Clinician’s Corner

Vaginal Dryness in Sjögren’s: A Common Sicca Symptom

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Background

Primary Sjögren’s (pSS) is commonly diagnosed in women in the fourth and fifth decades of life, also a time of declining sex steroids which culminates in the menopausal transition. Vulvar and vaginal dryness are common complaints of women during midlife, affecting around 50% of postmenopausal women. However, 68% of women with pSS and 81% of women with sicca syndrome experience vulvar or vaginal dryness. Furthermore, 93% and 95% of these patients respectively reported that this problem affected their sexual functioning, yet the majority indicated that they had never been asked about it and had never brought up the topic with a health care professional. While women are generally

Autoantibodies in Sjögren’s

by Julian L. Ambrus Jr., MD
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Sjögren’s (SS) is a chronic autoimmune disease in which damage to the salivary and lacrimal glands may be associated with damage to various other organs as well as with the development of lymphoma. The diagnosis of SS is often delayed, with the average time of disease onset to diagnosis being almost 5 years. Current research in SS aims to diagnose the disease earlier and develop strategies that will halt the course of the disease in its early stages.

The presence of autoantibodies in the sera of patients with SS is one of the pieces of evidence that have been used to designate it as an autoimmune disease. Exactly what these autoantibodies are doing, however, has never been clear. The traditional diagnostic criteria for SS include several autoantibodies, anti-nuclear antibodies (ANA), rheumatoid factor (RF), anti-Ro (also called anti-SSA) and anti-La (anti-SSB).

ANA are seen in many autoimmune diseases as well as in 15% of normal women. Rheumatoid factors are part of the normal immune response to chronic infections or
reluctant to discuss the topic of vaginal dryness with their partner, family or friends, most would feel comfortable reviewing this problem with their health care provider (HCP), and would, in fact, prefer their HCP initiate the discussion.³ The consequences of reduced sexual functioning for women include problems with mood, relationship discord, and even a lower sense of self-worth.⁴

**Vaginal Dryness Related to Sjögren’s Versus Menopause**

How does vaginal dryness differ in patients with Sjögren’s versus in those with vulvovaginal atrophy due to menopause? There are vaginal changes that occur both with aging and the menopausal transition. These include alterations in the vaginal microbiome that are driven by loss of estrogen at menopause. After menopause, the vaginal pH increases from a normally acidic environment (pH 3.8-4.5) to a more basic environment. This relates in part to a decrease in the acid-producing bacteria, lactobacilli, which in premenopausal women help prevent infections such as bacterial vaginosis, yeast infections, urinary tract infections, and sexually transmitted infections, including HIV.⁵ On physical examination, estrogen deficiency results in thinning, pallor, and dryness of the vulvovaginal tissues, as well as loss of rugae and folds. Symptoms include vaginal itching, burning, dysuria, and pain with intercourse. These symptoms may lead to decreased sexual desire and avoidance of sexual activity.⁵

However, the vaginal changes in the setting of Sjögren’s may not be due to estrogen deficiency alone and often do not respond to local vaginal estrogen therapy, particularly in women who are premenopausal. In Sjögren’s, lymphocytic infiltration and exocrine gland dysfunction result in dry eyes, dry mouth, and though rarely mentioned, a dry vagina. Indeed, Skopouli et al noted a perivascular lymphocytic infiltrate on vaginal biopsy in women with Sjögren’s.⁶ Though there is emerging evidence that women with Sjögren’s are androgen deficient, and circulating levels of DHEA-S are positively associated with mental wellbeing and quality of sex life, treatment with oral DHEA has not been found to be superior to placebo for management of fatigue and well-being in women with Sjögren’s.⁷⁻¹⁰

**Treatment**

Until there are evidence-based treatments for vaginal dryness specific to women with Sjögren’s, therapy is symptom-based and includes the use of vaginal lubricants and moisturizers in addition to local vaginal estrogen therapy or ospemifene for those who are post-menopausal and experiencing vulvovaginal atrophy. The goal of treatment is to relieve symptoms. Despite the experience of pain with intercourse, many women still engage in painful sex. Emphasizing the importance of pain-free sexual activity is important in order to avoid development of pelvic floor muscle dysfunction, which may ultimately exacerbate dyspareunia. Couples may benefit from expanding their definition of sexual activity to include non-penetrative activities. Involvement of a specialized physical therapist for initiation of pelvic floor physical therapy is often helpful for women who experience dysfunction of the pelvic floor. Women with vaginal dryness who are experiencing decreased sexual function, lower sexual satisfaction, or adverse effects on the relationship with their partner may also benefit from consultation with a sex therapist.⁵

Non-prescription therapies for vaginal dryness include the use of vaginal lubricants for sexual activity, though little efficacy data exists for these products. Vaginal moisturizers are used on a regular basis, several times per week, to help maintain vaginal moisture. While vaginal moisturizers can relieve symptoms of vaginal dryness for many women, they are less effective for management of menopause-related vaginal atrophy than hormonal options. Regular, painless sexual activity also helps maintain vaginal health.⁵ As vaginal lubricants and moisturizers can be irritating for some women, testing on a small patch of skin may be advisable prior to using these products intravaginally. Other cautions regarding the choice of lubricant include avoidance of the use of oil-based lubricants with condoms (may compromise the integrity of the condom) and avoidance of silicone-based lubricants with silicone-coated sexual aids, such as a vibrator (may degrade the surface of the sexual aid). In addition, silicone-based lubricants may not allow for sufficient friction for couples in
INDICATIONS: Aquoral is intended to provide relief from chronic and temporary xerostomia (dry mouth), which may be a result of disease such as Sjögren’s Syndrome, oral inflammation, medication, chemo or radiotherapy, stress or aging. Aquoral relieves symptoms of dry mouth such as difficulties in swallowing, speech, and changes in taste.

