Mouse Models for Sjögren’s Syndrome

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Over the past 40 years, several experimental mouse model systems have been developed to investigate the pathogenesis of Sjögren’s syndrome (SS). While several animal species have been explored, the greatest experimental activity has centered on mouse models, and they have proven to be valuable resources and generated much data. The question is: How representative are these mouse models of human disease?

Presence of lymphocytic infiltrates within the salivary and lacrimal glands is a characteristic feature of SS. These lymphocytes can recognize ubiquitously present antigens such as SSA and/or antigens that are specific to the salivary and lacrimal glands. Where these lymphocytes are first activated and how they start infiltrating the glands are major issues in SS re-

The Role of Sleep Disorders in Sjogren’s Disease

by Steven Mandel, MD, Professor of Neurology, Alan R. Taylor, PA-C and Ramon Manon-Espaillat, MD, MA, Clinical Professor of Neurology, Epilepsy, Sleep Medicine, Clinical Neurophysiology and Electrodiagnostic Medicine, Thomas Jefferson University, Jefferson Medical College, Philadelphia, Pennsylvania

Sleep disturbances are a common problem in patients with Sjögren’s syndrome (SS) and reported in 75% of patients (Tishler et al). This includes insomnia, daytime sleepiness and fatigue, nocturnal pain, and symptoms of restless legs. Sjögren’s patients complain of significantly more daytime sleepiness and fatigue and not feeling rested during the daytime. Sleep studies in patients with Sjögren’s have often shown increased sleep latency, frequent nocturnal awakenings, decreased sleep efficiency, frequent arousals, periodic leg movements and intrusion of alpha waves during slow wave sleep (alpha intrusion). Sleep apnea appears not to be a major problem in Sjögren’s patients.

Surprisingly, little effort has been made to diagnose and characterize sleep profile in Sjögren’s. In this article, we will examine potential causes of sleep disturbances in the Sjögren’s patient, clinical evaluation and treatment.

Causes of Sleep Disturbance in Sjögren’s

Sleep disturbances may be related to physical as well as psychological factors. The cause of insomnia is multifactorial and includes comor-

Continued on page 2 ▼
Other causes of poor sleep in patients with Sjögren’s include joint pain, muscle stiffness and discomfort, sicca symptoms and nocturia. Dry mouth and dry eye can interrupt sleep, causing patients to awaken to alleviate these symptoms. Sipping water throughout the night also leads to more frequent awakenings for trips to the bathroom.

The peripheral nervous system (PNS) is affected in many Sjögren’s patients and can result in pain which in turn can contribute to sleep difficulties. The reverse can be true as well, as PNS pain may be related to sleep disturbances including myalgias, arthralgias and other small fiber pain sensation. In addition, central nervous system involvement both focal and diffuse has been established in primary Sjögren’s and may contribute to sleep difficulties.

Comorbid diseases also can impact sleep in Sjögren’s patients. As many as 55% of SS patients also may have fibromyalgia (Tishler et al) which by itself is associated with sleep disturbances, particularly insomnia and alpha intrusion. Additionally, restless leg syndrome (RLS) may cause a disruption in sleep and has been reported repeatedly in Sjögren’s patients. In a brief report on rheumatological serologies in secondary restless leg syndrome, it is noted that RLS has been reported in approximately 25% of patients diagnosed with rheumatoid arthritis (RA) and Sjögren’s (Ondo et al).

Specific diagnostic criteria for RLS and sleep disorders in one paper on Sjögren’s (Gudbjörnsson et al) used a single symptom for diagnosing RLS – “Creeping sensations in the legs.” Ten patients with primary Sjögren’s who were not on regular medication for their disease underwent polysomnography and were shown to have a variety of sleep abnormalities. While periodic limb movements of sleep (PLMS) was not specifically mentioned in connection with these patients, they most likely did have this disorder as PLMS often accompanies RLS. PLMS occurs when sudden involuntary jerking or twitching movements occur in the legs during sleep.

