Clinician’s Corner

Small Fiber Neuropathy and Sjögren’s

Editor’s Note: Views from the rheumatologist as well as the neurologist are provided on managing small fiber neuropathy in Sjögren’s for an all-encompassing look at this common symptom in Sjögren’s.

A View from the Rheumatologist...

by Nancy Carteron, MD, FACP, Consultant, Rheumatology Immunology and Autoimmune Disease, Associate Clinical Professor of Medicine, University of California San Francisco, SSF Board Member, SSF Clinical Practice Guidelines Task Force Member

Rheumatologists are often presented with patients with diffuse symptoms occurring over an extended period of time. Creating a working hypothesis and thus a differential diagnosis is the first step. Accessing additional data to rule in or out possible diagnoses follows. Obtaining valuable information may be a challenge due to availability of specific testing within a given healthcare system, available regional expertise, and patient resources (time, financial).

Often, patients seen in our practice have as one of their symptoms severe neuropathic pain (burning, prickling, dyesthesia, allodynia) or autonomic symptoms (orthostatic dizziness, trouble

First Genetic Associations Established for Sjögren’s

by Kathy Sivils, PhD, Christopher Lessard, PhD and John A. Ice, MD

Oklahoma Medical Research Foundation, Oklahoma City, Oklahoma

A major milestone was achieved last October with the first definitive identification of genes associated with Sjögren’s syndrome (SS).1 This research, led by our group at the Oklahoma Medical Research Foundation in Oklahoma City, involved comparisons of thousands of genetic variants in about 2,000 SS patients and more than 7,000 healthy controls. Completion of this large-scale study was made possible through the collaborative efforts of the Sjögren’s Genetics Network (SGENE), an international consortium of clinicians and scientists through which blood samples are collected and clinical information is shared.

In addition to the previously known associations with HLA Class II genes, we have now established robust associations with six new genes and SS. Not surprisingly, the genetic susceptibility

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SLE, and possibly, as recently reported, but with a Focus Score of <1.0 focus/4mm². Frequently, gland biopsy often showed focal lymphocytic infiltration suggestive for SSA and/or SSB antibodies. Their labial salivary glands are normal, and patients have signs of vasculitis or other histological abnormalities. The number of epidermal nerve fibers that cross the basement membrane is counted on five separate tissue sections. The total number of fibers is divided by the length of the epidermis in the five sections, yielding the ENFD (fibers per millimeter of epidermis).

The ENFD is compared to values for normal controls. Lower limit of normal (95% confidence interval) is 3.1 for foot, 5.4 for calf, and 6.8 for thigh. Lower ENFD values are considered to be diagnostic of SFN.

The causes of the epidermal fiber loss are being investigated but may involve immune-mediated inflammation in dorsal root ganglion or genetic mutations in voltage-gated sodium channels. Mutations in genes that code for proteins – Nav1.7, 1.8, and 1.9 – result in hyperexcitability of dorsal root ganglion cells.

Patients benefit from having a further understanding of their pain and may or may not elect a therapeutic trial of neuroleptic agents, such as gabapentin, topiramate, or pregabalin or other modalities.  

References

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.

Neuropathies are common and underrecognized in Sjögren’s,¹ and this article underscores the frequent difficulties encountered in diagnosing and managing small fiber neuropathy in these patients.

**Clinical Presentations**

Small fiber neuropathy is a sensory neuropathy which may be manifest by paresthesias that are typically painful. Abnormal findings of small-fiber function should be investigated in the form of neurologic examination, specialized electrodiagnostic testing, or pathologic testing. Typical presentations include burning, aching, tingling, or pricking pain that is usually distal, often worse at night, and may advance to allodynia.² When autonomic fibers are affected, patients may experience facial flushing, changes in skin temperature, increased or decreased sweating, dry eyes and mouth, erectile dysfunction, or orthostatic hypotension.³

Neuropathy is frequently accompanied by autonomic dysfunction, or orthostatic hypotension.¹³ The presence of autonomic dysfunction is often the first sign of neuropathy and can precede the motor symptoms by years.¹⁴ Autonomic dysfunction may arise from the regeneration of sympathetic nerve fibers that are sprouting from the ventral roots.¹⁴ Autonomic dysfunction may affect the heart, gastrointestinal tract, and sweat glands.¹⁴ Autonomic dysfunction may affect the heart, gastrointestinal tract, and sweat glands.