IMPORTANT SAFETY INFORMATION
CONTRAINDICATIONS: Aquoral is contraindicated for any patient with a known history of hypersensitivity to any of its ingredients.
PRECAUTIONS: Read package insert carefully before using this spray. Avoid contact with eyes. Flush eyes with water if accidental introduction into eyes should occur.
INTERACTIONS: There are no known interactions with medicinal or other products. Please see full Prescribing Information provided.


Please see full Prescribing Information on next page.
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whom the male partner has erectile dysfunction, and a water-based lubricant may be a better option.

For postmenopausal women with vulvovaginal atrophy related to estrogen deficiency, local vaginal estrogen therapy is 80-90% effective for management of symptoms, even more effective than systemic estrogen therapy. Additionally, estrogen therapy has been associated with improved sexual function. Local vaginal estrogen therapy is available in several forms, including vaginal cream (Premarin® or Estrace® cream 1/2-1 gram inserted vaginally twice weekly), tablet (Vagifem® tablet inserted vaginally twice weekly) and ring (Estring® inserted vaginally and changed every three months). Vaginal estrogen may take 6-8 weeks or longer to become fully effective. There are no serious adverse events associated with the long-term use of local vaginal estrogen therapy, including no evidence of increased breast cancer risk. There is also no evidence suggesting the need for endometrial protection, though long-term data are limited. However, any woman with a uterus who is experiencing postmenopausal vaginal bleeding should undergo evaluation of the endometrial lining. Treatment with local vaginal estrogen can be continued as long as needed for management of symptoms. Preservation of vaginal health after menopause with regular sexual activity, vaginal dilators and vibrators as needed, as well as vaginal lubricants, moisturizers and local vaginal estrogen therapy should be considered. Maintenance of vaginal health is also advised for women without a sexual partner so that sexual activity may be feasible and comfortable in the future.

Ospemiphene is a selective estrogen receptor modulator (SERM) that is FDA-approved for treatment of moderate to severe dyspareunia. Efficacy studies reveal the 60 mg dose to be effective at 12 weeks, and safety data reveal no cases of venous thromboembolism, endometrial carcinoma or hyperplasia at 52 weeks. Though preclinical studies show ospemiphene to be favorable to breast and bone, this drug is not approved for use in those with or at increased risk for breast cancer or for treatment or prevention of osteoporosis. The most common side effect is hot flashes.

Intravaginal DHEA is a weak androgen that is not FDA-approved for treatment of vulvovaginal atrophy but has been found to result in improvement of vaginal symptoms and pH. However, intravaginal DHEA has not been studied for treatment of vaginal dryness associated with Sjögren’s. Vaginal testosterone has been shown to improve symptoms of dyspareunia and vaginal dryness but is not FDA-approved for use in women; additional study is needed to assess efficacy and long-term safety.

Conclusion

Women with Sjögren’s often suffer from vaginal dryness and uncomfortable or painful sexual activity and, with all of the associated problems, this can wreak havoc on quality of life, relationship with partner, mood and feelings of self-worth. Further, women frequently do not review this problem with their HCP but desire that their provider initiate the discussion. There are treatment options available for management of vaginal dryness in women with Sjögren’s, including vaginal lubricants, moisturizers, and regular sexual activity. Local vaginal estrogen therapy or ospemiphene are used for treatment of vulvovaginal atrophy in women who are postmenopausal and can be used in combination with vaginal lubricants and moisturizers. Additional study is needed to determine whether there is a role for local
androgen therapy in the management of vaginal dryness in women with Sjögren’s. Consultation with a physical therapist and sex therapist may be helpful for those with pelvic floor dysfunction and relationship concerns respectively. Expanding the definition of sexual pleasure allows women with sexual pain to maintain intimacy without pain.

References

Clinicians: Patient Education Sheets are available on the SSF website to download

Clinicians: Patient Education Sheets are available on the SSF website to download for your patients at www.sjogrens.org/home/about-sjogrens-syndrome/brochures-and-fact-sheets.

These sheets provide tips for coping and/or basic information about a particular problem or symptom in Sjögren’s that your patients will find useful.
Other chronic environmental challenges. They are often seen in patients with chronic infections such as hepatitis and tuberculosis in the absence of autoimmune disease. Some patients with SS were found to have ANA or RF years before their disease as well. It is unclear whether the presence of these autoantibodies says anything about whether or not a patient will develop SS or just that they may have a genetic makeup that along with the wrong environmental triggers might lead to SS. Anti-Ro was originally described in patients with systemic lupus erythematosus (SLE) and in that disease has been associated with skin disease and vasculitis. It can occasionally be seen in patients with other autoimmune diseases besides SLE and SS as well as in as many as 5-10% of normal people. Anti-La, like anti-Ro, was also first described in SLE and has been associated with less severe disease when it occurs together with anti-Ro in SLE patients. Anti-La occurs in 5-10% of normal people. Anti-Ro and anti-La recognize proteins that are in every cell, so it has been hard to understand why these autoantibodies should designate a disease of the salivary and lacrimal glands. The presence of ANA, RF, anti-Ro or anti-La alone do not designate particular forms of disease in SS, although patients with more systemic manifestations of SS, especially those that develop lymphoma, tend to have more different types of autoantibodies in their sera than patients with more localized disease. Some patients with SS lack either anti-Ro or anti-La antibodies.