The same study found that when compared to both RA patients and healthy controls, the primary Sjögren’s patients reported significantly more incidents of “too little sleep” as well as sleep deficiency, defined as the need for sleep versus actual sleeping time. RA patients with secondary Sjögren’s took significantly longer to fall asleep compared to RA patients without secondary Sjögren’s. And, pSS patients had significantly more trouble initiating and maintaining sleep than RA patients. Frequent awakening in the pSS patients was attributed to pain, headache, shortness of breath, palpitations and sweating and difficulties initiating sleep were attributed to muscular tension, RLS and anxiety.

Inflammation common in Sjögren’s patients may exacerbate sleep disturbance. It is well noted that cytokines may play an important role in sleep disorders. Furthermore, psychiatric abnormalities also have been reported. In an article on sleep disturbances associated with primary Sjögren’s syndrome, it is noted that psychiatric morbidity and personality disorders have frequently been investigated in autoimmune disorders.

Abnormalities seen with Sjögren’s can be varied and subtle, making it difficult to determine the exact cause or causes of sleep disturbance. There may be subclinical variances of sleep disorder as well.

Clinical Evaluation

The evaluation of sleep disorders in Sjögren’s starts with a sleep history to include bedtime, estimated time to fall asleep, number and causes of awakenings through the night, final get-up time and how the patient feels upon awakening, for example, whether the patient is still tired or refreshed. The sleep history includes daytime sleepiness, naps and fatigue as well as discomfort in the legs in the evenings consistent with restless leg syndrome. The sleep history includes daytime sleepiness, naps and fatigue as well as discomfort in the legs in the evenings consistent with restless leg syndrome.

After a comprehensive history is obtained, the use of the Mini Sleep Questionnaire (MSQ) might be appropriate for these patients. The MSQ is a 10-item questionnaire that significantly helps in differentiating between different causes of sleep disturbances and between healthy controls and those who suffer from sleep disorders. An overall score is determined that defines the severity of the sleep disturbance.
Treatment

Treatment of sleep problems in Sjögren’s patients starts with identification of the most obvious causes of sleep disturbance, such as sicca, anxiety and depression. Attempts to reduce sicca symptoms and obtaining treatment for anxiety and depression can be helpful. Sleep hygiene and cognitive behavioral therapy also may prove beneficial.

Medications such as sedating tricyclic antidepressants can be used in insomnia with comorbid depression. However, these medications could aggravate restless legs, periodic leg movements and sicca syndrome. Non-benzodiazepine agonist receptors such as Zolpidem, Zaleplon, and Eszopiclone can be used alone or in combination with antidepressant medications. Ramelteon, a melatonin receptor agonist, can be helpful. Benzodiazepines such as flurazepam, temazepam, triazolam, or estazolam can be used.

Sleep studies are only indicated if other sleep disorders such as sleep apnea, idiopathic hypersomnia, narcolepsy or periodic leg movements are suspected or if a patient has medically refractory or unexplained insomnia.

Conclusion

Sleep disturbances of various types are associated with Sjögren’s syndrome, making a comprehensive historical critical for the diagnosis and subsequent treatment. Use of the Mini Sleep Questionnaire and polysomnographic evaluations also can be useful. There may be subclinical involvement in sleep disorders, some of the most common of which are xerostomia, dry eye, restless leg syndrome and fibromyalgia. Additionally, psychiatric disorders including depression and anxiety also may interrupt sleep.

References


a very obvious dry eye in a mouse can become evident by visual examination. However, for most experimen-
tal models, rarely has this been the case. Most inves-
tigators rely on the Schirmer test, modified for use in
mouse models and known as the Phenol Red Thread
Test. Although this analysis can show reduced lacrimal
gland function, whether the mouse has dry eyes similar
to those observed in SS patients is difficult to address.
Clearly additional tests such as Rose Bengal staining or
Fluorescein staining should be performed. Moreover,
biochemical analysis of tears would provide additional
evidence for glandular dysfunction.

Two additional criteria focus on oral signs and
symptoms. Unlike SS patients, dry mouth in a mouse is
difficult to determine. Again, symptoms are not an
option. Some investigators have assessed weight loss
as a surrogate for reduced food intake presumably due
to dry mouth. The problem is that it can take several
months before the weight loss is apparent and moreover
an underlying autoimmunity or other factors can also
contribute towards this. Thus, a direct correlation be-
tween dry mouth and weight loss is not always feasible.

