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## Clinician's Corner

### Sjögren's in Childhood

by Minako Tomiita, MD, PhD

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Minako Tomiita, MD, PhD

#### Case presentation

It is said that Sjögren's syndrome (SS) is rare in children; however, the number of pediatric patients has increased over time.<sup>1,2,3</sup> Here, I present a typical case of childhood SS.

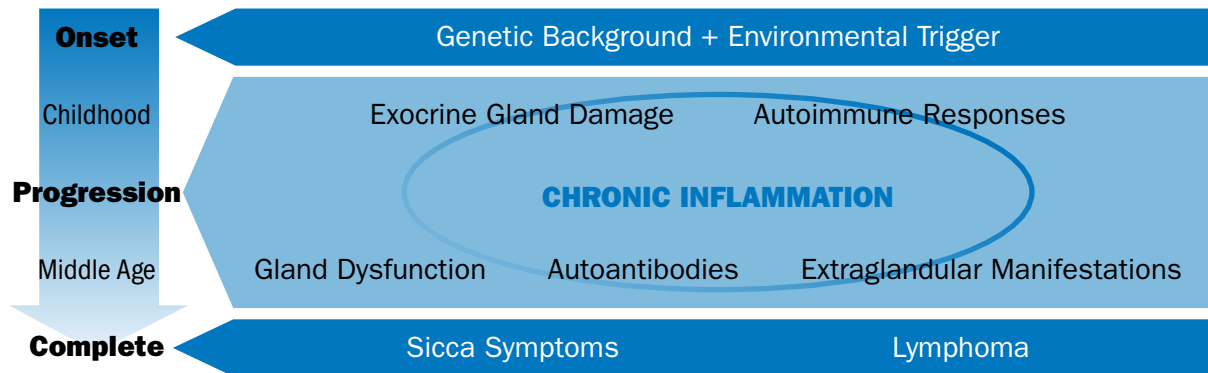
The patient was 11 years old at the time of admission. She presented with fever, headache, parotid gland swelling, and annular erythema. Examination of cerebrospinal fluid led to the diagnosis of aseptic meningitis. Blood examinations revealed that serum levels of IgG were high, and positive results were seen for antinuclear antibodies, anti-SS-A/Ro antibody, anti-SS-B/La antibody, and rheumatoid factor. SS was suspected, sialography was performed, and damage was defined as stage 1. Lip biopsy was not performed because the patient declined to undergo the procedure.

She followed up at our hospital, and at 20 years of age developed interstitial cystitis. She also complained of dry eye at age 27 and dry mouth at age 30. Now, we can say that her disease is typical of SS. Her disease had progressed very slowly. As noted by Sue Dauphin, "...it's interesting that many adults, once they have been diagnosed as having SS, will remember details from their younger years that seem to fit right in."<sup>4</sup> Our hypothesis is that SS may develop in an individual's pediatric years and may progress slowly; patients may not complain of sicca symptoms caused by exocrine gland damage until middle age (Fig. 1). If early diagnosis can be made, early treatment is possible.

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## Hypothesized Disease Course



Here, I would like to present the characteristics of pediatric SS that contribute to a definitive diagnosis.

### Characteristics of pediatric SS patients

From 1985 to 2011, we had 28 pediatric patients with primary SS who fulfilled the revised Japanese diagnostic criteria for Sjögren's (1999).<sup>5</sup> As in adult patients, a gender difference was shown with a gender ratio of M:F = 1:8. Sjögren's is a chronic disease, so it is difficult to determine the time of onset; we define it as the time at which at least one manifestation related to SS appears. In our patients, the age of onset was found across all ages of childhood (0.5~15); the major group comprised teenagers, and the mean was 10.1 years.

The symptoms or manifestations at first visit were very different from those in adult patients. Table 1 shows the symptoms at first visit observed in our patients. No one complained of xerostomia or xer-

ophthalmia. The most frequent symptom was recurrent parotid gland swelling; other frequently observed symptoms were extraglandular manifestations, such as fever, cutaneous manifestations, and arthralgia. In cutaneous manifestations, annular erythema was a major symptom. Lymphadenopathy, general malaise, Raynaud phenomenon, and morning stiffness also were observed. Thus, in pediatric patients with SS, extraglandular manifestations are important. In some patients, extraglandular organ involvement—uveitis, aseptic meningitis, thyroiditis, and thrombocytopenic purpura—occurred as a symptom of onset.

**Table 1. Manifestations at First Visit**

Glandular manifestations	Recurrent parotid gland swelling, ranula
Extraglandular manifestations	Fever, skin rash, arthralgia/arthritis, lymphadenopathy, general malaise, morning stiffness, Raynaud phenomenon
Extraglandular organ involvements	Uveitis, aseptic meningitis, thrombocytopenic purpura, thyroiditis
Others	Abnormal laboratory findings

As is the case with adult patients, hypergammaglobulinemia, rheumatoid factor, antinuclear antibodies, and anti SS-A/Ro antibodies were frequently observed. Anti SS-B/La antibodies also were observed in 46% of patients. In examinations for glandular damage, labial gland biopsy (95.7%) and sialography assessments (84.6%) were highly positive. On the other hand, the positivity of functional tests, such as the Saxon test (33.3%), Schirmer test (21.4%) and ocular staining test (45.8%), were low.

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This indicates that the dysfunction of the exocrine glands of pediatric patients with SS is not severe.

SS patients are known to have variable extraglandular organ involvements. As shown in Table 2, many similar complications occurred in our pediatric patients during the follow-up periods. Patients with thrombocytopenia, hemolytic anemia, peripheral neuropathy, severe chilblain, arthritis, uveitis, and recurrent fever need immunosuppressive therapy with corticosteroids and/or immunosuppressants. Over the ten years of follow-up, some of our patients progressed to complain of sicca symptoms and needed specific therapies such as pilocarpine or cevimeline.

**Table 2. Extraglandular organ involvements**

Hematologic	Thrombocytopenia, neutropenia, hemolytic anemia
Neurologic	Aseptic meningitis, peripheral neuropathy
Skin	Erythema, chilblain
Endocrine system	Thyroiditis, diabetes mellitus
Musculoskeletal	Arthritis
Others	Uveitis

The characteristics of pediatric SS patients are summarized as follows:

- At onset, sicca symptoms are rare in children, and extraglandular manifestations are major complaints.
- Immunological status is no different from that of adult patients.
- Glandular dysfunction is not severe, especially regarding ocular involvement.
- Variable extraglandular organ involvement is observed.

With these factors, SS may develop at the pediatric stage and may progress slowly. In some patients, severe extraglandular organ involvement occurs. Clinicians should be made aware of and diagnose pediatric SS even if patients do not complain of sicca symptoms.