Recently novel autoantibodies have been discovered using animal models for SS. One of the problems with studying patients with SS is their disease is frequently identified only after a significant amount of time has passed since the initial development of the disease. Animals that develop SS spontaneously, however, can be utilized to investigate early events in the disease and lead to understanding of how the disease evolves from one stage to another. One such animal model, the interleukin 14 alpha transgenic mouse (IL14aTG), has allowed this type of work to be done. Antibodies to CAVI were first identified in the IL14aTG mouse and shown to occur very early in the course of the disease, while antibodies anti-Ro and anti-La occurred late in the course of the disease, after significant loss of salivary gland function. Investigation of anti-CAVI autoantibodies in patients is ongoing, but initial studies demonstrate that anti-CAVI autoantibodies occur in many patients with SS lacking anti-Ro or anti-La autoantibodies and are found more frequently in patients that have not had severe injury to the salivary glands. Anti-CAVI has been found in many patients with unexplained dry eyes who have not yet expressed all of the features of classical SS. (Figure 1)
Two additional autoantibodies first identified in the IL14aTG mouse are anti-salivary gland protein 1 (SP1) and anti-parotid secretory protein (PSP). Like CA VI, SP1 and PSP are antigens restricted to the salivary and lacrimal glands. Furthermore, autoantibodies to SP1 and PSP occur early in the course of disease in IL14aTG mice.9 Numerous clinical studies evaluating these three organ-specific autoantibodies in patients with SS have revealed several interesting findings and are still in progress:

1. All of these autoantibodies occur in many patients with established SS lacking anti-Ro or anti-La;12,13
2. Anti-PSP and anti-CA VI autoantibodies often occur in the same patients;
3. Anti-SP1 autoantibodies can occur in SS patients independent of anti-CA VI and anti-PSP;
4. Anti-SP1 antibodies are found in more patients with early disease and fewer patients with severe, long-established disease than anti-Ro or anti-La;14
5. Anti-CA VI, anti-PSP and anti-SP1 occur in more patients with dry eyes and dry mouth of unknown cause (possibly very early SS) than anti-Ro and anti-La; (Figure 1)
6. Anti-SP1 antibodies identify many males with SS who are not identified by anti-Ro and anti-La antibodies; (Figure 2) and

A new advanced diagnostic panel is now commercially available. The test panel combines both traditional biomarkers (ANA, RF, anti-Ro and anti-La) as well as novel biomarkers (anti-CA VI, anti-PSP, and anti-SP1) to provide earlier detection of autoantibodies indicating Sjögren’s.

Additional autoantibodies that have been identified in SS often denote the primary autoimmune disease with which secondary SS has developed. These include anti-centromere antibodies of scleroderma and secondary SS, anti-mitochondrial antibodies of primary biliary cirrhosis and secondary SS, anti-cyclic citrullinated peptides (anti-CCP) of RA and secondary SS and anti-smooth muscle antibodies of autoimmune hepatitis and secondary SS.4

Preclinical and early clinical research is also ongoing to find autoantibodies that may correlate with particular disease manifestations of SS. For example, antibodies to muscarinic receptor 3.15 In normal individuals, when acetylcholine produced by nerves stimulates muscarinic receptor 3 (MR3), there is increased production of saliva by the salivary glands. Anti-MR3 antibodies have been shown to inhibit the production of saliva in animal models. Because of technical difficulties with the assay for anti-MR3 antibodies, there is limited information regarding how many patients with SS have these autoantibodies and whether these autoantibodies in patients contribute to decreased saliva production. Antibodies to MR3 may develop in patients with SS because MR3 has been damaged by some other mechanism. These autoantibodies may be part of a repair process.

Another autoantibody of particular interest is antibody to carbonic anhydrase II. Carbonic anhydrase II (CAII) is found throughout the body, and antibodies to this enzyme have been identified in 10-20% of patients with SS. Interestingly, the presence of these autoantibodies has been associated with renal tubular acidosis, presumably due to lack of production of bicarbonate needed to buffer the acid produced in the kidney.16 As CAII is found in most tissues, it is unclear why the clinical manifestations of its inhibition should be restricted to the kidneys.

In conclusion, autoantibodies are important markers in the diagnosis of SS. The utilization of a broad panel of autoantibodies including ANA, RF, anti-Ro, anti-La, anti-CA VI, anti-PSP and anti-SP1 gives the highest likelihood of identifying all patients with SS and identifying patients who are at various stages of the disease. Further study is needed to determine the sensitivity and specificity of each of these markers with regards to various disease manifestations of SS as well as particular types and stages of disease.

7 Anti-SP1 antibodies occur frequently in secondary SS patients with rheumatoid arthritis (RA) but not in patients with RA alone.9,14

A panel of anti-Ro, anti-La and anti-SP1 was shown to pick up 80% of patients with RA and secondary SS; only 50% of these patients were picked up with anti-SP1 alone.14

These data are derived from assays for anti-Ro, anti-La, anti-SP1, anti-CA6 and anti-PSP run by IMMCO Diagnostics during 2012 – 4 and involve 135 male and 222 female patients meeting criteria for Sjögren’s. Data shown are the percentage of these patients expressing either anti-Ro/anti-La or anti-SP1/anti-CA6/anti-PSP. Males with Sjögren’s are more likely to express anti-SP1/anti-CA6/anti-PSP than anti-Ro/anti-La.