Another challenge with evaluation of salivary gland
function in a mouse model is the inability to collect
unstimulated saliva. Thus, one has to rely on collection
of stimulated saliva, which is generally done through
the injection of pilocarpine hydrochloride, a muscarinic
receptor 3 agonist. Using appropriate dosing of the drug
(0.15-1.5 mg/Kg body wt), differences in saliva volumes
and flow rates between diseased mice and normal mice
can be readily detected. However, one has to exercise
cautions in interpreting these data. Decreases in saliva
volume, particularly if they are small in the range of 10-
20% may not be biologically relevant although statisti-
cally significant. Varying the pilocarpine dosage may
diminish or augment the differences. Further, differ-
ences in salivary function may be due to other factors.

Many investigators have used non-autoimmune
prone mice as controls when comparing saliva volumes
with the diseased mouse. It should be noted that basal
saliva volumes in different mouse strains can vary
considerably. Thus, a control strain should have similar
saliva volume as an age-matched, non-diseased experi-
mental mouse and the growth characteristics of the
strains should be similar. Ideally, longitudinal analysis
of saliva volumes within the same mouse or cohorts of
the same mouse strain should show a progressive drop
in volume and flow rate. Moreover, biochemical char-
acterization of saliva should be performed which would
provide further evidence for salivary gland dysfunction.

SS has a strong autoimmunity component, and one
criterion deals with the demonstration of serum auto-
antibodies to Ro/SSA or La/SSB. A high titer of these
autoantibodies is present in the majority of patients.
However, in mice, even in spontaneous mouse models
for lupus (some of these also develop SS-like disease),
these autoantibodies are not readily detected. This oc-
curs despite the presence of other anti-nuclear auto-
antibodies in high titers. To detect the Ro/SSA and La/
SSB autoantibodies in mice, recombinant antigens are
used in ELISA or western blots. In our experience, this
format detects polyreactive low affinity autoantibodies.
Thus, use of immunoprecipitation assays employing
antigen in its native form should be used for the detec-
tion of Ro/SSA and La/SSB antibodies in mice. Alter-
atively, if autoimmune response to other antigens is
demonstrated in a convincing manner, the insistence for
demonstration of anti-Ro/SSA and anti-La/SSB autoan-
tibodies in mouse needs to be re-examined.

The criterion for histopathologic changes in salivary
glands can be readily investigated in mice. The biggest
strength of mouse models for SS research is the abil-
ity to investigate early events that initiate inflamma-
tory cell infiltration within the exocrine glands and,
thereby, mechanisms of disease induction. Unlike other
autoimmune disorders, genetic predisposition alone
is not sufficient for manifestation of SS. Interaction
with environmental factors is a critical requirement for
disease development. Microbial infections, particularly
viral infections, have been long suspected as a major
environmental factor. Since no specific infection has
been conclusively associated with SS, it is possible that
multiple infections with different viruses provide a
trigger for SS development in genetically susceptible
individuals. The earliest consequence of a viral infec-
tion is the activation of innate immunity. Thus, we can
hypothesize that chronic activation of innate immunity
in genetically-susceptible individuals is a major event
for SS development.

Our recent studies in the New Zealand Black X New
Zealand White F1 (NZB/W F1) mice provide evidence for
this theory. As a surrogate for viral infection, we repeatedly
treated NZB/W F1 mice with a Toll-like receptor 3 agonist,
poly (IC). This treatment caused a rapid infiltration of
inflammatory cell infiltrates within the submandibular
glands of mice. The sialoadenitis in poly(IC)-treated mice
was much more severe and accelerated by 2-3 months
over the PBS-treated controls. Our studies further show
that rapid upregulation in the expression of multiple che-
mokines within the submandibular glands of poly(IC)-
treated mice can provide further evidence for salivary
gland dysfunction.
EVOXAC.

IMPORTANT SAFETY INFORMATION

EVOXAC (cevimeline HCl) is indicated to treat the symptoms of dry mouth in patients with Sjögren’s syndrome.