### How to diagnose Sjögren's in children

Sicca symptoms in SS are caused by dysfunction of the exocrine glands as a result of damaged glands related to an autoimmune disorder. Thus, patients in the early stage may rarely complain of sicca symptoms. Therefore, to make an early diagnosis, it is most important "to suspect SS."

Patients who have symptoms suggestive of rheumatic diseases, for example, fever of unknown origin, arthralgia and/or erythema, should be considered to have SS. In pediatric patients, recurrent swelling of the parotid glands is an important finding.

Serum IgG, rheumatoid factor, antinuclear antibod-

ies, anti SS-A/Ro antibodies, and anti-SS-B/La antibodies should be examined.

To demonstrate the presence of exocrinopathy, labial gland biopsy, sialography, scintigraphy, salivary flow rate, the Schirmer test, and ocular staining should be done. We recommend MR sialography instead of X-ray sialography, because it does not require contrast material and has no adverse effect.<sup>6</sup> Differential diagnoses, such as for some viral infections, malignant diseases, and sarcoidosis, are needed.

If patients fulfill one of the three major criteria for SS,<sup>5,7,8</sup> it is not difficult to diagnose. However, exocrinopathies are mild in pediatric patients and not all patients have anti SS-A/Ro antibodies or anti SS-B/La antibodies; in some patients, antinuclear antibodies are low. In such cases, about 20% of pediatric patients do not fulfill any of the three major criteria. Thus, new diagnostic criteria or guidelines for early diagnosis of SS are needed. These are in the process of being prepared.

Some patients also have other rheumatic diseases. Systemic lupus erythematosus (SLE) is the most frequently observed. Mixed connective tissue disease and polyarticular type of juvenile idiopathic arthritis also are observed.

### Treatment

There is no standard treatment for pediatric Sjögren's. Symptomatic therapies are mainly used for glandular manifestations. We recently reported on the efficacy and safety of oral pilocarpine hydrochloride for pediatric SS patients.<sup>9</sup> After four weeks of pilocarpine administration, salivary production increased significantly, and overall status was assessed as "improved" in all patients. One patient had excessive sweating. No serious adverse events or laboratory examination abnormalities corresponding to pilocarpine administration were found.

For extraglandular organ involvement, non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and some immunosuppressants are used. For mild arthritis and recurrent fever, NSAIDs may be the treatment of choice. However, in some patients, aseptic meningitis could occur as an adverse effect. In severe extraglandular organ involvement, such as hypergammaglobulinemic purpura, neuropathy, hemolytic anemia, and interstitial nephritis, corticosteroids are needed. If a poor response is observed, immunosuppressants (mizoribine, cyclosporine A, azathioprine, cyclophosphamide, mycophenolate mofetil) are used. Pessler *et al* reported the efficacy of infliximab and etanercept for severe arthritis in a young SS patient.<sup>10</sup>

In pediatric patients, there is no evidence that early intervention with immunosuppressive therapy can pre-

vent disease progression. Patients may require long-term therapy, and, as such, we recommend caution in choosing therapy during childhood. In particular, growth retardation and osteoporosis caused by corticosteroids can become severe problems in children. The adverse effects of long-term immunosuppressant therapy also are important considerations. Early interventions for pediatric SS patients are important questions and more research is needed.

### Conclusion

Pediatric SS patients rarely complain of sicca symptoms, so they are often under-diagnosed or misdiagnosed. Early diagnosis is important so that patients who develop Sjögren's in childhood can be followed and treated from the earliest stage of their disease. New diagnostic criteria and guidelines are required for pediatric patients. Finally, long-term follow-up of pediatric patients will provide a great deal of information about Sjögren's. ■

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# Highlights from the 12th International Symposium on Sjögren's Syndrome in Kyoto, Japan

by Takayuki Sumida, MD, PhD, Hiroto Tsuboi, MD, PhD, Hiromitsu Asashima, MD, Mana Iizuka, PhD and Isao Matsumoto, MD, PhD  
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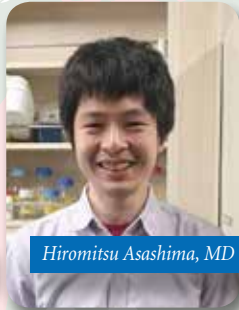
*Editor's Note: The Sjögren's Syndrome Foundation (SSF) was pleased to participate in the 12th ISSS. Interacting with clinicians and researchers from around the world; engaging in deliberations about pressing topics such as classification criteria; meeting with companies developing products and therapies for Sjögren's; and assisting in the leadership of the International Sjögren's Network made up of international patient groups are critical to the mission of the SSF. Please note that this summary of the 12th ISSS is available on the SSF website at [www.sjogrens.org](http://www.sjogrens.org) under "Scientific Initiatives."*



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The 12th International Symposium on Sjögren's Syndrome (ISSS) brought together a wide range of Sjögren's specialists in clinical care and research from around the world to meet in Kyoto, Japan from October 9-12, 2013. Since the first ISSS was held in Copenhagen, Denmark in 1986, similar conferences have been held in Europe, Japan, and the USA every 2-4 years. The 12th ISSS was organized by the Japanese Society for Sjögren's Syndrome (JSSS) in collaboration with the University of Tsukuba. Held in Kyoto, 337 delegates from 23 countries attended. The program included two symposia, two panel discussions, ten workshops, three plenary sessions, and two poster sessions. In this article, we provide highlights of the symposium.

## Symposia

In the first lecture, "Discovery of NKT cells and their clinical application in 1986," Masaru Taniguchi (RIKEN, Kanagawa, Japan) described his group's discovery of NKT cells, which express an invariant V $\alpha$ 14 antigen receptor that recognizes glycolipid antigens. He and his team discovered the NKT cell ligand,  $\alpha$ -galactosyl-ceramide and generated the NKT cell-deficient mouse (1997). Functions of NKT cells include: 1) anti-pathogen and anti-tumor responses; 2) maintenance of tolerance and protection against autoimmune disease; 3) development of allergic and non-allergic asthma. These functions are mediated by at least 4 NKT cell subtypes that express different cytokine receptors.

The research group led by Prof. Taniguchi generated

iPS from mature NKT cells and successfully developed functional NKT cells from NKT-derived iPS. Interestingly, NKT-derived iPS cells generated mainly NKT cells but not other cell types irrespective of their pluripotent activity. The iPS-derived NKT cells produced large amounts of IFN- both *in vitro* and *in vivo* upon stimulation with -GalCer, mediated bystander adjuvant effects of NK and CD8 T cells, and suppressed tumor growth *in vivo*.