Figure 2: Autoantibodies in Male and Female Patients with Sjögren’s

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Furthermore, research is needed to determine correlation of particular antibodies with particular disease manifestations of SS and to understand how auto-antibodies participate in the disease process. Not all autoantibodies are necessarily bad. The body may form some autoantibodies in an attempt to protect or repair a tissue that has been damaged by some environmental trigger (i.e. infection, pollutant, etc.).

References

**Hippo Signaling in Sjögren’s Disease**

by Maria Kukuruzinska, PhD, Associate Dean for Research, Boston University Henry M. Goldman School of Dental Medicine, Boston, Massachusetts

*Editor’s Note: Dr. Kukuruzinska is the recipient of an SSF Research Grant for her project entitled “Functional Role of the Hippo pathway in Sjögren’s Syndrome.” Her 2-year grant period ended July 1, 2014.*

**Introduction**

Sjögren’s (SS) affects salivary and lacrimal glands and is associated with high morbidity and an increased risk of developing non-Hodgkin’s lymphoma. Damage to salivary glands from SS leads to reduced tissue integrity, greatly impairing the ability to produce saliva and resulting in salivary gland hypofunction and xerostomia. In SS, loss of salivary submandibular gland (SMG) function is associated with loss of cell polarity, lymphocytic infiltration and fibrosis. SS affects at least 4 million Americans, or about 0.5% of adults in the western world, and its incidence may be higher as non-specific symptoms leave many patients undiagnosed. Thus, the health and economic burdens of impaired salivary function are high, and there is a great need to gain a better understanding of the molecular basis of SS initiation and progression.

As a complex autoimmune disease, SS has remained resistant to the identification of key mechanisms responsible for its development and pathophysiology. Although defects in the immune system have long been considered to be a cause of SS, emerging evidence has highlighted loss of cell polarity and structural integrity as having a major role in its etiology and autoimmunity. Typically, SS-affected salivary glands display large lymphocytic infiltrates, production of specific autoantibodies, acinar cell atrophy, mislocalization of proteins, aberrant dilation of ducts and impaired acinar cell secretory capacity. On a functional level, the main consequences of SS include hyposalivation and ocular dryness, conditions that promote susceptibility to opportunistic infections and difficulty with swallowing.

In the context of these features, the prevailing model for the loss of secretory function in SS has been a secondary effect of lymphocytic infiltrates. However, this dogma has been recently challenged by emerging evidence from human and mouse studies showing that in human patients, hyposalivation does not always correlate with tissue destruction due to lymphocytic infiltration. Some hypofunctional salivary glands from SS patients display acinar cell atrophy, loss of E-cadherin junctions, mislocalization of proteins, dilated ducts and remodeling of the ECM, and the extent of such pathology, including the degree of secretory defects, does not always correspond to the level of lymphocytic infiltrations. Therefore, at least in some patients, defective secretion and autoimmunity are not linked. Further, development of hyposalivation can be independent of increased glandular inflammation in a mouse model of SS. In light of these conflicting findings, an alternative model for a potential cause of this disease has been suggested to involve defective organ development followed by pathologic immune reaction.

Previous studies from other laboratories and our preliminary results highlighted a critical role for cell adhesion-regulating proteins in maintaining epithelial homeostasis, including exocrine secretion and immune responses. Indeed, our work has shown that E-cadherin is a key regulator of salivary acinar cell polarity and that it functions as a survival signal for differentiating salivary duct cells. We also have observed that knockdown of E-cadherin results in aberrant dilation of ducts due to excessive apoptotic death, a feature that phenocopies human SS8. Deregulated E-cadherin-mediated...
junctional complexes drive lymphocytic infiltration in mouse models, much like that observed in SS. Moreover, salivary glands from SS patients display defects in E-cadherin junctional localization. Given these findings, we searched for downstream effectors of E-cadherin as potential drivers of SS.

One recently identified pathway with critical roles in cell polarity is the Hippo signaling pathway. Hippo is the E-cadherin-based signal, likely to play key roles in the maintenance of structural integrity. Thus, we hypothesized that defective Hippo signals promote SS phenotypes. Signals lying downstream of AJs include the Hippo signaling pathway, a developmentally important pathway that mediates cell proliferation, apoptosis and cell fate.

The Hippo pathway transduces signals by controlling the localization of the transcriptional regulators TAZ and YAP (TAZ/YAP). The primary upstream regulators of TAZ/YAP are the Lats1 and Lats2 kinases, which phosphorylate TAZ/YAP to induce binding to 14-3-3 proteins and E-cadherin-associated junctional proteins, which prevent TAZ/YAP nuclear accumulation. Deregulated nuclear TAZ/YAP activity is associated with a range of diseases. Thus, we postulated that deregulation of E-cadherin-mediated control of cellular localization of TAZ/YAP was a key event in SS. Using mouse models and human SS tissue specimens we examined how the Hippo pathway and its effectors were associated with salivary gland development and with SS disease phenotypes and how these signals were linked to deregulation of AJs and TAZ/YAP activity.

Our Toolbox

Our studies employed several experimental systems. First, we used embryonic salivary glands grown in organ culture. We have exploited the embryonically developing mouse SMG. The SMG develops through a series of morphogenetic changes referred to as branching morphogenesis. In this process, the initial epithelial bud gives rise to a complex structure consisting of differentiated terminal secretory units, the acini, and an array of ducts, which connect to the principal excretory duct that connects to the oral cavity. The ability to culture mouse SMGs as ex vivo explants from as early as the initial epithelial bud stage at embryonic day E12.5, which then undergo development resulting in the formation of a branched structure of acini and ducts (Figure 1), provides an ideal reductionist model and a unique opportunity to determine the mechanisms driving development of salivary glands within a short time frame (13 days).