**Pathology/Etiology**

It is important to note that patients with known Sjögren’s and peripheral neuropathy should still be evaluated for other potential causes of the neuropathy, including diabetes mellitus, vitamin B12 deficiency, monoclonal gammopathy, amyloidosis, HIV, hereditary disease and paraneoplastic syndromes.⁴ A detailed work history may reveal occupational exposures to neurotoxic industrial solvents (i.e. hexane; methyl -n-butylketone; carbon disulfide). Antiretroviral or chemotherapeutic agents may induce similar presentations of neuropathy.⁵

**Diagnostic Tools**

Skin biopsy for pathologic quantification of epidermal nerve fiber density is frequently used to confirm a suspected diagnosis of small fiber neuropathy. It has been demonstrated that symptoms and pathologic skin biopsy findings in Sjögren’s associated small fiber neuropathy are non-length dependent, located in the thighs as well as the feet. This may help to differentiate distal predominant small fiber neuropathies, typically secondary to diabetes.⁶ Skin biopsies have been reported to be normal, with positive MRI neurography for abnormalities of dorsal root ganglia and which may be responsive to IVIG treatment. The etiology in these cases may be

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¹ Hofstra North Shore LIJ School of Medicine, Lenox Hill Hospital, New York and Steven Mandel, MD, Clinical Professor of Neurology
² by Matthew D. Wright, DO, Medical Resident, Department of Internal Medicine
³ A View From the Neurologist…
⁴ “Clinician’s Corner – Neuropathy” Continued from page 2
⁵ Rx Only – Prescription Medical Device
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cytotoxic autoimmunity with CD-8 positive lymphocytes in the dorsal root ganglia, leading to a vasculitic ganglioneuropathy and loss of cutaneous axons.

Quantitative Sensory Testing may be used to assess the function of both small and large sensory fibers by measuring sensory thresholds. Small fibers are assessed by measuring temperature thresholds for both heat and cold, and large fibers are assessed using vibratory thresholds.

Quantitative sudomotor axon reflex testing evaluates postganglionic sympathetic sudomotor function by evaluating sweat output from multiple locations on the body. It is a sensitive indicator of small fiber neuropathy and has been shown to be objective, reproducible and specific to peripheral nervous system.

Autonomic dysfunction due to small fiber neuropathy may be assessed using the Valsalva maneuver with measurements of blood pressure and heart rate variation. This is best performed in an autonomic laboratory. Similar to QST and QSART, the sensitivity and availability are variable, and cost may be prohibitive for many clinicians.

Potential Treatments

Symptomatic management of pain from Sjögren’s-associated small fiber neuropathy can be difficult. Many of the same medications used for other neuropathic pain syndromes are utilized for this patient population, including gabapentin, neurontin and topiramate, as mentioned by Dr. Carteron. SNRIs (duloxetine and venlafaxine), other anticonvulsants, and TCAs have been used as second line agents. IVIG therapy has been shown to be an efficacious option for patients with extreme neuropathic pain related to their Sjögren’s. The role of new biological therapeutic agents for Sjögren’s needs to be established, such as large-scale studies on the efficacy and safety of rituximab and other novel agents directed at B cell markers, interferon type 1 and cytokines such as IL-6.

It is unclear at this time whether patients with symptoms of small fiber neuropathy, or those with Sjögren’s who are asymptomatic who are found to have small fiber neuropathy, have an indication for medical treatment. We have not yet reached the stage where it is warranted for all asymptomatic Sjögren’s patients to undergo a thorough search of small fiber neuropathy with electrophysiologic studies and skin biopsies.

References

underlying SS has clear origins in both innate and adaptive immune responses. Armed with this new knowledge, we can now begin the task of understanding the ways in which specific genetic variants contribute to the development of this complex disease.

**Genetic contributions to disease**

Virtually all diseases are influenced to some degree by common genetic variants contained within the 3 billion base pairs of DNA that make up the human genome. In any given human population, there are millions of variants, or single nucleotide polymorphisms ("SNPs"), embedded within DNA sequence. Due to the diploid nature of the human genome, inheritance of traits, including disease susceptibility, may occur through the copy of a given variant that is passed on from a father and/or a mother.

Genome-wide association study (GWAS) approaches have been the workhorse of disease gene discovery. The goal of these studies is to identify those SNPs for which one allele at a SNP locus is found more frequently in diseased individuals when compared to the alternative allele at that SNP in healthy individuals. The power of GWAS scans is driven by the ever-expanding capacity for high-throughput genotyping technologies.

The most recent arrays allow genotyping to determine the alleles present in a given individual for up to 5 million SNPs in a single experiment. Allele frequencies are compared between cases and controls for each SNP to identify evidence of association with disease. The burden of statistical significance is adjusted to account for multiple testing (usually a p-value < 5 x 10^-8 is required to declare "genome-wide significance" in a study with ~1 million variants). Today’s standards also require confirmation of any association in additional, independent cohorts.

Scanning the human genome using GWAS approaches have been successfully applied to over 1,300 complex human diseases (www.genome.gov/gwastudies). Importantly, the vast majority of disease-associated variants are mapped outside of protein coding sequences and thus do not alter amino acid sequences. This implies that the functional mechanisms for most disease-associated variants will contribute to alterations in cellular processes such as regulation of gene expression levels, RNA splicing, translational control, or chromatin structure and functions.

The relatively huge proportion of intergenic sequences interspersed among the ~22,000 protein-coding gene sequences, or what was once thought of as “junk” DNA, is now known to be functionally important. Recent efforts by the ENCODE Project have focused on cataloging and understanding these genomic regulatory features. This massive effort has unveiled spectacular new insights into structural and functional elements of the human genome. Importantly, we now know that over 80% of the human genome is biochemically active through either RNA transcription or chromatin-associated activities (e.g. transcription into various coding and non-coding RNAs, short and long-range enhancers of gene transcription, histone function, and epigenetic markers such as methylation).^2 Many of these genomic elements, including transcription factor binding sites or methylation sites, are functional in a cell type-specific manner.