In the second symposium, Jacques-Olivier Pers (University of Brest, France) discussed the role of BAFF in Sjögren's (SS). BAFF is overproduced in SS, mainly by innate immune cells and to a lesser extent by epithelial cells. His research team discovered  $\Delta$ 4BAFF, which lacks exon 4-encoded segments, and was the first to describe in-house ELISA for the detection of various forms of BAFF. Pers discussed the role of BAFF not only on B cell growth and survival but also on the onset and ensuing severity of the disease.

## Pathogenesis

### Genetics

Lindsey Criswell (University of California, USA) presented genome analysis data using Sjögren's International Collaborative Clinical Alliance (SICCA) cohorts. Her group found multiple variants within the MHC region and the IRF5-TNP03 region that were strongly associated with susceptibility to SS, autoantibody production and focal lymphocytic sialadenitis. They did

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not find significant genetic associations with keratoconjunctivitis sicca (KCS), indicating the genetic heterogeneity specifically related to the oral, ocular or systemic manifestations of SS.

Kathy Sivils (Oklahoma Medical Research Foundation, USA) described the first Sjögren's-specific genes ever to be identified. Data was gathered from the genome wide association study (GWS) through a collaborative effort of the international Sjögren's Genetics Network (SGENE). The group established associations between Sjögren's and variants in the MHC/HLA, IRF5, BLK, STAT4, IL12A, CXCR5, and TNIP1 loci. Nine other regions include TNFAIP3, FCGR2A, IRAK1BP1, and PHIP. Furthermore, 21 additional loci previously implicated in other autoimmune and inflammatory phenotypes reach suggestive levels of association in SS that warrant further studies. (*Editor's Note: Dr. Sivils is authoring an article on this discovery for the Sjögren's Quarterly which is scheduled for inclusion in the spring 2014 issue.*)

Gunnel Nordmark (Uppsala University, Sweden) presented her group's genome data analysis focusing on anti-SSA/SSB-positive SS patients. Twelve SNPs (IKBKE; n=2, NFKB1; n=1, TNIP1; n=5, TNFAIP3; n=4) were genotyped, and they found that polymorphisms in TNIP1 are associated with antibody-positive pSS and possibly affect the NF- $\kappa$ B signaling pathway in disease development and clinical manifestations.

Pilar Brito-Zeron (Laboratory of Autoimmune Diseases Josep Font, Spain) focused on genetic variability in the CD5 receptor. He and his research team found that a specific genetic combination of allelic positions at SNPs 7 and 26 of the CD5 receptor gene is associated with higher extraglandular systemic activity and frequency of immunological abnormalities, including anti-La/SS-B antibodies and cryoglobulinemia.

### Viruses

Hideki Nakamura (Nagasaki University, Japan) described the high prevalence of HTLV-I in pSS patients in the endemic area of Nagasaki. They suggest that Fas-mediated apoptosis, anti-apoptotic molecules, mitogen activated protein kinase, chemokines, various adhesion molecules such as intercellular adhesion molecule-1, and secreted or interferon-induced 10 kDa protein in labial salivary glands are involved in pathological manifestations of SS with HTLV-1 infection.

Michele Bombardieri (Queen Mary University of London, UK) discussed the role of viral infection in the formation of tertiary lymphoid structures (TLS) in SS. TLS represent functional niches whereby autoreactive B-cells undergo *in situ* affinity maturation and differentiation into autoantibody producing cells, thus contributing to the progression and persistence of autoimmunity. In addition, TLS in SS have been linked to the development of non-Hodgkin marginal-zone MALT B-cell lymphomas, specifically in salivary glands. Their findings strengthen the argument that altered immune responses

to viral infection trigger SS immunopathology.

Hiroko Inoue (Nihon Pharmaceutical University, Japan) presented findings on reactivation of EBV by the ligand-activated aryl hydrocarbon receptor (AhR). AhR is a ligand-activated transcription factor that mediates a variety of biological effects by binding to environmental pollutants and elicits reactivation of EBV in activated B cells and salivary epithelial cells, suggesting their involvement in SS.

### T Cells

Mana Iizuka (University of Tsukuba, Japan) focused on the autoimmune response to M3 muscarinic acetylcholine receptor (M3R). His group found that M3R reactive CD3+ T cells play an important role in the development of autoimmune sialadenitis in mice, and IFN- $\gamma$  and IL-17 play critical roles in sialadenitis progression.

Seiji Nakamura (Kyushu University, Japan) discussed the Th subsets (Th1, Th2, Th17 and Tfh cells) involved in the pathogenesis of localized autoimmune damage in labial salivary glands of SS patients. His findings suggest SS might be initiated by Th1 and Th17 cells and progresses via Th2 and Tfh cells in association with GC formation.

Cuong Q. Nguyen (University of Florida, USA) focused on the profile of Th17 cells infiltrating the salivary glands of mice. At the clinical disease stage, extensive high-throughput sequencing of TCR and TCR chains demonstrated the expression of TCR V31 on the majority of Th17 cells, while TCR V15 and TCR V1 genes were expressed less frequently.

Jacques-Eric Gottenberg (National Reference Center for Autoimmune Diseases, France) investigated whether salivary gland epithelial cells induce differentiation of naive CD4+ T cells into Tfh cells. Intriguingly, results demonstrated that salivary gland epithelial cells from both patients and controls induce this differentiation.

Scott M. Lieberman (University of Iowa Carver College of Medicine, USA) described the role of Treg dysfunction in sex-specific disease manifestations. His studies demonstrate that a male-specific, Treg extrinsic factor mediates lacrimal gland-protective Treg dysfunction, promoting dacryoadenitis in male mice.

Based on previous studies demonstrating the presence of high serum levels of IL-10 in patients with primary Sjögren's (pSS) and the significant association between IL-10 promoter polymorphisms and pSS susceptibility, Keishi Fujio (The University of Tokyo, Japan) described a novel IL-10 induction pathway. Study results suggesting that STAT3-dependent IL-27 signal transduction through Egr-2 and Blimp-1 cascade plays an important role in this IL-10 cascade.

### Autoantibodies

Yoshinari Takasaki (Juntendo University School of Medicine) discussed recent advances in understanding mechanisms for autoantibody production and clinical usefulness of autoantibodies in SS. Antibodies to SSA/Ro and SSB/La are included in SS diagnostic criteria and



used as markers for specific organ involvement. Both genetic and environmental factors that alter innate and acquired immunity play critical roles in the induction of autoantibody production.

Hiroto Tsuboi (University of Tsukuba, Japan) discussed the epitopes and function of anti-M3R antibodies. Analysis shows that the effects of these antibodies on the secretion of saliva depend on the extracellular domain of M3R, several B cell epitopes on M3R are present in SS, and the effect of anti-M3R antibodies on salivary secretion varies accordingly.