The relevance of our mechanistic studies to SS was then investigated in a NOD mouse model of Sjögren’s-like disease, and in human minor salivary gland specimens from patients diagnosed with SS. Although the etiology of SS in mouse models and humans may not be identical, insights gained from the mouse studies are likely to make significant advances in characterizing classes of molecular genetic defects that will be aligned with SS development and progression. Furthermore, the availability of a mouse model for SS enabled the detection of developmental stage-specific defects in cell adhesion and ECM composition/function. Such defects could then be investigated in human patient samples and serve in the identification of targets for the development of diagnostics and therapeutics.

Results and Conclusions

Initially, our studies focused on tracing the expression and localization of the Hippo effectors TAZ and YAP during embryonic development of the SMG. We found that SMG development is associated with increased levels of phosphorylated and junctional TAZ in differentiating acinar and ductal cells. We found that TAZ was localized at cell–cell junctions in the polarized acinar progenitor cell layer. Moreover, in the newly-forming secondary duct regions, a fraction of TAZ changed distribution from diffuse in the cytoplasm to a more focused organization at intercellular junctions where it co-localized with F-actin. This junctional localization of TAZ was supported by the observed increases in TAZ phosphorylation during embryonic branching morphogenesis. Moreover, co-localization of TAZ with F-actin in duct-forming regions coincided with a progressive increase in the interaction of TAZ with E-cadherin and alpha-catenin, suggesting a role for junctional TAZ in defining polarity in secondary duct cells and cytodifferentiation. Further, during development, a fraction of TAZ was nuclear, supporting its role as a transcriptional co-activator of genes involved in remodeling the ECM at this stage of SMG development.

To document that Hippo signaling was critical for SMG development, we performed a partial knockdown of the Hippo effector, Lats2 kinase, to inhibit phosphorylation of TAZ. We showed that partial loss...
Clinical

Commentary from Nancy L. Carteron, MD, FACR

Rheumatology, Immunology and Autoimmune Disease, Associate Clinical Professor of Medicine, University of California - San Francisco:

Recent publications continue to shift our focus to Primary Sjögren's as a systemic disease and the disease as a risk factor for other conditions such as cardiovascular disease and high risk pregnancy. We look forward to studies elucidating the etiology of the profound fatigue affecting Sjögren's patients, which is their number one complaint.


Ocular

Commentary from Michael A. Lemp, MD

Clinical Professor of Ophthalmology, Georgetown University and George Washington University, Washington, D.C.:

The most important finding in the Akpek et al study was that the ocular signs of dry eye disease precede a diagnosis of Sjögren’s by about a decade. This should be emphasized. As stated in the conclusion: “…ophthalmologists should consider assessing for SS in patients with clinically significant dry eye.” Of note, Dr. Worst in Lexington, Kentucky has reported that he has a series of subjects with high tear osmolarity and no other discernible ocular signs who tested positive for Sjögren's by rheumatologists. This is available on The Dry Eye Review blog.

In another recent article of interest, the Darabad et al study concludes: “Our findings demonstrate that estrogen absence is not a risk factor for the development of SJS-like lacrimal gland inflammation or for aqueous-deficient dry eye in mice.”


of Lats2 kinase altered the localization of TAZ and resulted in defects in branching morphogenesis and in the formation of secondary ductal structures (Figure 2). To determine if structural defects caused by loss of junctional TAZ had relevance to SS, we examined SMGs from NOD mice, an animal model for SS. The localization and distribution of TAZ in SMGs from NOD mice displayed similar features to the Lats2 siRNA-treated normal glands, providing evidence that deregulation of the Hippo pathway may contribute to structural defects in the NOD SMG.

Importantly, while labial specimens from non-SS affected human subjects exhibited robust junctional TAZ in acini and ducts, SS patients exhibited almost complete loss of TAZ from cell-cell junctions and very high levels of nuclear TAZ (Figure 3). This coincided with accumulation of extracellular matrix components and potential targets of TAZ, such as fibronectin and CTGF. Collectively, our findings showed that Hippo signaling played a critical role in normal development of the SMG by contributing to salivary cell junctional integrity. As such, they were the first to implicate dysregulation of the Hippo pathway in the etiology of SS and to offer a new model for the onset of the disease. Indeed, our studies suggest that targeting nuclear TAZ/YAP may interfere with SS development and progression.13

Future Directions

The molecular mechanisms driving SS pathology are poorly understood. Further characterization of Hippo-based and novel pathogenic signals, including global expression studies using RNAseq and other omics-approaches, will prove critical. Moreover, a better understanding of cytokine signaling and cell polarity cues in SS using human tissue samples from different stages of disease progression will likely reveal complex interactions between cell polarity and immunity. In addition, mouse models, including ex vivo SMGs, will remain indispensable to deciphering molecular mechanisms and pathways contributing to the loss of salivary tissue structural integrity. These future studies promise to advance the SS research field by elucidating a novel mechanism for disease onset and progression and may reveal mechanistic insights into the means by which lymphocytic infiltration arises. They will lead to new avenues for the development of much needed therapies for SS and may reveal novel unappreciated markers of the disease.

References:

Hyposalivation Project is Now Recruiting

The Relman Lab at Stanford University in collaboration with clinicians at UCSF are now recruiting individuals with Sjögren's to participate in the hyposalivation project. The purpose of this research is to learn how saliva, or lack of saliva, shapes the composition of microbial communities in the human mouth (i.e. the oral microbiome). Ultimately, they are interested in developing novel, ecologically-based therapeutics that target the altered oral microbial communities present in individuals with low salivary flow rates due to medication usage, radiation therapy, and certain autoimmune disorders.

