgG(4)+MOLPS and SS. Based on the clinical features and good response to glucocorticoids, a new clinical entity has been described: IgG(4)+MOLPS. The preliminary diagnostic criteria include raised serum levels of IgG(4) (>135 mg/dl) and infiltration of IgG(4) (+) plasma cells in the tissue (IgG(4)+/IgG+ <10%) with fibrosis or sclerosis.

Incidence and Prevalence

Stefano Bombardieri summarized current literature on the incidence and prevalence of pSS around the world. Large variations have been shown. He suggested that this diagnosis may be underestimated when basing statistics on patients having an established diagnosis of pSS. Raphaelle Seror in 2007 estimated the prevalence in a cross-sectional study in a Parisian suburban county (France) at 128.0 per million adults (95% CI: 107.7–150.1) for those meeting the American-European Consensus Group (AECG) criteria and 201.7 per million adults (95% CI: 176.3–229.6) for patients meeting modified AECG criteria: 0.013–0.020%. Prevalence also was lower (0.05%) in a study conducted in Norway and presented by Karstein Haldorsen.

In contrast, prevalence is generally found to be higher when using a two-step methodology (detection-confirmation) which involves detection of all cases of sicca syndrome in a population
and confirmation of a Sjögren’s diagnosis using all tests included in the 2002 classification criteria. Using this technique, Valeria Valim in Brazil obtained an estimated prevalence of 0.28%, and other groups published prevalence between 0.2 and 2%. These methodological differences explain why it is so difficult to compare studies about epidemiology in pSS.

**Classification Criteria**

As discussed by Manuel Ramos-Casals and Stephen Shiboski, the 2002 AECG criteria for Sjögren’s could be improved, potentially by including information on ultrasonography, blood B cell subset profile (Jacques-Olivier Pers) or other future discoveries. After diagnosis, the use of recently published criteria for activity (ESSDAI) (Raphaële Seror, Claudio Vitali) should improve the management of the disease, particularly in evaluating treatment efficacy. Once validated, such a standardized evaluation of SS should facilitate clinical research and be helpful as an outcome measure in clinical trials.

A website has been created to facilitate exchanges (www.eularsjsogrenactivityindex.com) with an open-access space containing information on the scores, the most recent news about the project and a restricted area for members of the panel with questionnaires for all studies and material for ethical procedures. The two large cohorts of pSS patients in registries initiated in the UK (UKPSSR presented by Wang-Fai Ng) and France (ASSESS presented by Jacques-Eric Gottenberg) will facilitate this evaluation.

**Conventional Therapy**

David Isenberg covered currently available and frequently used treatments for Sjögren’s including ocular and oral moisturizers, prescription medications such as pilocarpine and cevimeline for dry mouth, topical cyclosporine for dry eye and hydroxychloroquine for systemic features. Frederick Vivino presented favorable results of initial trials using a novel cholinergic agonist, NGX267, for dry mouth. The use of hydroxychloroquine to increase salivary flow was presented by Ulya Cankaya.

**Biologics**

Because conventional therapies do not modify the course of the disease, we are turning more and more to biologics as a potential new means for treatment – especially those that act on B cells. Robert Eisenberg presented a review of biologics that have been studied in pSS (Table 1). Rituximab is currently the best-evaluated biologic in pSS. Results of several open-label studies using rituximab for SS have been published and presented by various groups and document that rituximab can induce rapid depletion of B cells in the blood and salivary glands, is generally well-tolerated (except for occasional infusion reactions or serum sickness) and may alleviate various glandular and extraglandular manifestations of SS.