Michael W. Jackson (Flinders University, Australia) presented on long-term humoral autoimmunity in SS by analyzing autoantibody response against epitopes of Ro/SSA using Orbitrap mass spectrometry. The discovery of clonotypic autoantibodies directed against immunodominant epitopes on Ro/SSA supports a model of systemic autoimmunity in which humoral responses against protein-RNA complexes are driven by pathophysiological mechanisms that are virtually identical among patients.

Marie Wahren-Herlenius (Karolinska Institutet, Sweden) reviewed the relationship between congenital heart block and maternal anti-Ro/SSA and La/SSB antibodies. Recent studies indicate that the risk for fetal heart block may be higher in women whose antibody reactivity targets Ro52 rather than the Ro60 component of the Ro/SSA complex. Furthermore, specificity for amino acids 200-239 (p200) of the Ro52 protein increases the risk of fetal cardiac involvement, and both immunization with Ro52 p200 peptide and passive transfer of Ro52 p200-specific monoclonal antibodies induces atrio-ventricular block in experimental models.

Yasunori Suzuki (Kanazawa University Graduate School of Medicine, Japan) reported that clinical findings in SS patients, such as Raynaud's phenomenon, sclerodactyly and salivary production, varies when comparing those who are both anti-centromere anti-

body (ACA)+ and anti-SSA antibody (SSA)+ and those who are ACA- but SSA+. These findings suggest that the clinic-pathological features of ACA+SSA+ SS differ from those of other phenotypes.

#### B cells

The pathogenicity of B lymphocytes in SS was reviewed by Pierre Youinou (European University of Brittany, France). These lymphocytes not only contribute to the lymphocyte infiltrate in exocrine organs but also favor the expression of recombination-activating genes as well as the activation of T cells through the synthesis of IL-6. Undue synthesis of BAFF, or irregular distribution of its variants, activates the pathway. Future exploration of B lymphocyte targeting remains worthy of pursuit.

Malin V. Jonsson (University of Bergen, Norway) analyzed the relationship between germinal centers (GCs) in minor labial salivary gland biopsies and certain pSS phenotypes. Lymphoid organization into GC-like structures is observed in 20-25% of pSS patients. Comparison of GC+ and GC- patients shows that the former group included younger patients who presented with lower unstimulated whole saliva levels, higher mean focus scores, higher frequency of classical hypoechogenic pattern by ultrasound of major salivary glands, higher frequency of anti-Ro/SSA and/or anti-La/SSB autoantibodies and high serum IgG levels. GC+ patients also had higher levels of IL-4, IL-10, GM-CSF, IFN-alpha, CCL3 (MIP-1alpha), CCL11 (Eotaxin) and soluble BAFF (sBAFF) compared to healthy controls. GC+ and GC- patients also differed in CCL2 (MCP-1) expression. The study concluded that CCL11 (Eotaxin), IFN-gamma and sBAFF could be useful biomarkers for GC.

Elisa Astorri (Queen Mary University, UK) discussed the involvement of Fractalkine (CX3CL1) in SS ectopic lymphoneogenesis. High serum levels of CX3CL1 pro-

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tein were observed in sera of 21 pSS patients compared with controls as well as up-regulation of mRNA levels of chemokines and their receptors in SS salivary glands. Moreover, cells expressing CX3CL1 and its receptor, CX3CR1, were identified histologically in the salivary glands of SS patients, which were localized within tertiary lymphoid structures.

#### Innate Immunity and Other Cells

Athanasios Tzioufas (University of Athens, Greece) reported that epithelial cells appear to be the major source of autoantigens, with epitope spreading and regulation via the idiotype-anti-idiotype network. Recent experiments involving TLR3 ligation of epithelial cells resulted in upregulation of the autoantigens via the IFN type I pathway, probably in association with the break of immune tolerance.

Maria-Julieta Gonzalez (University of Chile, Chile) discussed the role of mucins in SS pathophysiology. Mucins are O-glycosylated glycoproteins synthesized by specialized epithelial cells such as salivary and lacrimal acinar cells. Salivary mucins function as inducers of pro-inflammatory cytokines, a process mediated by the TLR4-dependent pathway. This response could be active in the extracellular matrix of labial salivary glands of SS patients, promoting the infiltration of inflammatory cells and leading to the initiation of SS pathogenesis.

Naomi Maria (Erasmus Medical Center, Rotterdam, the Netherlands) conducted genome-wide microarray analysis on BDCA4+CD123+ cell-sorted pDCs from SS patients and detected the presence of an IFN type I signature in pDCs. Type I-IFN is known to play a key role in SS. Understanding the genome-wide abnormalities of pDCs could shed light on their role in SS pathogenesis and IFN type I production in SS.

Petra Vogelsang (University of Bergen, Norway) compared the phenotype and functional properties of immature and TLR7/8-stimulated monocyte-derived dendritic cells (mDC) of pSS patients with controls. Results showed no difference between the groups in the expression levels of surface molecules such as HLA-DR, CD86, CD80, CD83 or CD40 and apoptosis-related molecules, such as Bim, IRF-8 and Ro52, on mDC. The mDC also appear phenotypically and functionally similar in both groups. However, production levels of IL-1RA, CCL5 and IL-12p40 from mDC of SS were significantly higher in SS than in controls.

Gaetane Nocturne (Paris-Sud University, France) discussed the role of NK cells in pSS pathology. Her group performed a case-control study of genetic polymorphisms of the NCR3/NKp30a gene, NK-specific activating receptor regulating the cross-talk between NK and dendritic cells, and type II IFN secretion. They found that rs11575837 (G>A) residing in the promoter was protective for pSS and associated with reduced gene transcription and function. They also demonstrated significantly higher circulating levels of NCR3/NKp30

among pSS patients compared with controls, which correlated with higher NCR3/NKp30-dependent IFN $\gamma$  secretion by NK cells. Accumulation of NK cells in minor salivary glands correlated with the severity of the exocrinopathy, and NK cells are believed to promote NKp30-dependent inflammatory state in salivary glands.

#### Vaccination

Yehuda Shoenfeld (Tel Aviv University, Israel) presented a newly defined condition termed "Autoimmune Syndrome Induced by Adjuvants (ASIA)". ASIA is characterized by a hyperactive immune response which is triggered by adjuvant activity. Such a mechanism also could be involved in SS pathogenesis.

Ulf Müller-Ladner (Justus-Liebig University, Germany) indicated that the risk of infectious complications was about twice as high in patients with rheumatic disease, including SS, than in the general population. He recommended that the 2011 EULAR-based recommendations on vaccination in patients be extended to address new studies on influenza and pneumococcal vaccination. He also advised implementing vaccines early in the disease course and before commencement of immunosuppressive therapy if possible.

