Identifying Sjögren's Syndrome

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Author's Bio

Melissa Barnett, OD, FAAO is a Principal Optometrist at the UC Davis Medical Center in Sacramento. She specializes in anterior segment disease and specialty contact lenses. Dr. Barnett lectures and publishes extensively on topics including dry eye, anterior segment disease, contact lenses, corneal collagen cross-linking and creating a healthy balance between work and home life for women in optometry. She serves on the Board of Women of Vision (WOV), Gas Permeable Lens Institute (GPLI) and The Scleral Lens Education Society (SLS). Dr. Barnett is a spokesperson for the California Optometric Association and has appeared on several television shows. In her spare time she enjoys cooking, yoga and spending time with her husband, Todd Erickson, also an optometrist, and two sons, Alex (7) and Drew (5).

What is Sjogren's syndrome?

The European-American consensus group classified two forms of Sjögren's Syndrome. Primary Sjögren's Syndrome consists of aqueous-deficient dry eye, dry mouth in combination with autoantibodies, reduced salivary secretion, and a positive focus score on minor salivary gland biopsy.[1] Secondary Sjögren's Syndrome consists of all of the classifications of Primary Sjögren's Syndrome combined with autoimmune connective tissues disease, most commonly rheumatoid arthritis. Nine out of ten patients with Sjogren's disease are women.

In Sjogren's syndrome the lacrimal and salivary glands are targeted by circulation antibodies in an autoimmune process directed against muscarinic receptors within the glands.[2]

Aqueous deficient dry eye and dry mouth are hallmarks of Sjogren's syndrome. Ocular surface disease in Sjogren's syndrome is a product of disease of the lacrimal functional unit (LFU).[3] The lacrimal functional unit is composed of ocular surface tissues (cornea, conjunctiva, conjunctival blood vessels and eyes), the main and accessory lacrimal glands, meibomian glands, conjunctival goblet and epithelial cells and their neural connections. This network connects the sensory tissues and secretory glands that provide homeostasis of the ocular surface.

The lacrimal functional unit receives input from sensory nerve endings in the cornea, conjunctiva and eyelids.[4,5] Inflammation in the lacrimal gland can lead to foreign body sensation, keratoconjunctivitis sicca, altered tear composition and tear instability. Chronic inflammation and interruption in the feedback between various components in Sjögren's syndrome may cause dysfunction or death of tear-secreting epithelium in the lacrimal gland and conjunctiva.

There are numerous mechanisms for lacrimal gland dysfunction in Sjögren's syndrome.

These include cholinergic blockade from autoantibodies to muscarinic acetylcholine

receptor 3, inhibition of acinar secretion by inflammatory cytokines such as IL-1, cytokine-mediated epithelial cell death or replacement of acini by lymphocytes.[6-10]

Multiple substances are produced by the lacrimal gland that support and protect the ocular surface.[11] These include growth factors (e.g., EGFs), antimicrobial factors (e.g., lactoferrin, defensins), anti-inflammatory factors (e.g., IL-1RA) and mucins. It has been demonstrated that reduced concentrations of these substances have been

found in tears of patients with Sjögren's syndrome.

Inflammatory mediators that cause ocular surface epithelial disease in Sjögren's Syndrome include the matrix metalloproteinases (MMPs), inflammatory cytokines and T helper (Th) cell associated cytokines. Increased production of MMP-3 and MMP-9 by ocular surface cells has been observed in Sjögren's Syndrome SS.[12, 13]

Ocular Symptoms in Sjögren's Syndrome

Henrik Sjögren first described aqueous deficient dry eye in 1933 as an ocular finding in patients with primary Sjögren's disease. Ocular symptoms in patients with Sjögren's Syndrome include eye irritation (foreign body sensation) that is constant and can affect their quality of life and photophobia due to tear dysfunction and ocular surface disease.[14] Other ocular symptoms include dryness, pain, stinging, burning, itch, epiphora and blurring or interrupted vision**.**

It has now been demonstrated that clinically significant ocular surface disease in Sjögren's Syndrome patients may be present with normal tear production and tear volume.