- Cevimeline HCl is contraindicated in patients with uncontrolled asthma, known hypersensitivity to the drug, and when miosis is undesirable, e.g., in acute iritis and narrow-angle (angle-closure) glaucoma.
- Cevimeline HCl can potentially alter cardiac conduction and heart rate and produce transient changes in hemodynamics. Cevimeline HCl should be administered with caution and under close medical supervision to patients with a history of cardiac disease, controlled asthma, chronic bronchitis, or chronic obstructive pulmonary disease.
- Cevimeline HCl should be administered with caution to patients taking beta-adrenergic antagonists because of the possibility of conduction disturbances and to patients with a history of nephrolithiasis or cholelithiasis.
- If a patient sweats excessively while taking cevimeline HCl, dehydration may develop.
- Caution should be advised while driving at night or performing hazardous activities in reduced lighting.
- Safety and effectiveness in pediatric patients have not been established.
- Cevimeline HCl is metabolized by the P-450 isozymes CYP2D6 and CYP3A4. Thus, there may be potential for interaction between cevimeline HCl and other compounds.
- Special care should be exercised when cevimeline HCl is taken by geriatric patients, considering the greater frequency of decreased hepatic, renal, or cardiac function.
- The most frequently reported adverse events associated with the pharmacologic action of a muscarinic agonist (>10% incidence) in clinical trials of cevimeline HCl were: excessive sweating, nausea, rhinitis, and diarrhea. Consult the full Prescribing Information for other adverse events.


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Understanding Dry Mouth: Signs, Symptoms, Solutions and Sjögren’s

Attendees at the California Dental Association (CDA) conference packed the room to overflowing to hear the educational session on dry mouth and Sjögren’s. In fact, many had to be turned away because all 400 seats were filled. The Sjögren’s Syndrome Foundation (SSF) co-sponsored the CE course together with the CDA Foundation, and the two organizations are considering future programs on the topic because of the high level of enthusiasm. In addition, the SSF is pleased that the Florida Dental Association is interested in holding a similar program in 2012.

Ava Wu, DDS, Michael Brennan, DDS, MHS and Vidya Sankar, DMD, MHS developed a Continuing Education program that covered: 1) How to identify dry mouth; 2) How to identify possible causes of a patient’s dry mouth; and 3) How to manage, treat and prevent complications from dry mouth. Educating oral professionals about dry mouth and Sjögren’s is critical in order to prevent the many complications that can occur in dry mouth, manage complications when they do occur, and ensure that Sjögren’s patients are identified and obtain regular care from their dentist and other specialists such as a rheumatologist and ophthalmologist.

About 25 million Americans suffer from dry mouth, the top three causes for which are medications, Sjögren’s, and radiation therapy to the head and neck. Dry mouth is more prevalent in women than in men and occurs more frequently in Caucasians. Advanced age is not related to salivary gland dysfunction and dry mouth, but dry mouth occurs more frequently in older adults largely due to side effects of medications.

Dr. Wu is a Clinical Professor and Director of the Salivary Gland Dysfunction Clinic at the University of California, San Francisco, School of Dentistry, San Francisco, California; Dr. Brennan is Associate Chairman of the Department of Oral Medicine and Director of the Sjögren’s Syndrome and Salivary Disorders Center at the Carolinas Medical Center, Charlotte, North Carolina; and Dr. Sankar is an Associate Professor in the Department of Comprehensive Dentistry at the University of Texas Health Science Center, San Antonio Dental School. San Antonio, Texas.

Clinicians can ask their patients key questions to determine whether dry mouth, and potentially Sjögren’s, might be a problem.

- Does the amount of saliva in your mouth seem too little, too much, or do you not notice it?
- Do you have difficulties swallowing?
- Does your mouth feel dry when eating a meal?
- Do you sip liquids to aid in swallowing dry food?

treated mice are responsible for initiating lymphocytic infiltration. Clearly these studies have significant implications for understanding the etiopathogenesis of SS and demonstrate the utility of mouse models in SS research.

Many genetic defects in mice (induced or spontaneous) can lead to some features of SS. However, a careful evaluation of each mouse model needs to be conducted, keeping in mind the inherent pitfalls, before it can be accepted as a relevant model for SS. The recent advances in gene expression studies and genome wide associations in SS patients have opened up a vast area of research. Clearly, exploring how different gene polymorphisms observed in SS patients contribute toward disease development in experimental mouse model systems will be a more efficient strategy than the reverse approach of investigating whether a certain mutation observed in mice is present in SS patients. We feel that the former strategy might lead to the development of biomarkers for SS and suggest novel therapeutic strategies to treat human disease.