#### Lymphoma

The research group led by Haralampos M. Moutsopoulos (National University of Athens, Greece) focused on the risk of lymphoma in SS. They compared 3 groups of SS patients – A) (nonspecific) arthralgia/arthritis, Raynaud's phenomenon and fatigue; B) extension of peri-epithelial lymphocytic infiltrates into parenchymal organs, e.g. lungs, kidneys and liver, which usually run a benign course; and C) immunocomplex-mediated pathology presenting more often with raised purpura, peripheral neuropathy and glomerulonephritis. Group C patients were at highest risk of lymphoma. In addition, his team found that the combination of chemotherapy with anti-CD20 monoclonal antibodies improved survival in SS-lymphoma patients.

Xavier Mariette (Paris-Sud University, France) focused on the risk of lymphoma by comparing germinal and somatic abnormalities of TNFAIP3, which encodes the A20 protein and is known to play a key role in NF- $\kappa$ B activation in SS patients with and without lymphoma. The rs2230926 exonic variant was associated with increased risk of lymphoma. Moreover, in 60% of SS patients with lymphoma, TNFAIP3 sequence analysis showed functional abnormalities of A20, suggesting a key role for germinal and somatic variations of A20 in lymphoma development. The presence of germinal and/or genes somatic abnormalities could lead to impaired control of NF- $\kappa$ B activation in B cells continuously stimulated by autoimmunity, enhancing the risk of lymphoma.

Costantino Pitzalis (Queen Mary University of London, UK) reported that the formation of ectopic lymphoid structures (ELS) in SS salivary glands supports the concept that these structures represent functional niches whereby autoreactive B cells undergo affinity

maturation, clonal selection and differentiation into autoantibody producing cells, thus contributing to autoimmunity over and above secondary lymphoid organ responses. Recent evidence suggests that ELS identify a subset of SS who are at increased risk of developing systemic manifestations and lymphoma.

Michael Voulgarelis (University of Athens, Greece) reviewed the clinical and immunological features of SS-associated non-Hodgkin lymphoma (NHL). Chronic antigenic stimulation by exoantigens or autoantigens plays an important role in the development of SS-associated lymphoproliferation. Additional molecular oncogenic events, such as microsatellite instability, loss of B cell cycle control, and forced overproduction of specific B cell biologic stimulators appear to contribute to the emergence and progression of NHL. The presence of palpable purpura, low C4, and mixed monoclonal cryoglobulinemia represent the main predictive markers for NHL development in SS.

Chiara Baldini (University of Pisa, Italy) assessed the prevalence of anticentromere antibodies (ACA) in SS patients and compared their clinical features with systemic sclerosis (SSc) patients who are ACA-positive and without sicca symptoms. The prevalence of NHL was higher in the "overlap patients" characterized by mild SSc compared to SS alone.

### Diagnostic Criteria

Diagnostic criteria for Sjögren's comprised the first panel discussion and included the revised Japanese criteria of 1999, the revised American European Consensus Group (AECG) classification criteria of 2002, and SICCA-ACR classification criteria of 2012.

Caroline H. Shiboski (University of California, USA) described the data registry and biorepository for public access of the Sjögren's International Collaborative Clinical Alliance (SICCA). As of September 30, 2012, 3,516 participants had been enrolled in SICCA, and nearly half the cohort (1574 participants) satisfied the ACR classification criteria for SS. To date, 27 applications for dissemination of data and/or specimens have been received, 19 of which have been approved.

Stephen Shiboski (University of California, USA) described the next steps toward validation of ACR classification criteria for SS. Analyses of SICCA data showed an approximate 6% discordance between ACR and AECG classifications, indicating a high rate of overall agreement. External validation is needed to develop classification criteria approved by both ACR and EULAR.

Claudio Vitali (Como and Casa di Cura di Lecco, Italy) proposed modification of the ACR criteria and concluded that the need to reach an agreement on universally-accepted classification criteria was paramount.

Hiroto Tsuboi (University of Tsukuba, Japan) presented validation data for the JPN, AECG, and ACR criteria in Japanese patients. Agreement between the JPN and ACR criteria was high (kappa coefficient; 0.74) as well as the sensitivity and specificity for the JPN and AECG.

Minako Tomiita (Chiba Children's Hospital, Japan) proposed special diagnostic criteria for early stage SS in children. *See cover article by Dr. Tomiita.*

Divi Cornec (Brest University Hospital, France) evaluated the level of agreement and discrepancies between the ACR 2012 and AECG 2002 criteria. ACR and AECG criteria were shown to have moderate agreement, suggesting that cohorts of pSS patients selected using different classification criteria are not comparable.

Astrid Rasmussen (Oklahoma Medical Research Foundation, USA) also discussed these criteria in a multicenter study including gene expression profiles. Data analysis and biological perspective demonstrated that the new criteria are not better than the old ones.

Naoto Yokogawa (Tokyo Metropolitan Medical Center, Japan) tried to modify the ACR 2012 classification criteria based on the diagnosis of childhood SS, including: 1) positive anti-SSA and/or anti-SSB or (positive RF + ANA titer  $\geq 320$ ), 2) labial salivary gland biopsy, and 3) parotid gland involvement. The sensitivity and specificity of the selected parameters were 0.86 (0.80-0.91) and 0.60 (0.25-0.87), respectively.

Valerie Devauchelle-Pensec (Cavale Blanche University Hospital, France) discussed the role of salivary gland ultrasonography (SGUS) in Sjögren's diagnosis. The echostructure of the parotid and submandibular glands was graded and parotid blood flow assessed indicating that this parameter should be included in future classification criteria.

## Clinical Findings

### Clinical features

Manuel Ramos-Casals (ICMiD, Hospital Clinic, Spain) described the refinement of the definition of systemic organ involvement in pSS. The steering committee of the EULAR-SS Task Force on disease activity indexes has selected a list of clinical manifestations for SS-related systemic involvement. The list includes: arthritis/synovitis, annular erythema, vasculitis, pericarditis, pulmonary arterial hypertension, pleuritis, pulmonary involvement, dysphagia, autoimmune pancreatitis, renal tubular acidosis, glomerulonephritis, interstitial cystitis, focal CNS involvement, diffuse CNS involvement, myelitis, meningitis, cranial nerve involvement, axonal polyneuropathy, multiple mononeuropathy, sensory ataxic neuropathy, small fiber painful sensory neuropathy, demyelinating polyneuropathy, restless leg syndrome, autonomic neuropathy, myositis, hearing loss, and symptomatic cytopenia.

Eric Gershwin (University of California, USA) discussed the initiation and perpetuation of primary biliary cirrhosis (PBC). He reported that chemical xenobiotics modification of the lipoyl domain of PDC-E2, such as excessive acetaminophen or similar drug, is sufficient to break self-tolerance, with subsequent production of anti-mitochondrial antibodies (AMA) in patients with PBC.