If you have patients who are potential candidates for participation in this project, view the exclusion criteria and full description of the study by visiting http://hyposalivation.org/participate/ for an overview; additional details by clicking on “Participate in the Chronic Hyposalivation Study;” and/or contact Danielle Drury, Clinical Coordinator at danielle.drury@ucsf.edu or 415-696-2377.

Clinical Study Recruiting for Dry Mouth Mouthwash

A clinical study taking place at Tufts University School of Dental Medicine in Boston is looking for Sjögren’s and dry mouth patients to participate. The study is testing an experimental mouthwash. For more information, contact Dr. Athena Papas, Athena.Papas@tufts.edu, 617-636-3934 or Liz at Elizabeth.Tzavaras@tufts.edu, 617-636-3931.

Fall Salivary Symposium

The first annual North American Saliva Symposium (NASS) will be held at Tufts University School of Dental Medicine, Boston, Massachusetts October 24-26th. Designed to advance salivary research across all ages and demographics to improve clinical care and outcomes, this unique forum will highlight the latest in salivary research and offer attendees an opportunity to network with international leaders in the field. Please visit www.salivasymposium.com for complete program details.

Industry News

Nicox Extends Marketing of New Diagnostic

Nicox S.A., an international ophthalmic company, has acquired the rights to market its advanced diagnostic panel for early detection of Sjögren’s to all healthcare practitioners in North America. This expansion builds on the June 2013 agreement with Immco Diagnostics Inc. to promote Sjö™ test to eye care specialists in the U.S., Canada, Mexico and Puerto Rico.

After successfully targeting eye care practitioners who are in a unique position to identify Sjögren’s due to the high frequency of dry eye patients they see, Nicox will extend its marketing platform to other health care professionals – especially rheumatologists. Encouraging a partnership between specialists who see Sjögren’s patients has been a priority for the company and fits in well with the goals of the Sjögren’s Syndrome Foundation (SSF). Nicox is an SSF Corporate Partner.

Phase 3 Trials Pronounced Successful for New Dry Eye Therapy

Mimetogen Pharmaceuticals Inc. has announced results of its Phase 3 trials for MIM-D3, an ophthalmic solution for dry eye. The multi-center, randomized, double-masked placebo controlled clinical study involved 403 dry eye patients and demonstrated significant improvement in both signs and symptoms of dry eye. MIM-D3 is a novel growth factor mimetic and was tested using a challenge-controlled adverse environmental model for treatment of dry eye.

Commentary from Donald MacKeen, PhD
MacKeen Consultants Ltd, Venice, Florida:

Lacritin is a tear component with tearing and cell maintenance properties. The authors have shown a reduced level of lacritin in Sjögren’s patients when compared with healthy controls. In a study with autoimmune dry eye mice, they found that regular instillation of lacritin was well-tolerated and resulted in significant improvement of surface characteristics. This suggests its use as a new treatment for SS and other dry eye patients.


Basic Science

Commentary from Jacques-Olivier Pers, DDS, PhD
Director, Laboratory of Immunology, Brest, France:

A potential novel mechanism for the development of multiorgan autoimmune diseases

Twelve years ago, Winer et al in The Lancet, observed that the disruption of the ICA69 locus prevented lacrimal gland disease and salivary gland disease in NOD mice. ICA69 is a self-antigen expressed in brain, pancreas, salivary and lacrimal glands. Researchers from the University of Pittsburgh, Pennsylvania have found that thymic deletion of ICA69 expression was sufficient to induce inflammation inside multiple organs. Their findings highlighted a potential role for ICA69 as a target in multi-organ autoimmune disorders. Findings were published as:


Activated monocyte-derived dendritic cells influence the pathogenesis of primary Sjögren’s

Researchers from the University of Bergen, Norway, analyzed phenotypical and functional properties of in vitro generated monocyte derived dendritic cells (moDC) from patients with primary Sjögren’s (pSS). They observed that moDC from pSS patients expressed increased levels of surface HLA-DR and CCR7 molecules and that mature moDC secreted altered amounts of several cytokines and presented an overactivated NF-κB pathway. Mimicking viral single-stranded RNA components with a TLR7/8 stimulation they found that moDC from pSS patients expressed less Stat-1, a transcription factor that directs transcription of IFN-regulated genes. Results were published as:


Neurology

Commentary from Steven Mandel, MD
Clinical Professor of Neurology, Hofstra North Shore LIJ, School of Medicine, New York:

Anti NR2 glutamate receptor antibodies may enter the CSF by a breakdown of the Blood Brain Barrier, with the development of hippocampal atrophy. This may lead to cognitive impairment, an acute confusional state, mood disorder, psychosis, amnesia,
anxiety, depression, and lead to neuronal death. Glucocorticoids, type 1 interferons, immunomodulation therapies and novel therapies, may target these antibodies leading to neuroprotection and improvement.