In summary, the mouse models for SS are a valuable resource for investigating the mechanisms of disease pathogenesis, although there is no single model which is ideal for all investigations or fully replicates the human disease. Further research is needed to define more completely the existing mouse models and to develop new models. Further, mouse models will provide a valuable test of emerging concepts of mechanisms of disease development and new therapies.

Editor’s Note: Co-author Dr. Umesh Deshmukh received the SSF Innovative Concept Grant in 2008 and 2009 for his project, “Adenosine receptor agonists: Novel therapeutic agents for Sjögren’s syndrome.” His grant was made possible by support from the Leach Family. He recently received an R21 research grant from the National Institutes of Health to continue his work in innate immunity activation in the pathogenesis of Sjögren’s.

Further Reading:

Acknowledgements
Grant support by SSF and the National Institutes of Health. We are thankful to Dr Philip C. Fox for helpful suggestions for this article.

Table 1 Mouse Models Mimicking Different Aspects of Human Disease

<table>
<thead>
<tr>
<th>Type</th>
<th>Mouse Strain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous</td>
<td>NZB/WF1, MRL Ipr/Ipr, IqI/Jic, Aly, NOD, NOD based (C57BL/6-Aec1Aec2, NOD.B10-H-2b)</td>
</tr>
<tr>
<td>Transgenic</td>
<td>Baff, RbAp48, Il-10, Il-12, Il-14, HTHL-tax</td>
</tr>
<tr>
<td>Gene knockouts</td>
<td>Tgfl, Pik3, Foxp3, Aromatase, kB enhancer, Act1, Tsp, Ifry, Id3, NOD based (Ccrf, E2ft, Ifry, Ifry, Il-2, Stat6, Aire)</td>
</tr>
<tr>
<td>Immunization</td>
<td>Tissue extracts, Carbonic anhydrase II, Ro60 peptides</td>
</tr>
<tr>
<td>Other</td>
<td>NFS/sld d3Tx, MCMV infection, Retrovirus, Estrogen deficiency, GVHD</td>
</tr>
</tbody>
</table>

Further reading:
Transitions...

New Director Takes the Helm of the NIDCR in August

The Sjögren’s Syndrome Foundation welcomes Martha J. Somerman, DDS, PhD as the new Director of the National Institute of Dental and Craniofacial Research (NIDCR) at the National Institutes of Health (NIH). Dr. Somerman begins her new position on August 29, 2011. Dr. Somerman brings a background in periodontics as well as geriatrics and leaves her position as Dean at the University of Washington School of Dentistry in Seattle, Washington.

Dr. Isabel Garcia has held the interim position since August 2010, when Larry Tabak, former Director of NIDCR, left the directorship at the NIDCR to become second in command at the NIH as Deputy Director under Dr. Francis Collins. Both Drs. Tabak and Garcia have been excellent partners with the SSF and outstanding leaders, and the Sjögren’s Syndrome Foundation looks forward to continuing its relationship with Dr. Somerman and the exceptional staff at the NIDCR.

The NIDCR is home to the NIH Sjögren’s Syndrome Clinic and a leader in Sjögren’s research intramurally and through its extramural grants award system. SSF Vice President Katherine Hammitt completed her tenure on the NIDCR national advisory council the end of 2010.

Lindsey Criswell, MD, MPH, Dsc becomes UCSF Chief of Rheumatology

Lindsey Criswell, MD, MPH, Dsc has been appointed Chief of Rheumatology at the University of California

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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.

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SSF Partners with Professional Organizations for a Second Year to Award Student Fellowships

Current Sjögren’s Syndrome Foundation (SSF) partnerships with professional organizations to award student fellowships are proving so successful for all parties that the SSF will be collaborating with these groups again this year. In 2010 and 2011, the SSF provided student awards through the American College of Rheumatology (ACR) REF Preceptorship Program, the Contact Lens Association of Ophthalmologists Education and Research Foundation (CLAO ERF), and the American Association for Dental Research (AADR). These partnerships allow the SSF to increase awareness of Sjögren’s and the SSF, reach more students and their mentors, and, overall, offer more funding than ever before.