<table>
<thead>
<tr>
<th>Evaluated in pSS</th>
<th>Evaluated in pSS</th>
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<tbody>
<tr>
<td>Anakinra (IL-1Ra)</td>
<td>Anakinra (IL-1Ra)</td>
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<tr>
<td>Etanercept (TNFR-Ig)</td>
<td>Etanercept (TNFR-Ig)</td>
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<tr>
<td>Epratuzumab (anti-CD22)</td>
<td>Epratuzumab (anti-CD22)</td>
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<tr>
<td>Infliximab (anti-TNFα)</td>
<td>Infliximab (anti-TNFα)</td>
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<tr>
<td>Interferon-α (cytokine)</td>
<td>Interferon-α (cytokine)</td>
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<tr>
<td>IVIg (human IgG)</td>
<td>IVIg (human IgG)</td>
</tr>
<tr>
<td>Rituximab (anti-CD20)</td>
<td>Rituximab (anti-CD20)</td>
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</table>

Two small double-blind randomized studies (Jiska M. Meijer and Shouvik Dass) have been conducted and now published (Table 2). In addition, two double-blind studies are currently ongoing or planned. The first, the TEARS study, is being conducted in France to evaluate the Tolerance and Efficacy of Rituximab in pSS (TEARS). This multicenter, randomized double-blind placebo-controlled trial expects to enroll 120 patients. The primary objective is a 30% improvement between Day 1 and Week 24 on two of the four VAS measuring global scores of the disease, joint pain, fatigue and dryness. Patients are eligible if they fulfil the American-European Consensus Group criteria for pSS and have a recent diagnosis (less than 10 years) and active disease as assessed by the presence of at least one of these parameters and/or at least one of the following severe signs: parotidomegaly, arthritis, purpura, pulmonary involvement, renal tubular disease, neurological involvement or thrombocytopenia.

The second study, the ‘TRACTISS’ Study (Anti-B Cell Therapy in Patients with Primary Sjögren’s Syndrome), is led...

Table 2: Studies evaluating rituximab in pSS

<table>
<thead>
<tr>
<th>Author</th>
<th>Criteria for inclusion</th>
<th>Principal objective</th>
<th>endpoint</th>
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<tbody>
<tr>
<td>Meijer et al</td>
<td>AECG criteria, salivary flow (stimulated) &gt;0.15 mL/min, Anti-SSB or anti-SSA and RF, SGLB grade III or IV</td>
<td>Salivary flow (stimulated)</td>
<td>12 weeks</td>
</tr>
<tr>
<td>DASS et al</td>
<td>AECG, Ro/La Ab, fatigue &gt;50</td>
<td>20% reduction in fatigue VAS score</td>
<td>24 weeks</td>
</tr>
<tr>
<td>TEARS</td>
<td>AECG, 2 of 4 VAS &gt;50 – Recent, active (autoantibodies or cryoglobulinaemia, hyperglobulinaemia, beta 2-microglobulinaemia, or hypocomplement) – Or extraglandular</td>
<td>30% improvement on 2 of the 4 VAS (dryness, pain, fatigue and global)</td>
<td>24 weeks</td>
</tr>
<tr>
<td>TRACTISS</td>
<td>AECG, Recent, Ro/La Ab, salivary flow, reduced dryness and fatigue &gt;50 and at least one systemic feature</td>
<td>30% improvement in oral dryness and fatigue</td>
<td>24 weeks</td>
</tr>
</tbody>
</table>

Do we have your e-mail address?

If you want to receive all the latest updates from the Sjögren’s Syndrome Foundation, then you should make sure we have your most up-to-date e-mail address! The SSF is starting to share more information via e-mail, from news about the SSF and Sjögren’s, to information about the latest treatments and medicines, to local Support Group updates and more. So contact us at ssf@sjogrens.org to be certain we have your latest e-mail address in our database, and then keep an eye out in your Inbox for Sjögren’s news.

Just like all information you give the Foundation, your e-mail address will remain private and will never be given or sold to an outside organization.
Inflammation is a component of Sjögren’s syndrome and essentially all autoimmune disease. From a naturopathic perspective of treating the cause of disease, one of the first ways to address this is through an Anti-Inflammatory Diet. This upstream approach to treatment focuses on avoiding pro-inflammatory foods and eating a diet rich in anti-inflammatory foods. Additionally, since medical research is converging on inflammation as the common link in most diseases (i.e., heart disease, Alzheimer’s, asthma, diabetes, cancer, etc.), eating an anti-inflammatory diet is a great model of dietary health for everyone.