Of these biochemically active regions, 62% of the bases in the genome are transcribed into RNA molecules of >200 nucleotides in length, yet of these transcripts, only 5.5% are derived from protein coding exons. Over 19,000 of these long non-coding RNAs (IncRNAs) have been identified to date and are thought to play critical roles as decoys, scaffolds, guides, enhancers, and signals for assembly and function of cellular transcriptional and translational machinery – yet their role in disease is essentially unexplored. Because so many disease-associated variants fall within active regions coding for these RNAs or other functional genomic elements, studies to define their role in disease will be a major focus in the coming years. Understanding protein function is important, but in order to grasp precisely how proteins are dysregulated in disease states, we must understand their function within the context of alterations to transcriptional and translational machinery resulting from variants lying in critical sites of genomic regulatory activity.

**Putting Sjögren’s on the Genetic Map**

Sjögren’s is considered a complex genetic disease, meaning that more than one gene is involved. Anywhere from tens to hundreds of genes could be involved. The exact number of genes that influence SS is not known, but of the approximately 22,000 known genes, more than 6,000 are known to play a role in immune system function and are potential candidates. Genes involved in the functioning of non-immune cells, including exocrine cells, neurons and others, could also be important. Knowing precisely which genes are associated with SS is vital to understanding the causes of this complex disease.

Unfortunately, genetic studies in SS have lagged far behind those performed in systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, and many other related autoimmune diseases. In some of these conditions, more than 100 disease-related genes have already been identified. Previous genetic studies in SS were limited to the evaluation of only one or a few genes at a time and in relatively small groups of patients. Current scientific standards for establishing true and convincing genetic associations, however, require stud-
ries involving thousands of patients and healthy individuals. To overcome this hurdle, we formed SGENE, a consortium of researchers from across the U.S. as well as from France, the United Kingdom, Germany, Colombia, Australia, Norway and Sweden.

Having performed an initial GWAS to scan the DNA, we have identified association signals that provide us with good clues about some of the genes involved in SS. These signals are important landmarks that guide us to specific regions of the genome, but they often serve as close markers and do not necessarily tell us exactly what variant within or around an associated gene leads to disease. More detailed molecular studies of each SS gene need to be performed to identify the precise variant that truly leads to disease and to determine the effect it has on the disease itself.

Despite the high-throughput genotyping technology employed by our study, there are still millions more variants that could be tested. As a result, we know that there will be some signals we have missed. Studies are underway to both expand the number of genes now known to be associated with SS and to characterize the ones discovered thus far, ensuring that we are continually advancing our understanding of SS genetics. We also continue to expand our sample sizes and welcome new partners in this global effort.

What have we learned?

We have learned several important lessons from this first large-scale genetic study in SS. First, we saw that several of the genes associated with SS, including IRF5, STAT4, BLK, TNIP1 and others, also have previously been shown to be associated in autoimmune diseases strongly related to SS, such as systemic lupus erythematosus and rheumatoid arthritis. It is far from surprising that these genes would be associated with SS, but it also helps us begin to explain why some individuals have SS in addition to other autoimmune diseases.

Second, we observed that some genes, such as CXCR5 and IL12A, are somewhat unique to SS. Focused studies in these genes could help determine the precise molecular mechanisms that give SS its specific features and make it distinct from related autoimmune diseases. Third, in some instances, the same gene is implicated in multiple autoimmune diseases, but the variant that shows the strongest genetic association is different. This indicates that while disruptions in the same gene may occur in two distinct diseases, the way in which the gene is disrupted may differ, ultimately leading to different disease mechanisms and features.

Another major lesson we have learned is that the variants associated with SS thus far do not change the
respective protein structure, so we hypothesize that they function to alter the regulatory elements of genes as previously found for most other common, complex diseases. These “on/off” switches control when and how a gene is activated, dictate the cell types in which this dynamic process occurs, and lead to altered amounts of proteins made by a particular gene in certain situations, possibly contributing to increased risk for disease. This underscores the importance of studying RNA and characterizing transcriptional profiles in patients in order to study the effects of how risk variants contribute to the dysregulated expression of important disease genes and pathways.

**Functions of Genes Associated with Sjögren’s**

The strongest association and greatest risk for susceptibility to SS is with HLA (“Human Leukocyte Antigen”) Class II genes located within the Major Histocompatibility Complex (MHC) region on chromosome 6. In fact, we found many risk variants in this region through our study. This was to be expected, as prior studies performed in the 1970s identified HLA associations with SS and multiple other autoimmune and inflammatory conditions.5

The MHC is a very large genetic region that includes hundreds of genes, the vast majority of which are important to the immune system. The HLA genes are responsible for aiding the immune system in distinguishing “self” from “non-self” via antigen presentation of peptides to govern immune responses. The precise mechanisms of autoimmunity that lead to an inability to distinguish self from non-self are poorly understood, but these findings will help us design better studies in the future.