"ISSS Highlights" Continued from page 7 ▼

David Isenberg (University College London, UK) presented the long-term outlook for SS patients followed at The University College Hospital London since 1986. The overall malignancy rate was 19.7% (with NHL found in 16 patients) and 49% of patients had one or more additional autoimmune diseases, hypothyroidism being the most common.

Wan-Fai Ng (Newcastle University, UK) introduced The United Kingdom primary Sjögren's syndrome registry (UKPSSR). The aims are to 1) create a large cohort and biobank of clinically well-characterized pSS patients to facilitate research and clinical trials; 2) collect high-quality epidemiological data; 3) foster collaborations, and 4) raise the profile of pSS research.

Joern Kekow (University of Magdeburg, Germany) listed the criteria for early detection and intervention in SS. He suggests clinicians watch carefully for the following: extra-gradients in electrophoresis, low complement, vasculitis, lymphopenia, and new cryoglobulins in the blood.

Juan Scali (Durand University Hospital Buenos Aires, Argentina) discussed thrombotic events in pSS. All patients evaluated by his group with thrombotic events were SSA+ and half also were SSB+; 4 were SSB+ and had APS manifestations such as livedo reticularis or racemosa, DVT, and/or stroke, leading to the suggestion of SSB/LA as a possible marker for APS.

Kazuo Tsubota (Keio University School of Medicine, Japan) reviewed recent advances in the diagnosis and treatment of dry eye in SS patients. Effective mucin-stimulating agents, such as diquafosol sodium, have been introduced recently into the Japanese market, and treatment of patients with unstable tears film is available.

#### Clinical biomarkers

Roland Jonsson (University of Bergen, Norway) reviewed currently-known biomarkers for SS. Analysis of a large SS serum registry showed autoantibodies appearing many years before clinical onset of the disease. The presence of germinal center-like structures in diagnostic labial gland biopsies also was proposed as a highly predictive marker for NHL. Biomarkers could be valuable in early diagnosis, disease prevention, drug target identification, and drug response.

Aigli Vakrakou (University of Athens, Greece) described low serum activity and weak mRNA expression in minor salivary glands and salivary gland epithelial cell lines of DNase-I in SS patients. DNase-I deficiency may lead to accumulation of undigested chromatin in necrotic cells with subsequent inflammatory and autoimmune reactions.

Arjan Vissink (University Medical Center Groningen, the Netherlands) reported several breakthroughs in salivary diagnostics, important to diagnosis, monitoring disease activity and gauging effectiveness of new therapeutics. Proinflammatory cytokines and chemokines could help distinguish potential responders for a particular type of biological therapy.

Menelaos Manoussakis (University of Athens, Greece) reviewed common immunologic and genetic features of SS and SLE. Interestingly, similar to SLE, approximately half of SS patients manifest deficiency in ex-vivo phagocytosis of apoptotic cells and of particulate targets by peripheral blood monocytes and monocyte-derived macrophages. These functional impairments correlate strongly with disease activity indices and may play key roles in the pathogenesis of both diseases.

Pilar Brito-Zeron (Laboratory of Autoimmune Diseases, Josep Font, Spain) discussed the Eular Sjögren's Syndrome Disease Activity Index (ESSDAI) in the prediction of lymphoproliferative disease in a cohort of Spanish patients with pSS. Key predictive clinical features were fever  $>38.5^{\circ}\text{C}$ , night sweats, and/or significant weight loss. Laboratory predictors included cytopenia, hypocomplementemia, monoclonal band and cryoglobulinemia.

Troy Daniels (University of California, USA) characterized sialadenitis patterns in labial salivary glands (LSGs) from SICCA patients. Patterns were divided into 4 groups: focal lymphocytic sialadenitis (FLS); focal-sclerosing lymphocytic sialadenitis (FSLs); sclerosing chronic sialadenitis (SCS); and non-specific chronic inflammation (NSCI). FLS and FSLs, with focus scores  $\geq 1$ , represent the salivary component of SS. Interstitial fibrosis in LSGs reflects a gradually progressive degenerative aging process unrelated to SS and is consistent with similar findings in the general population (Scott J, 1980).

Elke Theander (Skåne University Hospital, Malmö, Sweden) evaluated serological factors before diagnosis and symptom-onset of pSS. Her group found that at least one autoantibody could be detected in 81% of patients up to 20 years before diagnosis.

#### Clinical measures

Raphaële Seror (Hôpital Bicêtre, France) reviewed the EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI), and the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI). Both indexes were shown to be feasible, valid and reliable instruments in an independent international cohort.

Susumu Nishiyama (Kurashiki Medical Center, Japan) reported similar results with the Japanese version of ESSDAI and ESSPRI. Although no correlation was found between ESSPRI and ESSDAI, a significant correlation was found between ESSPRI and PtGA ( $r=0.59$ ) and ESSDAI and PhGA ( $r=0.80$ ).

Walter Hermann (Kerckhoff-Klinik, Germany) explained that nailfold capillaroscopy can help distinguish pSS from sSS and should be performed routinely in newly diagnosed SS patients.

## Treatment

### General Treatment

Ann Parke (University of Connecticut Health Center, USA) described the development of clinical practice guidelines (CPG's) for patients with pSS. The Sjögren's

Syndrome Foundation established three working groups to develop recommendations for the oral, ocular, and rheumatic/systemic manifestations. To date the rheumatology/systemic group has developed draft recommendations for three topics: 1) management of fatigue, 2) use of oral disease-modifying antirheumatic drugs (DMARDs) for inflammatory musculoskeletal pain, and 3) use of biologic therapy for sicca and systemic symptoms in SS. These recommendations currently are undergoing a Delphi consensus process.

Robert Fox (Scripps Memorial Hospital, USA) reported that while recent clinical trials indicated that treatment improved a spectrum of extraglandular manifestations and biomarkers, it had no significant affect on disabling ocular and oral symptoms, fatigue or myalgia. Since the integration and cortical processing of pain signals are modulated by chronic exposure to cytokines released from microglial cells, better cooperation is needed between neuroscientists and immunologists at clinical and drug development levels.

Ayhan Dinç (Patio Clinic, Turkey) reviewed the current status of recommendations for clinical management of SS.

### Biologics

Fred K.L. Spijkervet (University of Groningen, the Netherlands) described the restoration of parotid gland tissue architecture after treatment with rituximab (RTX) in pSS patients. All RTX-treated patients, but no placebo-treated patients, showed significant reductions in lymphocytic infiltrates and in the B/T-cell ratio. The relative number of lymphoepithelial lesions and germinal centers was significantly reduced in RTX-treated but not in placebo-treated patients.

Rodney P.E. Pollard (Groningen University Medical Center, the Netherlands) discussed the impact of RTX therapy on T cells in pSS patients. In a double-blinded, placebo-controlled trial in which sequential parotid biopsies were taken, no difference was observed in Treg numbers (in either the placebo or RTX groups).