Avoid most packaged foods with a long list of ingredients. When preparing foods select raw, fresh, steamed, or broiled options over fried, BBQ’d or highly-processed choices. Specific recommendations are:

▷ Eat More
  - **Colorful Whole Fruits and Vegetables** – Eating foods with deep red, yellow, orange and green colors provides vitamins and minerals, phytonutrients, fiber and potent antioxidants that minimize inflammation. Eating foods as close to their unrefined state preserves the content of these beneficial nutrients.
  - **Healthy Fats** – This includes the omega 3 oils found in fatty fish (salmon, mackerel, sardines) and foods such as avocados, extra virgin olive oil, raw nuts and seeds.
  - **Fiber** – Fiber promotes adequate bowel movements, creates a favorable environment for healthy bacteria in your gut, and supports the body’s overall detoxification process. A few tablespoons of ground flax seeds daily are a great way to add soluble and insoluble fiber.
  - **Moderate Amounts of Organic Meat** – Grass-fed beef or bison is higher in anti-inflammatory essential fats. Organic free-range chicken tend to be lower in antibiotics and are fed a vegetable/grain based diet which tends to offer cleaner sources of protein.
  - **Spices/herbs** – Seasonings such as garlic, ginger and turmeric add an anti-inflammatory component to the diet.

▷ Eliminate / Eat Less
  - **Trans or Hydrogenated Fats** – The body has no mechanism to use these unnatural fats that ultimately cause inflammation. These should be eliminated from your diet.
  - **Refined Oils** – Commercial safflower, corn, and canola oils have had much of their health-promoting content removed for shelf-storage purposes and tend to be high in omega 6 fats that can be converted to inflammatory arachadonic acid, a type of fat that stimulates inflammation in the body.
  - **High Glycemic or Processed Foods** – Highly processed carbohydrates such as bread, pastas, cakes, candy, fruit juice and corn syrup are quickly digested leading to a rapid rise in blood sugar and a subsequent inflammatory cascade stimulated by insulin.
  - **Red Meat** – Avoid these meats when possible or eat organic grass-fed meat to reduce ingesting high levels of pro-inflammatory arachadonic acid.
  - **Common Food Allergies** – Milk products, eggs, gluten from wheat and peanuts can cause inflammatory reactions in many people and are best avoided.
  - **Artificial Sweeteners & Preservatives** – These additives have no nutritional value and tend to promote inflammatory reactions.
The Sjögren’s Syndrome Foundation is proud to announce that SSF CEO Steven Taylor has assumed the position of Chairperson for the Board of Directors of the National Health Council. This widely-esteemed and nationally-recognized health organization represents patients and leading patient advocacy groups throughout the country, including the Sjögren’s Syndrome Foundation.

The National Health Council strives to provide a united voice for people with chronic diseases and disabilities. It brings many stakeholders together to accomplish its goals of improving the health of all people; increasing support for health research; and strengthening the community of patient advocacy organizations. In addition to fifty of the nation’s leading voluntary health organizations, National Health Council members are comprised of professional and membership associations, nonprofit organizations with an interest in health, and major pharmaceutical, medical device and biotechnology companies.

“I am honored to take on a lead role for a unique organization that accomplishes so much for Sjögren’s and other patients,” says Taylor. “The National Health Council succeeds in providing a powerful voice for the more than 133 million people with chronic diseases and disabilities, and I share its vision of a world in which all people receive health care that meets their personal needs and goals.” Election to the Chairmanship position is a first for the Sjögren’s Syndrome Foundation, and we congratulate Steven Taylor on this tribute to his leadership.

For more information on the mission and programs initiated and implemented by the National Health Council, visit www.nationalhealthcouncil.org.