We also replicated previously implicated associations with SS in the region of the genes IRF5 and STAT4, which for the first time have passed the established benchmark for true association, the genome-wide significance threshold of p<5x10^-8. The gene IRF5, or Interferon Regulatory Factor 5, encodes a transcription factor protein that activates numerous other genes related to innate and adaptive immune responses after viral infection. The gene STAT4, or signal transducer and activator of transcription 4, encodes another important transcription factor protein that activates genes in response to viruses in T cells.

Interestingly, the gene STAT4 acts downstream of the newly-identified SS-associated gene known as IL12A, which encodes half of the functional protein dimer known as IL12. The protein IRF5 initiates the production of IL12B, the other half of the IL12 protein dimer. IL12 is a cytokine produced by monocytes and dendritic cells and binds to receptors on the surface of T cells and natural killer (NK) cells. In T and NK cells, IL12 triggers activation of two STAT4 proteins, and these coupled proteins activate additional genes, including those that are required for the development of Th1 cells and production of interferon-g.

Together, these genes function in innate immune signaling pathways that involve interferons. Our group and others have previously demonstrated strong transcriptional dysregulation of these pathways in salivary glands and in peripheral blood.6 Moreover, overexpression of this interferon “signature” is correlated with increased levels of two important autoantibodies in SS, anti-Ro/SSA and anti-La/SSB.

The NF-kB pathway is another very important immune system pathway that is triggered by a variety of stimuli and controls cellular responses through transcriptional control. For example, the NF-kB pathway responds to molecules present on the surface of bacteria, such as lipopolysaccharide. These molecules are recognized by toll-like receptors on the surface of some immune cells. Once these receptors are bound, a series of signaling events activate NF-kB, which then acts upon DNA to initiate the production of downstream cytokines and other inflammatory proteins.

Our GWAS identified two interesting genes in this pathway, TNFAIP3 and TNIP1. The gene TNFAIP3, or tumor necrosis factor alpha-induced protein 3, encodes a protein known as A20 that acts as the brakes for NF-kB, inhibiting the action of this pathway. Although this gene just missed the genome-wide threshold described above, many other autoimmune diseases have reported associations with this gene, and we are confident that we will soon be able to show that this gene is definitively associated with SS through our ongoing, expanded GWAS.

TNIP1, or TNFAIP3 interacting protein 1, encodes a protein that can bind A20; however, the nature of this interaction is not well understood. In addition, TNIP1 can bind one of the precursor molecules for a subunit of NF-kB, preventing it from becoming fully functional form.

The last two SS genes established in our study are important in adaptive immune responses. The gene CXCR5, or chemokine (C-X-C motif) receptor 5, which was previously known as BLR1, or Burkitt’s Lymphoma Receptor 1, is a membrane receptor for the chemokine CXCL13 and is expressed on both T and B cells. This receptor plays a major role in lymphocyte migration and, specifically, migration into different parts of germinal centers. Whether or not variants in this gene region affect the migration of lymphocytes into exocrine glands is currently unknown, but it is certainly an attractive hypothesis.

BLK, or B lymphoid kinase, was also identified in our GWAS. After the B cell receptor (BCR) is activated, one of the primary downstream molecules responsible for the activation of the signaling cascade is BLK. Improper signaling through the BCR can lead to the production
of autoreactive B cells and, subsequently, the production of autoantibodies.

**The future in Sjögren’s genetics, treatment, and diagnosis**

The work described above represents a critical step in our efforts to define the underlying genetic architecture of SS that will eventually help explain the pathogenic mechanisms at work. In addition to the genes we have identified thus far, ongoing work is beginning to reveal new candidate genes in SS. For those genes our work has identified thus far, we must continue to perform more detailed studies to understand exactly which variants in an associated region are truly responsible for the biological mechanisms that lead to disease and how they act to influence those mechanisms.

The genetic studies in SS to-date have primarily focused on samples obtained from European-derived populations, so further work needs to be done in other ancestral backgrounds. This information will help us determine which genes are disrupted in specific ancestral populations and could be very helpful in appropriately targeting specific therapies to the populations that will benefit most from them.

Also, although genetics are absolutely important key factors in SS, we know that environmental factors, including infections and diet, influence disease processes. Studying the genetics within the context of the environmental factors also provides promising hope for understanding this disease, and detailed studies evaluating these complex interactions must be conducted as well. To reach these goals, we need to continue to expand the size and scope of our studies.

As we look to the future, we are extremely hopeful. Precise knowledge of which genes are involved in SS will allow us to focus future studies on understanding those gene targets in order to identify those that have the greatest potential to lead to new, simplified diagnostic approaches targeting the specific cell types and proteins affected. Development of more tailored therapies, and hopefully ones that minimize side effects and maximize effectiveness, should be more attainable with this knowledge as we move towards personalized medicine approaches that take into account the genetic information being generated. With the work described here and new discoveries on the horizon, we have no doubt that exciting opportunities lie ahead for improving the lives of all who suffer the devastating effects of SS.