This expansion of the SSF student fellowship program has been made possible by The Bannon Humphery Foundation of Charleston, South Carolina, which joins the SSF in believing in the importance of fostering future scientists and clinicians in Sjögren’s. The SSF will once again appoint a Sjögren’s expert to join each organization’s review committee.

### 2011/2012 Student Fellowships

<table>
<thead>
<tr>
<th>Organization</th>
<th>Application Deadline</th>
<th>Qualifications</th>
</tr>
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<tbody>
<tr>
<td>ACR REF</td>
<td>08/01/2011&lt;br&gt;11/01/2011&lt;br&gt;03/01/2012</td>
<td>Medical or graduate student in rheumatology</td>
</tr>
<tr>
<td>AADR</td>
<td>10/14/2011</td>
<td>Graduate or undergraduate student working toward a DDS, DMD or PhD</td>
</tr>
<tr>
<td>CLAO ERF</td>
<td>10/30/2011</td>
<td>May be an ophthalmology resident, fellow or medical student; an optometry student; or ophthalmologist, optometrist, technician or nurse working toward an advanced degree</td>
</tr>
</tbody>
</table>

Once an award is made, no more applications for future cycles will be considered.

For more information, visit the SSF website at www.sjogrens.org/home/research-programs/student-fellowships or email research@sjogrens.org

San Francisco (UCSF). Having joined the faculty in 1992, Dr. Criswell has excelled in the research areas of genetics and epidemiology, focusing on systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) and most recently on Sjögren’s. She is the recipient of a 2010 and 2011 SSF research grant entitled “Epigenetic Profiling of Multiple Cell and Tissue Types in Sjögren’s Syndrome.”

In addition, in August 2010, Dr. Criswell became Co-Director of the international registry on Sjögren’s (the Sjögren’s Syndrome International Collaborative Clinical Alliance or SICCA) based at UCSF. She also has spoken at numerous national and international meetings, including the recent SSF luncheon meeting at the fall 2010 American College of Rheumatology annual meeting for the program, “The Role of Human Genetics and Epigenetics in the Identification of Relevant Clinical Targets for the Development of Novel Therapies in Autoimmune Disease – Particularly Sjögren’s: A Critical Review.”

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“Transitions” Continued from page 9

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War. Signs and Symptoms

Warning Signs and Symptoms

Sjögren’s syndrome often is undiagnosed or misdiagnosed. Symptoms of dry mouth can include difficulty swallowing, a burning sensation or pain in the mouth, and a change in taste or smell. Increased peeling lips, severe and progressive tooth decay, oral infections (parotid or submandibular gland infection), severe dryness or cracking at the corners of the mouth, and very sensitive teeth characterize the condition. The SSF encourages all women and men to alert their physician to the presence of these symptoms. If the patient is even aware of his or her dry mouth, the condition persists for months or years, a patient may suffer from dry mouth. Other early signs to look for would be dental decay located at the necks of teeth next to the gums, in the sense of taste, a burning sensation or pain in the mouth, a change in taste or smell, increased peeling lips, a change in taste or smell, increased sensitivity to heat or cold, and in the mouth.

Hisrry

A complete medical and prescription drug history is taken. Other sites (eyes, nose, throat, skin, vagina) is documented. The disease was first identified by a Swedish physician, Henrik Sjögren, in 1933. Sjögren’s (pronounced SHOW-grins) syndrome is a chronic autoimmune inflammatory disease in which the immune system attacks the glands that produce saliva and tears. The disease was first identified by a Swedish physician, Henrik Sjögren, in 1933.

What is Sjögren’s Syndrome?

Sjögren’s syndrome is one of the most prevalent autoimmune diseases. Nine out of ten patients are women. The average age of diagnosis is late 40s although it can occur in all age groups in both sexes. Sjögren’s syndrome is treatable. Early diagnosis is important in managing the disease.

What are the symptoms of Sjögren’s Syndrome?

Sjögren’s syndrome is a chronic autoimmune inflammatory disease in which the immune system attacks the glands that produce saliva and tears. The disease was first identified by a Swedish physician, Henrik Sjögren, in 1933. It is a chronic autoimmune inflammatory disease in which the immune system attacks the glands that produce saliva and tears. The disease was first identified by a Swedish physician, Henrik Sjögren, in 1933.