Commentary from Joanne R. Festa, PhD
Assistant Professor of Neurol- 
yogy, Icahn School of Medicine at Mount Sinai, New York

In seeking to identify the mechanism of memory dysfunction in primary Sjögren’s (SS), Lauvsnes et al (2013) examined the relationship between memory performance and anti-NR2 antibodies in both the CSF and serum. Hippocampal volumes were also estimated from MRI. There is sufficient evidence from systemic lupus erythematosus and other autoimmune disorders to implicate the anti-NR2 antibodies in disrupting cognitive functions and several of these studies are cited. Lauvsnes et al advances the literature by demonstrating an association between elevated anti-NR2 antibodies and memory dysfunction in primary SS patients with only a weak association between the anti-NR2 and hippocampal volume. The results suggest that in primary SS, neuronal dysfunction exists in the absence of neuronal loss. This result highlights a potential target for neurological intervention that can reduce the neuropsychiatric effects of primary SS and restore neuronal functioning. As the authors also underscore, the findings also suggest a possible role for anti-NR2 antibodies as a global mechanism for cerebral dysfunction in autoimmune disorders.

Commentary from Robin Lipschitz MD
Rheumatologist, Lenox Hill and Mount Sinai Hospitals

Following the clinical suspicion of disease, the serologic confirmation of connective tissue diseases is problematic. This is certainly the case with Primary Sjögren’s Disease (pSS). Once suspected, patients will often express frustration with memory, mood and cognition and upon further questioning, admit to depressive symptoms. The astute rheumatologist or neurologist, recognizing that in addition to the classic symptoms complex expected (with subsequent ACR, EULAR or 2002 American-European Consensus Group criteria being met), will find that there is still lack of consensus regarding criteria which contribute to the uncertainty about regarding the extent of neuropsychiatric involvement in pSS. The first observation of CNS involvement with focal or diffuse symptoms was the series of 8 patients described by Alexander et al in 1982, in which the significance of CNS involvement in pSS as well the possibility of a direct etiopathogenetic role of the anti-Ro (SSA) antibodies was observed. Numerous series have confirmed the complete absence of any association of CNS-Primary Sjögren’s with P-anti-ribosomal Ab, eliminating this biomarker as a diagnostic tool.

The recognition and use of immunodiagnostic markers for neuropsychiatric and/or CNS involvement in pSS is critical and lacking in mainstream clinical diagnosis and treatment of pSS. The paper by Lauvsnes et al (ref) which describes the association of anti-NR2 antibodies with memory dysfunction in PSS contributes to filling this gap once validated in larger clinical series. Both serum and CSF anti-NR2 levels were present in a significant number of patients with pSS with levels associated with worse performance in memory and learning as well as correlating with depression in a higher proportion of patients. Similar findings have been observed in neurocognitive SLE in which NR2 antibodies were found to be associated with cognitive dysfunction and depression with confirmatory neuroimaging (ref). The percentage varies in different studies between 14-35% (and as high as 81% in one study of diffuse neuropsychiatric SLE).

The role of other glutamate receptor antibodies in neurologic disease has been extensively explored. This family of anti-glutamate receptor antibodies that includes anti-NMDA-NR2A/B, anti-NMDA-NR1, anti-AMPA-GluR3, anti-mGluR1 and/or R5, may collectively result in excess glutamate with resulting glutamate mediated neurotoxicity resulting in acute or chronic autoimmune brain injury, seen in many different CNS/PNS syndromes including pSS. Thus the study by Lauvsnes et al adds to the evidence of the role of anti-NMDA-NR2 in neuropsychiatric pSS. In the attached discussion, note is made of the cross-reactivity of some of the anti-NMDA-NR2A/B Abs with double stranded-DNA in neuropsychiatric SLE while other antibodies do not. While research shows that low constitutive levels result in positive modulation of receptor function, (with increased NMDA receptor mediated excitatory postsynaptic potentials resulting), excess levels are pathogenic and result in what is termed “Excitotoxicity.” The resulting impaired glutamate signaling via NMDA receptors may lead to neurocognitive or behavioral abnormalities affecting hippocampal neurons and other white matter.

The latter phenomena are addressed in the article by Lauvsnes et al (ref) in which they describe cerebral white mater loss in 60 pSS patients. Differences in focal vs diffuse white matter (WM) and grey matter (GM) volume was explored using voxel-wise and global brain volume analysis. Although there was no difference in localized areas of GM or WM volume differences, the study did demonstrate that patients had diffuse reduction of cerebral WM volume vs healthy patients. The clinical relevance of these findings

Continued on page 16 ▼
must be confirmed in larger studies, but for now we can benefit from these observations by assessing WM volumes in our patients with suspected pSS CNS disease.

Future therapeutic choices for pSS may be influenced by these studies. Similar to the use of Rituxan® in the treatment of conventional apocrine glandular pSS, future studies should explore brain volumetric, functional and psychiatric outcomes using immunosuppressors (Rituxan®) or immunotherapy (IVIG) or a combination of these.


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5) Levite M. Glutamate receptor antibodies in neurological diseases: Anti-AMPA-GluR3 antibodies, Anti-NMDA-NR1 antibodies, Anti-NMDA-NR2A/B antibodies, Anti-mGluR1 antibodies or Anti-mGluR5 antibodies are present in subpopulations of patients with either: Epilepsy, Encephalitis, Cerebellar Ataxia, Systemic Lupus Erythematosus (SLE) and Neuropsychiatric SLE, Sjögren’s syndrome, Schizophrenia, Mania or Stroke. These autoimmune anti-glutamate receptor antibodies can bind neurons in few brain regions, activate glutamate receptors, decrease glutamate receptor’s expression, impair glutamate-induced signaling and function, activate Blood Brain Barrier endothelial cells, kill neurons, damage the brain, induce behavioral/psychiatric/cognitive abnormalities and Ataxia in animal models, and can be removed or silenced in some patients by immunotherapy. *J Neural Transm.* 2014 Aug;121(8):1029-75.
13th INTERNATIONAL SYMPOSIUM ON SJÖGREN’S SYNDROME

May 19th — May 22nd, 2015
Bergen, Norway

www.sicca.org/isss2015
Complimentary *What is Sjögren’s?* brochures are available for you to distribute to your patients so that they can learn about the many resources available from the SSF.