**References**


**Editor’s Note: This work was partially funded by the SSF Research Grants program. Two of the authors are recipients of an SSF research grant: Kathy Sivils received a two-year grant for her project “The Genetic Basis of Human Sjögren’s Syndrome” in FY2010 and 2011, and Christopher Lessard is a current grantee (FY2013 and 2014) for his project, “Validation and Characterization of Long Non-coding RNAs in SS.” Dr. Sivils received the highest scientific award given by the Oklahoma Medical Research Foundation this spring for her work in Sjögren’s. See page 14 for more information.**

**Industry News**

**Nicox Recognized for Dry Eye Campaign with the SSF**

Nicox, Inc. and its strategic partner Dudnyk were highlighted in PM360’s Greatest Creators annual issue for its educational campaign about Sjögren’s. Nicox, which bought the rights for promoting a novel diagnostic test for Sjögren’s from Immco Diagnostics, Inc., has been reaching out to ophthalmologists and optometrists to ensure that they are aware of Sjögren’s, help patients get diagnosed as soon as possible, and send those patients to knowledgeable rheumatologists to coordinate overall care and help establish a full healthcare team.

Nicox’s and Dudnyk’s unbranded “Drying Sunflowers” campaign, created in partnership with the Sjögren’s Syndrome Foundation, emphasizes the urgent need to look for Sjögren’s as a possible diagnosis in the many dry eye patients that eye care professionals see. The Sjögren’s Syndrome Foundation applauds Nicox for the novel and far-reaching campaign that will significantly increase awareness of Sjögren’s as well as provide the opportunity for patients to obtain an earlier diagnosis.

An investigative team led by Dr. Julian Ambrus at the University of Buffalo identified three proteins as early biomarkers in Sjögren’s that appear earlier than Ro or La. These biomarkers provide the basis for the new Stjö™ diagnostic panel. PM 360 is one of the nation’s leading trade publications in healthcare marketing and advertising.

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Every year, the Sjögren’s Syndrome Foundation (SSF) recognizes the best abstracts on Sjögren’s from the American College of Rheumatology (ACR) annual meeting. Highlighting the investigators who are early in their careers and show potential for the future of Sjögren’s research is a priority for the SSF. In the spring 2014 issue of *Sjögren’s Quarterly*, the work of Gaetane Nocturne, MD, PhD-Candidate was highlighted. Dr. Nocturne was the recipient of the SSF Outstanding Abstract Award at ACR. This year saw some very competitive abstracts, which resulted in the committee also recognizing four honorable mention awards. The following recipients were recognized for their exciting and promising research.

**Damage Accrual In a Single Centre Cohort Of Patients With Primary Sjögren’s Syndrome Followed Up For Over 10 Years**

by Chiara Baldini, MD, PhD

Activity and damage indices for Sjögren’s have been developed only recently, and, therefore, few studies have attempted to quantify the disease-related damage over time. The Sjögren’s Syndrome Clinic of the University of Pisa (Italy) decided to conduct a clinical study aimed at describing the overall prevalence and progression of damage occurring over time and to estimate the affect of disease activity on that damage.

The study cohort consisted of 155 Sjögren’s patients, 7 males and 148 females with a mean age of 49 years. All of the patients included in the study had been followed since their diagnosis, according to a standard protocol. This protocol included history, physical examination and laboratory assessments performed at yearly intervals.

Damage scores were retrospectively determined 1, 3, 5 and 10 years after the diagnosis, using two indices: the Sjögren’s Syndrome Damage Index (SSDI) and the Sjögren’s Syndrome Disease Damage Index (SSDDI). In addition, the EULAR Sjögren’s Syndrome Disease Activity Index (ESSDAI), the clinical index designed to measure disease activity, was calculated.

We observed that the damage - especially the oral and the ocular damage - steadily increased over time with a significant correlation between SSDI and SSDDI scores. More specifically, 77 patients out of 155 (49.5%) presented tooth loss and/or caries, 53 patients (34%) showed severe salivary flow impairment and 22 (14%) had persistent salivary gland swelling. Ocular damage was observed in 35 (22.6%) patients with corneal ulcers found in 17 (11%), and severe tear flow impairment was found in 31 (20%). Systemic damage manifestations were observed in 21 out of 155 patients (13.5%). In particular, 7 patients (4.5%) developed a lymphoproliferative disorder that was a slow progressive low grade non-Hodgkin Lymphoma. High levels of disease activity increased the risk of subsequent organ damage. In fact, there was a significant correlation between patients’ maximum ESSDAI score and both SSDDI and SSDI scores 5 and 10 years after the diagnosis.

In conclusion, this study demonstrated that the vast majority of Sjögren’s patients developed damage over time, mostly at the glandular level. Fortunately, systemic damage manifestations were observed only in 10-15% of patients. It is reasonable that an effective treatment lowering the disease activity might help in preventing glandular and extraglandular damage manifestations.