Who is most likely to get Sjögren’s Syndrome?

Sjögren’s syndrome is often undiagnosed or misdiagnosed. Symptoms of dry mouth can include difficulty swallowing, a burning sensation or pain in the mouth, and a change in taste or smell. Increased peeling lips, severe and progressive tooth decay, oral infections (parotid or submandibular gland infection), severe dryness or cracking at the corners of the mouth, and very sensitive teeth characterize the condition. The SSF encourages all women and men to alert their physician to the presence of these symptoms. If the patient is even aware of his or her dry mouth, the condition persists for months or years, a patient may suffer from dry mouth. Other early signs to look for would be dental decay located at the necks of teeth next to the gums, in the sense of taste, a burning sensation or pain in the mouth, a change in taste or smell, increased peeling lips, a change in taste or smell, increased sensitivity to heat or cold, and in the mouth.

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Contact us for more information: 800-475-6473 • www.sjogrens.org
Two Ophthalmic Companies with Therapies for Sjögren’s Are Sold

TheraTears® Acquired by Akorn, Inc.

The company that produces TheraTears®, Advanced Vision Research (AVR), Inc., was acquired this spring by Akorn, Inc. TheraTears® has long been a key supporter of the Sjögren’s Syndrome Foundation and produces a wide range of products for dry eye, including moisture drops and gels, eyelid cleansers and nutritional supplements containing omega 3s. The SSF mourned the loss of AVR Founder and CEO Jeffrey Gilbard, MD in 2009. Akorn, Inc. is a niche pharmaceutical dealing mostly in generic drugs and also supplies lissamine green dye and strips and threads to evaluate tear production.

Inspire Pharmaceuticals, Inc. Acquired by Merck & Co., Inc.

Merck & Company, Inc. this spring purchased the ophthalmic company, Inspire Pharmaceuticals, Inc. Inspire receives a royalty on two therapies for dry eye disease – Restasis® (cyclosporine) and Diquas® (diquafosol tetrasodium). The company also developed Azasite® (azithromycin ophthalmic solution) for bacterial conjunctivitis and was in the process of conducting trials for the drug’s use in blepharitis, which commonly occurs in dry eye and Sjögren’s.

Approval in Europe Follows U.S. Approval for New Anti-BLyS Drug

After winning approval by the U.S. Food and Drug Administration in March, the first lupus therapy in over 50 years just won approval in May in Europe. Benlysta®, the first of its kind in a class of B-lymphocyte stimulator (BLYS) inhibitors, was developed by Human Genome Sciences (HGS), and partners HGS and GlaxoSmithKline are working together to market the therapy. Preliminary trials are underway for use of Benlysta® in Sjögren’s in France and Italy.

New Market Study on Dry Mouth Treatment

Invado Pharmaceuticals of Pomona, New York announced in May that a recent market research study demonstrated significant symptomatic relief of dry mouth in 90% of Sjögren’s patients using their prescription oral rinse. Forty Sjögren’s patients with xerostomia participated in the study of NeutraSal®. No adverse effects were reported. The average dose was 2.3 times a day and average duration of relief was 71 minutes. NeutraSal® is a supersaturated calcium phosphate rinse.

Award Given for Proposed New Treatment for Dry Mouth

Georgia Health Sciences University College of Dental Medicine investigators have received one of three International Innovation in Oral Care Awards for their study of a new lozenge for dry mouth. Co-investigators Drs. Stephen Hsu and Douglas Dickinson have launched a clinical trial to study a lozenge containing green tea polyphenols, xylitol and jaborandi leaf extract from a plant in South and Central America and providing a slow-extended release of the formula in the mouth. The award is sponsored by the International Association of Dental Research and GlaxoSmithKline.
The 11th International Symposium on Sjögren’s Syndrome (ISSS) will be held September 28 – October 1, 2011 in Athens, Greece. Visit the ISSS website at www.sjogrensypmosium-athens2011.org to register for this major international event in the Sjögren’s world and view the scientific program.

The 11th ISSS is organized by the Department of Pathophysiology, School of Medicine, University of Athens, Greece.