Vladimir Vasilyev (Russian Academy of Medical Science, Russia) reported on his group's study of RTX which found a complete clinical response in 25% (5/20) and partial response in 65% (13/20) of pSS patients. In 7 patients, complete and partial response was observed in 43% (3/7) and 57% (4/7) cases, respectively. None had severe infection.

William St. Clair (Duke University Medical Center, USA) discussed B cell-targeted therapies under investigation for pSS other than RTX. In small open studies, encouraging results have been reported using epratuzumab, an anti-CD22 antibody, and belimumab, a BAFF inhibitor. Baminercept (LT receptor fusion protein), an inhibitor of LT, currently is being tested in a placebo-controlled clinical trial. A randomized, placebo-controlled clinical trial of tocilizumab (anti-IL-6 receptor antibody) plans to enroll 80 pSS patients in the near future.

Raphaële Seror (Hôpital Bicêtre, France) discussed

the results of the BELISS study on the effects of belimumab (BAFF inhibitor) in pSS patients. Treatment tended to reduce lymphocytic infiltration and B-cell/T-cell ratio in labial salivary glands. A poor response to belimumab was noted in patients with a large number of foci and high numbers of NK cells in peripheral blood, suggesting that these subsets are linked to the IL-12/IFN $\gamma$  TH1/ NK axis rather than to the BAFF/B-cell axis.

Hendrika Bootsma (Groningen University Medical Center, the Netherlands) reviewed the most recent biological agents in clinical trials in pSS. These are: 1) Cytokine-blocking agents, such as BAFF antagonists, 2) B cell blockers (anti-CD20), and 3) co-stimulation blockers, such as abatacept. Two open-label phase II studies indicate that abatacept is well-tolerated, safe and induces a clinically meaningful improvement in disease activity.

Hiroto Tsuboi (University of Tsukuba, Japan) described the results of the ROSE trial (Rheumatoid Arthritis with Orencia Trial Toward Sjögren's syndrome Endocrinopathy) on the efficacy and safety of abatacept in patients with SS associated with RA. Midterm analysis showed that 6-month treatment of 12 patients resulted in a significant decrease in SDAI with 3 patients (25%) achieving remission and 6 patients (50%) achieving low disease activity. Salivary and tear flow also significantly increased.

### Non-biologics

Philip Cohen (Temple University School of Medicine, USA) focused on the effects of fingolimod (FTY-720), a sphingosine analogue approved for multiple sclerosis, in the treatment of SS. Fingolimod markedly reduced circulating T and B lymphocyte counts, significantly increased stimulated saliva secretion, and decreased salivary lymphocytic infiltration.

Hirotake Inomata (Nihon University of School of Medicine, Japan) reviewed mizoribine (MZR) treatment in rheumatic disease. Along with mycophenolate mofetil, MZR is known to inhibit the *de novo* pathway of purine synthesis involved in the proliferation and various functions of cells, particularly immune cells. In SS patients, 16-week MZR treatment produced subjective and objective amelioration of glandular symptoms. Smaller studies and case reports have suggested that MZR also is effective in pediatric SS.

Falk Hiepe (University Medicine Berlin, Germany) showed the potential of therapies targeting plasma cells. He described a new technology capable of inducing lysis of only plasma cells that secrete antibodies against specific autoantigens *in vitro*, which could lead to autoantigen-specific depletion of plasma cells *in vivo*.

Etsuko Takamura (Tokyo Women's Medical University, Japan) reviewed current trends in dry eye treatment in Japan. Conventional treatment modalities include artificial tears, sodium hyaluronate solution (1% and 3%) and corticosteroids. Two novel agents include the recently available mucin secretagogues, diquafosol and rebamip-

ide. In Japan, 3% diquafosol ophthalmic solution became available in 2010 as an effective and safe agent for dry eye treatment, and 2% rebamipide ophthalmic suspension was introduced in 2012. In severe dry eye disease associated with SS, the combined use of diquafosol and sodium hyaluronate solution produce a sustained effect of increased tear retention compared to monotherapy.

### IgG4-Related Diseases

Hiroki Takahashi (Sapporo Medical University School of Medicine, Japan) reviewed IgG4-related disease (IgG4-RD), a recently recognized disease entity in Japan. IgG4-RD is characterized by tumefactive and hyperplastic lesions in various organs, including lacrimal and salivary glands (so-called Mikulicz's disease; IgG4-MD). Accordingly, differential diagnosis of sialadenitis might offer an opportunity to discover new cases of IgG4-RD. When IgG4-RD is suspected, serum IgG4 levels and immunostain tissue specimens with anti-IgG4 antibody should be measured and the disease suspected in patients with serum IgG4 levels exceeding 135 mg/dl together with prominent IgG4-positive plasma cell infiltration in tissues with fibrosis. Corticosteroids promptly induce remission upon initiation of treatment, and low-dose corticosteroids can maintain remission in most patients.

Hisanori Umehara (Kanazawa Medical University, Japan) described the concept of and diagnostic criteria (CDC criteria) for IgG4-RD as established by the Japanese IgG4 team. The CDC criteria consist of: 1) organ enlargement, mass or nodular lesions, or organ dysfunction; 2) serum IgG4 concentration >135 mg/dl; and 3) histopathological findings of >10 IgG4+cells/high power field and IgG4+/IgG+ cell ratio of >40%.

Motohisa Yamamoto (Sapporo Medical University School of Medicine, Japan) summarized clinical practice in IgG4-related dacryoadenitis and sialadenitis. Their database shows the average age of onset of IgG4-RD is in the sixties with no sex difference. 58.9% of patients have systemic organ involvement. Glucocorticoid treatment effectively induces rapid clinical remission. Systemic examination, relapse, and potential malignancy were emphasized in IgG4-RD.

Kenji Notohara (Kurashiki Central Hospital, Japan) described the pathological features of type 1 autoimmune pancreatitis, with special emphasis on the diagnostic findings of storiform fibrosis and obliterative phlebitis. Both pathological changes, scarce in some

organs, are IgG4-RD-related lesions, suggesting the heterogeneous nature of histological findings in IgG4-RD.

Takako Saeki (Nagaoka Red Cross Hospital, Japan) described the clinical and pathological features and treatment of IgG4-related kidney disease (IgG4-RKD). Tubulointerstitial nephritis (TIN) is the most dominant feature of IgG4-RKD. Histopathologically, plasma cell-rich TIN with a large number of IgG4-positive plasma cells and fibrosis (often storiform fibrosis) are the major findings in renal parenchymal lesion of IgG4-RKD. Corticosteroid therapy is usually effective in amelioration of renal dysfunction, radiological and serological abnormalities.