By referring your Sjögren’s patients to the Sjögren’s Syndrome Foundation, you are helping them stay up to date and connected to information about managing their disease.

By connecting with the SSF, patients will discover how they can receive:

- *The Moisture Seekers* newsletter: This 10 issue a year print newsletter contains the latest information on Sjögren’s, practical tips for daily living, and answers to medical questions from the experts.

- Helpful educational brochures, patient fact sheets as well as our sought-after *Product Directory*, which lists products that patients find helpful in treating their Sjögren’s.

- Access to a network of knowledgeable volunteers and local support groups.

- Exclusive access to the patient member-only section of www.sjogrens.org, featuring resources unavailable to other site visitors such as archives of the most popular newsletter articles, our online product guide and access to our online community.

- Discounts on a variety of products and services such as *The Sjögren’s Book* and registration for our educational conferences.

Patients can either visit www.sjogrens.org or call the Foundation at 301-530-4420 to get connected! Information on membership is also available in the SSF’s *What is Sjögren’s?* brochure. Receive complimentary copies for your office by calling us today!
Patient Education Sheet
Health Insurance Tips – Part 1

Obtaining healthcare reimbursement can be a major challenge. Having Sjögren’s places a high enough burden on patients, and adding the barriers patients face in obtaining health insurance reimbursement increases that burden greatly. This tip sheet should help you increase your chances of success when requesting reimbursement and appealing denials for a claim.

Know your insurance policy and what it covers.
- Note whether prior authorization is needed for a specific therapy or procedure.
- Understand co-pays and how much you will be expected to contribute to the cost.
- Know whether your insurance company requires “step therapy,” which means you must try and fail one therapy before the next level of therapy can be covered.

Make sure your medical records are accurate.
- Maintain copies of your medical records. You have the right to receive copies of all of your medical records. Note that you can be charged a copy fee.

Include a Letter of Medical Necessity.
- A Letter of Medical Necessity is usually written by the physician explaining why a therapy or other treatment is medically necessary. This can be included with an initial claim or included in the appeals process.
- A Sample Letter of Medical Necessity for dental treatment can be found on the SSF website under “Brochures and Resource Sheets.”

Know how your insurance company handles biologics if you are considering one.
- Insurance companies can exclude a drug from coverage or it might be a “tiered” drug, meaning one that is designated at a certain level for how much the patient must cover.
- If not covered, or if the patient coverage is too high, request an exemption along with an explanation about why you need the drug from your physician.

Always appeal denials!
- Appeal a denial at every level. Most patients receive at least partial reimbursement upon appealing a negative decision from their insurance company.
- Involve your doctor in helping you respond to a denial.
- Familiarize yourself with your insurance company’s guidelines and deadlines for appeal. This information is usually included in the denial letter.
- Make sure you have the necessary documentation showing that your case meets the insurance provider’s guidelines and demonstrates medical need.
- Maintain records of your communication with the insurance company and document every time you speak or hear from a company representative. Record the person’s name, date, time and key messages from the conversation.
- Understand why you were denied, so you can address the reason(s) directly.
- If you are communicating with the Customer Service office of the insurance company and are dissatisfied with the response, ask for a Nurse Case Manager or a Supervisor who might be more understanding of your situation.
- When possible, demonstrate that treatment is more cost-effective than alternatives or non-treatment.

If you are still denied following the final round of appeals, contact the advocacy or patient assistance program for the company that produces the therapy. Most companies have divisions that take applications for financial assistance for their therapies.

For more information on Sjögren’s, contact the Sjögren’s Syndrome Foundation at: 6707 Democracy Blvd, Suite 325, Bethesda, MD 20817 • 800-475-6473 • www.sjogrens.org • ssf@sjogrens.org.

Clinicians: Please make multiple copies of this Patient Education Sheet and distribute to your patients.
November 15th – 19th

BOSTON CONVENTION AND EXHIBIT CENTER

SSF EXHIBIT BOOTH - #432
Sunday, November 16 – 10:00am - 5:00pm
Monday, November 17 – 10:00am - 5:00pm
Tuesday, November 18 – 10:00am - 2:30pm

Saturday, November 15
8:00am-4:00pm Pre-Meeting Course / ACR Review Course Session:
Management of Salivary Gland Involvement in Sjögren’s Syndrome
(Separate registration fee required)

Monday, November 17
7:45-9:15am Meet the Professor: Controversies in Sjögren’s Syndrome
– Fredrick Vivino, MD (Advanced registration required)
2:30-4:00pm Clinical Challenges in Sjögren’s Syndrome: Neurological Complications and Lymphoma Risk

Tuesday, November 18
7:45-9:15am Meet the Professor: Controversies in Sjögren’s Syndrome
– Fredrick Vivino, MD (Advanced registration required)
1:00-2:00pm ACR Study Group: Sjögren’s Syndrome
– Moderator: Hal Scofield, MD (Room 102A)

Abstract Sessions TBA
Sjögren’s Syndrome: Pathophysiology, Presentation and Treatment
(Watch for time and date for this session and additional abstract sessions that will include Sjögren’s posters and talks)

Check ACR final program for additional Sjögren’s sessions and potential changes in dates, times and locations of programs.