**Does Prenatal Exposure to Antimalarials Decrease the Risk of Neonatal Lupus: A Bayesian Perspective**

by Julie Barsalou, MD, FRCPC

It has been suggested that prenatal exposure to hydroxychloroquine reduces the risk of cardiac NLE. The primary aim of our project was to assess if prenatal exposure to antimalarials (AM) decreased the risk of cardiac NLE. The secondary aim was to analyze the effect of AM exposure on the risk of non-cardiac NLE.

A retrospective cohort study was performed on a large single-center cohort of children exposed to anti-Ro and/or anti-La antibodies on whom prospective data has been collected since 1984. Inclusion criteria were: 1) 1st
Positive Phase 2 Trial Results are in for Green Tea Product

The MighTeaFlow® formula for dry mouth provided a significant restoration of salivary function in recently completed Phase 2 clinical trials. The news was reported in April during the Frontiers in Oral Medicine international meeting in Orlando, Florida and is in the process of being published (see citation below).

The double-blind, placebo-controlled, randomized clinical trial looked at 60 dry mouth patients, including Sjögren’s patients, who consumed a lozenge containing the antioxidant green tea every four hours over eight weeks. The lozenges increased unstimulated salivary flow four-fold (about 419%) and stimulated saliva output 2-fold (about 218%). The placebo, 500 mg of xylitol, did not affect salivary output significantly. In comparison, MighTeaFlow® increased salivary flow rate significantly and without adverse effects.

Principal investigators, Drs. Scott DeRossi and Stephen Hsu, are based at the College of Dental Medicine, Georgia Regents University. The trial was supported by a grant awarded by the International Association for Dental Research (IADR), a GlaxoSmithKline Innovation in Oral Care Award, and a grant from the Georgia Research Alliance.

In addition to a lozenge, the MighTeaFlow® formula is available in a chewing gum, rinse and oral spray and can be found at www.camellix.com.


Remineralization of Teeth – In the Works:

A new technique has been developed that U.K. researchers believe can ultimately prevent dental caries from developing by remineralizing the teeth and eliminating the need for “drill and fill.” Nigel Pitts, BDS, PhD and Christopher Longbottom, PhD of Kings College London have designed a method called “Electrically Accelerate and Enhanced Remineralisation (EAER)” involving preparing the damaged outer layer of the tooth enamel and then using a low level electric current that remineralizes teeth. When pre-curious lesions are seen by the dentist, providing remineralization could help prevent these lesions from developing into full-blown caries.

Remineralization is an especially important tool for Sjögren’s patients with dry mouth, because the demineralization of teeth that occurs in dry mouth leads to caries acceleration. The device is expected to be available within three years and will be launched by a company called Reminova which was established in Perth, Scotland to commercialize key research findings by Drs. Pitts and Longbottom. Electric frequencies used are much lower than currents already in use by dentists to check the pulp and nerve of teeth.

Additional Research News and Resources on Remineralization:


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child born from a woman positive for anti-Ro and/or anti-La antibodies with a diagnosis of cutaneous lupus, systemic lupus erythematosus, Sjögren’s, dermatomyositis or rheumatoid arthritis; 2) the mother underwent fetal echocardiography screening during pregnancy and/or the child had a postnatal ECG; and, 3) the child was ≥6 months old as of October 2013. We used univariable and multivariable (adjusting for anti-Ro and anti-La antibody titers and maternal diagnosis) Bayesian analysis to study the association between prenatal use of AM and NLE.

The study population consisted of 265 children of whom 72 were exposed to AM (hydroxychloroquine or chloroquine) throughout gestation. Full laboratory data was available on 216 infants: 101 (46.8%) developed NLE and 115 (53.2%) remained unaffected. Forty-nine children were classified as having no cardiac NLE but could not be diagnosed as true unaffected children as >1 blood test components were missing. These children were only included when the outcome studied was cardiac NLE.

On univariable analysis and under a non-informative prior, the probability that prenatal AM exposure would be protective (RR < 1) was 97.1% for cardiac and 66.9% for non-cardiac NLE. On multivariable analysis, the probability that prenatal AM exposure would be protective (RR < 1) for cardiac NLE was 87.6%. Using a more stringent RR cutoff (RR < 0.75), the effect on the development of cardiac NLE remained significant, with a 79.8% probability to obtain at least a 25% risk reduction of cardiac NLE. The probability to obtain at least a 25% risk reduction of non-cardiac NLE dropped significantly at 20.2%.

In conclusion, in this study of the largest single-center cohort of children born to anti-Ro and/or anti-La antibody positive women with a connective tissue disease, we have shown that the probability that AM exposure was associated with a decreased risk of cardiac NLE was >87%. A clinically significant beneficial effect from AM exposure on non-cardiac NLE features was less likely. These findings need to be confirmed in an independent cohort.

Neonatal lupus (NL) is a passively transferred autoimmune disease occurring in about 1 to 2 percent of babies born to mothers with autoimmune disease, primarily systemic lupus erythematosus (SLE) and Sjögren’s or asymptomatic but with antibodies to SSA/Ro and/or SSB/La. About half of these mothers go on to develop autoimmune disease (more commonly Sjögren’s than SLE).