Mitsuhiro Kawano (Kanazawa University Hospital, Japan) summarized the clinical features and treatment of 46 patients with IgG4-related aortitis/periaortitis, periarteritis, and inflammatory aortic aneurysm. The average age at diagnosis was 66.7 years, and most patients were male (91.3%) with involvement of several body organs. Only 21.7% of the patients had high serum levels of C-reactive protein (CRP). Prednisolone (PSL) was used in 94% of patients which resulted in reduction in perivascular lesion size.

Shoko Matsui (University of Toyama, Japan) described intra-thoracic involvement in IgG4-RD. Radiological findings included mediastinal lymphadenopathy, thickening of the bronchial wall and bronchovascular bundles, interlobular septal thickening and centrilobular nodules, and subpleural and/or peribronchovascular consolidation. Histopathological findings were lymphoplasmacytic inflammation with IgG4-positive plasma cells in the interlobular septa, peribronchovascular interstitium, bronchus and pleura. Almost all cases responded well to corticosteroid treatment including those with autoimmune pancreatitis or Mikulicz's disease.

Yasufumi Masaki (Kanazawa Medical University, Japan) presented results of the multicenter prospective clinical trial for the establishment of standard glucocorticoid therapy for IgG4-RD patients in Japan. Response rate was 88.9%.

John Stone (Massachusetts General Hospital, USA) described B cell depletion therapy in IgG4-RD. All patients with clearly active inflammation (as opposed to fibrosis) at the time of treatment achieved swift clinical response to rituximab.

### 13th ISSS

The next ISSS will take place in May 2015 in Bergen, Norway and will be chaired by Roland Jonsson. ■



## 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](mailto: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.

*The SSF thanks John R. Fenyk, Jr., MD, Professor Emeritus of Dermatology and Adjunct Assistant Professor of Family Practice and Community Health, University of Minnesota, and clinical dermatologist, University of Minnesota Lupus and Sjögren's Clinic, for authoring this Patient Education Sheet.*

Dry skin often is overlooked as a major feature of Sjögren's syndrome but deserves greater recognition as a frequent issue for patients. Dry skin can occur as the result of immune dysfunction and destruction of the structures which moisturize and lubricate the skin – a process similar to that which causes dry mouth and dry eye in Sjögren's. These skin structures include the hair and oil glands as well as sweat glands. Once destroyed, these oil and sweat glands cannot be restored. Although most common in fall, winter and early spring, dry skin occurs throughout the year. Areas most often affected are legs, arms and abdomen (especially the beltline/waist).

### Major features of dry skin are:

- Scaling
- Redness
- Itching
- Cracking of the skin

### Tips for dealing with dry skin:

- Take short, warm baths or showers. They do not remove skin oils as completely as hot water.
- Use gentle bars (Dove®, Basis®, Cetaphil® or the low/no residue glycerin bars such as Neutrogena®) instead of harsh true "soaps." Detergents are not the same as soap and are not necessarily bad; in fact, most bath bars are detergents and not soaps. Often, detergents are able to control the acid/base balance of the skin better than true soaps.
- After bathing, pat dry and use one or more of the moisturizing techniques mentioned in the next item.
- Apply moisture frequently. In reality, there are relatively few ways of maintaining or adding to your skin's moisture content. These are:
  - Trap moisture in the skin immediately after bathing or showering while your skin is still damp or moist by applying a thin layer of petroleum jelly (Vaseline®), bath oil, vitamin E oil or even some cooking oils such as coconut, olive, and safflower oil.
  - "Drag" moisture into your skin by using products that contain chemicals such as urea, glycerin, lactic or similar "metabolic" or alpha-hydroxy acids (AmLactin® Cream, Carmol®).
  - Repair the skin's protective function by retaining or trapping the skin's natural moisture with a relatively new group of products based on naturally occurring chemicals called ceramides (CeraVe®).
  - Aloe vera works to heal dry skin, is widely available and most beneficial when used in gel form, either straight from the plant or purchased in a bottle. If buying a lotion with aloe vera, be sure "aloe vera gel" is listed as one of the first few ingredients.
- Avoid fabric softeners in the washer and dryer.
- Drink plenty of water and remain well-hydrated.
- Use a humidifier, especially if you have forced-air heat which is especially drying.
- After swimming, make certain that you shower and then immediately use a moisturizer.

## Sjögren's Quarterly

Sjögren's Syndrome Foundation Inc.  
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## In the News...

### First Genes Specific to Sjögren's Identified!



Kathy L. Sivils, PhD



Christopher Lessard, PhD

Scientists at the Oklahoma Medical Research Foundation have identified the first-ever Sjögren's-specific genes. Six genes in Sjögren's and additional genes already linked to autoimmune disease were discovered by the international consortium, Sjögren's Genetics Network (SGENE), led by Kathy L. Sivils, PhD. Her group identified disease-related genes in the area of IRF5, STAT4, CXCR5, TNIP1 and TNFA1P3, IL12A, and BLK. About 2,000 patient samples

from around the world were compared to about 7,000 healthy controls. Lead author on the publication, Christopher Lessard, PhD, states, "Now that we've identified these genes, we can dig down and start to understand how these genetic variants alter normal functions of the immune system."

In addition to funding through the Sjögren's Syndrome Foundation research program with grants to both Drs. Sivils and Lessard, funding for the project was provided by the National Institutes of Health (NIH) through grants #P50 AR0608040 from the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), 5R01 DE015223, 1R01 DE018209-02 and 5R01 DE018209 from the National Institute of Dental and Craniofacial Research (NIDCR), and 5U19 AI082714 from the National Institute of Allergy and Infectious Diseases (NIAID).



A full article on the findings will be published in the spring issue of the *Sjögren's Quarterly*. The journal publication is: Lessard CJ et al. Variants at multiple loci implicated in both innate and adaptive immune responses are associated with Sjögren's syndrome. *Nat Genet.* 2013 Nov;45(11):1284-92. doi: 10.1038/ng.2792.

### Vulvovaginal Atrophy

The North American Menopause Society (NAMS) issued an updated guidance document this fall on treatment of vulvovaginal atrophy symptoms. While common in postmenopausal women, these symptoms also occur in conjunction with the dryness associated with Sjögren's. Vulvovaginal atrophy can impair quality of life and sexual function significantly but can be addressed by clinical therapy including vaginal lubricants and moisturizers, vaginal estrogen, hormone therapy, and the prescription therapy for dyspareunia, Ospemifene® (ospemifene). NAMS also provides a Vulvovaginal Symptoms Questionnaire.

For more information, visit the NAMS website at [www.menopause.org](http://www.menopause.org). The guidance document was published as: Management of symptomatic vulvovaginal atrophy: 2013 position statement of The North American Menopause Society. *Menopause.* 2013;20(9):973-9. ■