Systemic Manifestations of Sjögren's Syndrome

There are numerous systemic manifestations of Sjögren's Syndrome. These range from mouth and skin, neurological to cardiovascular, and central nervous system. In order to simplify the review of the extensive amount of systemic symptoms, these are listed in Table 1.

Systemic Manifestations of Sjögren's Syndrome	
Organ	**Manifestation**
Neurological	Trouble with concentration, memory loss and brain fog
Nose and throat	Dry nose, recurrent sinusitis, nose bleeds, chronic cough
Mouth	Xerostomia (dry mouth), mouth sores, dental decay, difficulty with chewing, speech, taste and dentures
Skin	Dry skin, vasculitis, palpable purpura, uticarial lesions
Cardiovascular	Pericarditis, autonomic disturbances
Gastrointestinal	Stomach upset, gatroparesis, autoimmune pancreatitis
Peripheral nerves	Peripheral neuropathy (numbness and tingling in the extremities), mixed polyneuropathy
Digestion	Difficulty swallowing, heartburn, reflux esophagitis
Lungs	Obstructive chronic pneumopathy, intersitital pneumopathy, recurrent bronchitis, pneumonia, interstitial lung disease
Joints	Arthritis, muscle pain, arthralgias
Liver	Abnormal liver function tests, chronic active autoimmune hepatitis, primary bilary cirrhosis, associated hepatitis C infection
Kidneys	Renal tubular acidosis, glomerulonephritis
Vagina	Vaginal dryness, painful intercourse
Central nervous system	White matter lesions, cranial nerve involvement V, VII, VIII), myelopathy
Liver	Associated hepatitis C virus infection, primary bilary cirrhosis, autoimmune hepatitis
Thyroid	Autoimmune thyroiditis
General symptoms	Low-grade fever, generalized pain, myalgias, fatigue, weakness, fibromyalgia, Raynaud’s phenomenon

How is Sjögren's Syndrome diagnosed?

Sjögren's syndrome has been diagnosed with autoantibodies as diagnostic markers. Specifically, anti-Ro / SSA, anti – La / SSB, and anti-nuclear antibodies (ANA) are elevated in patients with Sjögren's syndrome.[15] SS-A (or Ro) and SS-B (or La) are the marker antibodies for Sjögren's Syndrome. A positive SS-A is found in 70% of Sjögren's patients; a positive SS-B is found in 40% of Sjögren's patients.

> Anti-nuclear antibodies (ANA) are a group of antibodies that react against normal components of a cell nucleus. About 70% of Sjögren's patients have a positive ANA. Rheumatoid Factor (RH) is positive in many rheumatic diseases. This antibody test is performed for the diagnosis of rheumatoid arthritis (RA), but is positive 60-70% of patients with Sjögren's.

Erythrocyte Sedimentation Rate (ESR) measures inflammation. An elevated ESR indicates the presence of any inflammatory disease, including inflammation in Sjögren's Syndrome. Immunoglobulins (IGs) are normal blood proteins that are involved in immune reactions; these are elevated in Sjögren's patients.

A New Option – Sjö

A new test for Sjögren's Syndrome, Sjö, tests the traditional biomarkers of Sjögren's including anti-Ro / SSA, anti – La / SSB, anti-nuclear antibodies (ANA) and rheumatoid factor (RF).[16] In addition, three novel, proprietary biomarkers are tested. These are salivary protein-1 (SP-1, IgA, IgG, IgM), carbonic anhydrase (CA-6, IgA, IgG, IgM), and parotid secretory protein (P SP, IGA, IgG, IgM). All three of these biomarkers provide high specificity and sensitivity for the early detection of Sjögren's syndrome. A Sjö test is performed with a finger prick, obtaining a blood sample, applying the sample to the collection card and then sending the card to be analyzed.