The most serious complication of NL is complete heart block (about 10 percent have an associated cardiomyopathy at the initial diagnosis or develop it later). The mechanisms by which these antibodies result in cardiac injury have not been fully elucidated, but our work at the Jill Buyon lab at NYU School of Medicine has highlighted a potential role of the urokinase-type plasminogen activator (uPA)–uPAR system.

Our previous in vitro studies have shown that uPAR expression and plasminogen activation are upregulated following the binding of anti-Ro and anti-La autoantibodies to cultured cardiocytes, and the plasmin that is generated has been suggested to have profibrotic effects through activation of TGFbeta signaling. Our recent studies have confirmed the relevance of the uPA–uPAR system in an in vivo setting by measuring the levels of soluble uPA, uPAR and plasminogen in umbilical cord blood obtained from neonates exposed to anti-Ro antibodies.

Median levels of all three factors were significantly higher (each P <0.0001) in cord blood from neonates with cardiac neonatal lupus (n = 35) than in cord blood from anti-Ro antibody-exposed neonates without cardiac manifestations (n = 26). Immunohistochemical staining of cardiac tissue samples from three fetuses that died from cardiac neonatal lupus demonstrated that plasminogen and uPA were expressed by inflammatory cells that had infiltrated conductive cardiac issue.

Our current work indicates that activation of TGFbeta by anti-Ro mediated uPA activation leads to macrophage infiltration and their polarization towards an M2 type, an effect that amplifies the profibrotic and inflammatory cascade phenotype observed in cardiac NL. Thus, our study adds support to the idea that the uPA–uPAR system is involved in cardiac neonatal lupus. Future goals in our lab will focus on delineating the molecular events, so as to potentially identify factors that can serve as diagnostic tools early in the pregnancy.
**Conclusion**

CPP-ACP has a long-term remineralizing effect on early caries lesions in comparison with placebo, although this does not appear to be significantly different from that of fluorides. The advantage of using CPP-ACP as a supplement to fluoride-containing products is still unclear. High-quality, well-designed clinical studies in this area are still required before definitive recommendations can be made.

**Saliva Substitutes: Is One Better Than Another?**

Saliva substitutes are an important tool in the arsenal against caries in xerostomia patients. But is one better than another? To find out, saliva substitutes were compared to gauge their effect on tooth enamel in a study published in June 2014 in the *Journal of Dentistry*.

Products included many of those frequently used by Sjögren's patients and familiar to their dentists. Several reduced enamel erosion significantly (by 60-90% and in the same range as the positive control cited below), while four actually increased enamel erosion. For the full list of products and the results, see the article cited below. In conclusion, investigators found that high-viscous saliva substitutes performed the best and recommended that dry mouth patients avoid those saliva substitutes with a low pH and/or those containing citric acid.


**Dental Restorations: Repair or Completely Replace a Restoration?**

When dental restorations fail, is it better to repair the restoration or completely repair it? Several recent studies looked at this question, although much more research needs to be done.

A study published in June 2014 in the *Journal of Dentistry* found equal results when comparing repair of failed restoration versus complete replacement. As a result, the researchers concluded that repair is preferable because a repair is less invasive, increases the longevity of a restoration, and is safe and effective. The study was a clinical randomized, triple-blind study.


Two review articles published earlier in 2014 found no research studies to help elucidate the question of repair versus complete replacement of a restoration. One review looked at resin composite and the second at amalgam and both examined whether repairing these restorations versus replacing them was preferable. No studies that met pre-established criteria were found, leading the authors to highly recommend that research projects be designed and executed on these questions.


**Other Industry News...**

**Takeda and Macrogenics Join Forces for an Autoimmune Therapy**

Takeda Pharmaceutical Ltd and Macrogenics, Inc. have announced an agreement for the development and commercialization of a new potential therapeutic in autoimmune disease. MacroGenics held ownership of the Dual-Affinity Re-Targeting (DART) to target both CD32B and CD79B, two B cell surface proteins. The therapy, MGD010, currently is in pre-clinical development.

**Arena Moves Forward with New Therapeutic**

Arena Pharmaceuticals, Inc. announced in June that it has begun Phase 1b trials of a therapy that targets the sphingosine 1-phosphate subtype 1 (S1P1) receptor in autoimmune disease. APD334 is administered orally.
(TEARS study) had an ultrasound examination before the first infusion (placebo or RTX) and at 6-month follow-up. They had scores above 50 mm on at least two of four visual analog scales (VASs) evaluating dryness, pain, fatigue, and global disease and recent-onset (<10 years) biologically active pSS and/or systemic pSS. Patients were randomly assigned (1:1) to RTX (1 g at weeks 0 and 2) or placebo. Both parotid and submandibular glands were assessed for echostructure (using a semi quantitative scoring 0 to 4 and considering an improvement if the score of the glands was improved more than 1), size of each gland, and vascularisation using the resistive index of the transverse facial artery of the parotid glands before and after stimulation with lemon juice.