Registration Today
for the 11th International Symposium on Sjögren’s Syndrome
www.sjogrensypmosium-athens2011.org
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There are many different types of neuropathies in Sjögren’s syndrome. These neuropathies can have different causes and may require different diagnostic techniques and different therapeutic strategies. Unlike other autoimmune disorders, in which the neuropathies predominantly cause weakness, the neuropathies in Sjögren’s primarily affects sensation and also can cause severe pain. Recognition of unique patterns and causes of neuropathies in Sjögren’s is important in arriving at appropriate therapies.

- Recognize that neuropathic pain is a chronic disease. Just as most causes of neuropathies and neuropathic pain in Sjögren’s do not come on suddenly, reduction of neuropathic pain can take a while.

- Initial and predominant neuropathies in Sjögren’s can occur anywhere — in the feet, thighs, hands, arms, torso and/or face.

- Many different symptomatic therapies for neuropathic pain are available. Both physician and patient awareness of potential benefits and side-effects can help tailor an appropriate approach.

- While the class of tricyclic anti-depressants (TCAs) often constitute a first-line tier of therapy in other neuropathy syndromes, the TCAs can increase mouth and eye dryness and therefore are not routinely used as front-line therapies in most Sjögren’s patients.

- Electrophysiologic tests may help in the diagnosis of neuropathies affecting larger nerves which are coated by an insulator called myelin. However, neuropathies affecting smaller-fiber nerves that lack this myelin coating cannot be detected with these tests.

- Special diagnostic tests, including the technique of superficial, punch skin biopsies (small biopsies of 3 millimeters and not requiring any stitches), can help in the diagnosis.

- A relatively rare neuropathy can cause significant weakness in Sjögren’s patients. In contrast to other neuropathies which develop slowly, this neuropathy can present with very abrupt-onset of weakness. This so-called “mononeuritis multiplex” occurs because the blood flow through vessels which nourishes nerves is suddenly compromised.

- In general, immunosuppressive medications are almost always warranted to treat “mononeuritis multiplex” neuropathy. In contrast, the role of immunosuppressives is not well-established in other neuropathies, including neuropathies that cause pain but are not associated with weakness.

- Sjögren’s patients frequently wonder whether pain associated with a neuropathy means they are at an increased risk for more severe motor weakness. While there are exceptions, if weakness is not present at onset, it most likely will not occur.

- Neuropathic pain can be alleviated and assuaged, although there may initially be a “trial-and-error” process with different and perhaps multiple agents.
New Product for Meibomian Gland Dysfunction

Clinicians now can offer patients a new product specifically for Meibomian Gland Dysfunction (MGD) which often accompanies the dry eye that occurs in Sjögren’s patients. The maker of SYSTANE®, Alcon Labs, has introduced SYSTANE® BALANCE Lubricant Eye Drops to restore the natural tear’s lipid layer and provide long-lasting dry eye relief. MGD may diminish the oily component in tears, causing tear film instability and the tears to evaporate too quickly.

For more information on Meibomian Gland Dysfunction, see the article in the Spring 2011 issue of Sjögren’s Quarterly on the release of the Meibomian Gland Report from the workshop sponsored by the Tear Film and Ocular Surface Society (TFOS). Also watch for a future Clinician’s Corner article in the Quarterly treatment of MGD.

Dry Eye Study Scheduled for the Detroit, Michigan Area

Patients are needed for a double blind study of patients with severe dry eye. Led by Steven P. Dunn, MD, Division Head, Cornea and External Diseases, Department of Ophthalmology, William Beaumont Hospital/Oakland University, Royal Oak, Michigan, the study will assess the agent Thymosin Beta 4 which has been shown to promote healing of the corneal surface and has been studied in patients with recalcitrant corneal ulcers and erosions with significant success (Dunn SP, Heidemann DG, Chow CY, Crockford D, Turjman N, Angel J, Allan CB, Sosne G. Arch Ophthalmol. 2010 May;128(5):636-8; Dunn SP, Heidemann DG, Chow CY, Crockford D, Turjman N, Angel J, Allan CB, Sosne G. Treatment of chronic nonhealing neurotrophic corneal epithelial defects with thymosin beta4. Ann N Y Acad Sci. 2010 Apr;1194:199-206.) Thymosin Beta 4 is found in serum and, thus, might be one of the key “ingredients” of serum tears which are often used as a last resort in patients with severe ocular surface disease.

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