Recent studies have indicated additional autoantibodies in Sjögren's Syndrome to salivary gland protein 1 (SP-1), carbonic anhydrase 6 (CA6), and parotid secretory protein (PSP).[17] Autoantibodies were present in two animal models for Sjögren's Syndrome and occurred earlier in the course of the disease. Patients with Sjögren's Syndrome also produced antibodies to SP-1, CA6 and PSP. Antibodies were found in 45% of patients meeting the criteria for Sjögren's Syndrome who lacked antibodies to Ro or La. Thus, SP-1, CA6 and PSP may be useful markers for identifying patients with Sjögren's Syndrome at early stages of the disease or those that lack antibodies to either Ro or La.

Current Advances in Sjögren's Syndrome

There have been numerous advances in our knowledge of Sjögren's Syndrome. A variety of genetic and environmental risk factors as well as cellular and molecular pathways have been identified. This new knowledge can provide multiple targets for new therapies. In addition, advances in technology in the past ten years have led to innovations in genetics, genomics and epigenetic research. An example is the characterization and analysis of DNA and RNA in patient samples on a genome-wide scale. These new techniques will help to identify additional risk factors for the diagnosis and treatment of Sjögren's Syndrome.

The relationship between primary Sjögren's Syndrome and mucosa-associated lymphoid tissue lymphomas is well established.[18,19] Clinical and immunological characteristics have been described as lymphoma predictors in several studies. Recent studies report a predominance of diffuse large B-cell lymphomas.[20] There are distinct

differences in both disease severity and prognosis between patients with various types of lymphoma. It is important to identify the risk factors that can predict the development of subtypes of lymphoma, since the outcome and clinical behavior of lymphoma is affected by a range of biological variables. Biological and molecular advances can lead to potential novel therapies for Sjögren's Syndrome.

There are numerous viruses that have been associated with Sjögren's syndrome. It is unclear if viruses start or perpetuation Sjögren's syndrome. Recent data indicates a viral infection is linked with tertiary lymphoid structures (TLS) in the salivary gland. This suggests that viral–host interactions may lead to the development of autoimmunity in Sjögren's Syndrome.[21]

Viruses might provide a link between interferons (IFNs) production and the IFN signature (the expression of type I IFN-inducible genes) that is present in responding cell types.[22] Type I IFN consists of many different subtypes and is not easily measured using conventional ELISA testing. Salivary gland tissue and blood can indication type 1 IFN activity. IFN type I could serve as a novel biomarker in the pathogenesis of Sjögren's Syndrome. This information could define disease activity, sub-classification of patients, and how a patient responds to therapy. In addition, IFN type 1 could be used as a target for therapeutic intervention.

Ocular testing for Sjögren's Syndrome

It is important to note that primary and secondary Sjögren's Syndrome can present with any form of dry eye. There are numerous tests to evaluate the ocular surface in Sjögren's Syndrome. This article will highlight some tests, however it is not a comprehensive review.

The Schirmer's test is used to evaluate aqueous tear production. It is helpful in the assessment of patients with signs and / or symptoms of dry eye. A Schirmer's test uses a special filter paper (no. 41 Whatman), which is 5mm wide and 35mm long. Schirmer I is performed with anesthetic and Schirmer 2 is performed without anesthetic. In theory, both Schirmer 1 and 2 evaluate baseline secretion; Schirmer 2 also measures reflex secretion. A Schirmer's test is performed by placing a Schirmer's strip under the lower lid. After five minutes, the results are analyzed. More than 10mm of moisture on the filter paper in 5 minutes test result is normal. Another method to evaluate tear production is the Phenol red cotton thread test (otherwise known as Zone Quick). This test is 15 seconds per eye and no anesthetic is needed. The color change in the cotton thread can be confirmed hours after testing.