Results demonstrated that the echostructure of the parotid parenchyma scoring was improved in 50% of pSS patients in the RTX group versus 7% in the placebo group (p = 0.03). The US submandibular scoring was also improved in 35% of pSS patients in the RTX group compared to 16% in the placebo, but the difference was not statistically significant (p = 0.16). There were no changes concerning the gland size or resistive index. The concordance between ultrasonography and anatomo-pathology showed that the focus score was lower after treatment in 3 of 10 patients who had minor salivary glands biopsy (MSGB) after treatment in both groups. Concordance between ultrasonography and anatomo-pathology scores changes was low (kappa 0.1).

This study is the first to demonstrate ultrasound changes in the salivary glands after treatment of pSS, suggesting that some characteristics may be reversible. Surprisingly, it is not the gland size but the structure that changed with treatment. The low concordance between MBG and ultrasonography could be explained by the fact that we perform ultrasonography on parotid and submandibular glands whereas biopsies are done on the minor salivary glands. We know that there is an anatomical difference between these 2 structures resulting in a potential bias in our results.

In our pSS population treated by RTX or placebo, ultrasound evaluation showed a greater improvement of the echostructure of the salivary glands in treated patients than in the placebo group. In contrast, RTX did not modify the size of the salivary glands or the vascularisation inside the parotid glands. In the future, it would be interesting to compare these results with parotid biopsies. As a matter of fact, the ultrasonography and the minor salivary gland biopsy could provide different information when evaluating pSS patients. The main limit of our study is the low number of patient and the lack of a clear definition of gland enlargement or atrophy before inclusion.

Special Honors and Other SSF Grantee News

**Kathy Sivils, PhD Receives Highest OMRF Award**

Outstanding accomplishments in Sjögren’s were highlighted when former SSF Research Grantee Kathy Sivils, PhD was awarded the highest honor given for scientific research by the Oklahoma Medical Research Foundation (OMRF). Dr. Sivils is the Director of the OMRF Sjögren’s Research Clinic, a former SSF research grantee, and a current SSF Board of Directors member. OMRF President Stephen Prescott applauded Dr. Sivils for helping to establish OMRF as one of the world leaders in Sjögren’s research and deserving of OMRF’s highest praise with the Edward L. and Thelma Gaylord award.

Dr. Sivils led the group that recently discovered the first-ever specific genes linked to Sjögren’s. (See the lead article on page 1 of this issue.) Her 2010 and 2011 SSF research grant project was entitled “The Genetic Basis of Human Sjögren’s Syndrome” and involved a large, multidisciplinary, international effort to identify genes associated with Sjögren’s.

**Patricia Mongini, PhD Publishes Sjögren’s Work**

The first SSF Innovative Concept Grant winner, Patricia Mongini, PhD has just been published in *Clinical Immunology*. Her newest article describes how gene mapping of novel NOD.B10 COX-2/flox strains with/without xerostomia has significantly narrowed the candidate Chr 1 genes for xerostomia in Sjögren’s in mice. Dr. Mongini was awarded the Innovative Concept Grant for 2008 through 2010 for her project “B Cell-Expressed COX-2 and Sjögren’s Syndrome Development” carried out at the Feinstein Institute for Medical Research, North Shore – LIJ Health System, Manhasset, New York.

Patient Education Sheet

Vaginal Dryness

The SSF thanks Elisa R. Trowbridge, MD, Assistant Professor of Obstetrics and Gynecology and Urology, University of Virginia School of Medicine, Charlottesville, Virginia, for reviewing this Patient Education Sheet.

Some fast facts:

- Because moisture-producing glands are targeted in Sjögren’s, it is not surprising that dry vagina can be a common symptom.
- Dry vagina in post-menopausal women is 2-3 times more common when the patient also has Sjögren’s.
- Dryness from both Sjögren’s and menopause can be exacerbated by a condition called atrophic vaginitis in which dryness and inflammation lead to the thinning of the vaginal lining. Estrogen can help.
- Vulvodynia and Interstitial Cystitis can occur in Sjögren’s and are additional conditions that can increase pain in the genital area.
- Vaginal dryness and subsequent pain with intercourse can be presenting symptoms that can lead to the diagnosis of Sjögren’s.

Quick Tips:

- Make sure your gynecologist is aware that you have Sjögren’s.
- Try daily vaginal moisturizers such as Luvena®, Replens® and Feminease ®.
- Discuss the use of vaginal creams, rings or suppositories with your gynecologist for moderate to severe vaginal dryness.
- Use water soluble lubricants such as KY jelly when engaging in sexual activity. Avoid Vaseline.
- Apply natural lubricants such as Vitamin E or aloe vera to see if they work for you.
- Stay away from using irritating substances such as soap, detergent, and fragrances in toilet paper or cleaning agents.
- Avoid tight underwear and pressure to the genital area during activities such as biking and horseback riding.
- Try cold compresses to the area if in pain.
- Recognize potential contributing factors to genital pain, such as vaginal infections (especially Candida), interstitial cystitis, urinary leakage, vulvodynia and vaginal atrophy.
- Call your gynecologist if you suffer any bleeding following intercourse.
The 13th International Symposium on Sjögren’s Syndrome
19th-22nd May 2015, Bergen, Norway

www.sicca.org/isss2015