A newer test of aqueous tear production is the fluorescein clearance test. This test may be more accurate, however it is rarely performed in clinical practice. The fluorescein clearance test measures the clearance of a fixed amount of fluorescein dye instilled into the eye after intervals of time using fluorophotometry. Dry eye causes delayed clearance of fluorescein. The rate of clearance relates to tear production. Five milliliters of 2% sodium fluorescein is instilled, then after 15 minutes the color of the lateral tear meniscus is matched to a scale. A value of three is the threshold between normal and symptomatic patients.

Ocular staining includes fluorescein, rose Bengal and lissamine green stains. Fluorescein stains defects in the corneal and conjunctival epithelium. A wet fluorescein strip is applied to the conjunctiva in order to evaluate staining. Rose Bengal is used to stain dead conjunctival cells or cells unprotected by the normal mucin layer. Rose Bengal stains the conjunctiva more than the cornea. This correlates well with the degree of aqueous tear deficiency, tear break up time (TBUT), and reduced mucus production by conjunctival goblet cell and non-goblet epithelial cells. Rose Bengal is available in a strip or 5ml bottle of 1% Rose Bengal. The downside of Rose Bengal is that may irritate the ocular surface. Lissamine green has the same mechanism as Rose Bengal,

however it is less irritating. A wet lissamine green strip is applied to the conjunctiva in order to evaluate staining.

Inflammadry (Rapid Pathogen Screening, Sarasota, Fla.) is a test that is similar to an at-home pregnancy test.[23] Inflammadry takes a sample of a patient's tears and gives a positive (ocular surface disease) or negative (no ocular surface disease) result. The test takes ten minutes. A red line indicates elevated MMP-9. A stronger red line indicates more significant ocular surface disease. The test is based on a quantifiable value of the amount of matrix metalloproteinase-9 in the tears. Over 40 ng / ml of MMP-9 indicates a positive Inflammadry test. MMP-9 is a proteolytic enzyme from stressed epithelial cells on the ocular surface and is a non-specific marker of inflammation. These are cells that have been subjected to dry eye. The inflammadry test does correlate with dry eye, ocular surface disease and some clinical findings. More positive results are associated in both Sjögren's Syndrome and meibomian gland dysfunction.

Impression cytology is a method of collecting conjunctival epithelial cells for analysis of ocular surface disorders. A cytology membrane is pressed against the conjunctival surface, removed, and then stained with acid Shiff or antibodies. The analysis includes shape, number, density and pathologic modifications of epithelial cells, goblet cells and inflammatory cells. Although impression cytology provides information about ocular surface disease, it is not practical for clinical practice.

Tear osmolarity is important for many aspects of epithelial and nerve cell function. In healthy tears, the electrolyte concentrations are maintained to ensure correct osmolarity. However in unhealthy tears, proteases are activated which degrade the extracellular matrix and the tight junctions between adjacent cells of the corneal epithelium. Activated proteases are responsible for cleavage of cytokines into an activated pro-inflammatory form. A subsequent increase in electrolyte concentration increases tear osmolarity. Elevated osmolarity can cause less regulation of the tear film, more damage to the ocular surface, and more inflammation. The TearLab Osmolarity System (TearLab Corporation) measures the osmolarity of proteins in the tears and is a sensitive marker for dry eye.[24] A 50 nanoliter (nL) sample of tears in taken in vitro for diagnostic use. Increased rates of tear evaporation lead to a more concentrated tear film (increased osmolarity). Increased tear evaporation is present with both aqueous deficient and evaporative dry eye disease. The TearLab Osmolarity Test Card determines tear osmolarity using nanoliter (nL) volumes of tear fluid collected directly from the eyelid margin. The system utilizes a temperature-corrected impedance measurement to provide an indirect assessment of osmolarity. After applying a lot-specific calibration curve, osmolarity is calculated and displayed as a quantitative numerical value. Osmolarity values above 308 mOsms/L are generally indicative of dry eye disease

LipiView introduced in United States in 2011 by Tear Science, Inc (Morrisville, NC).[25] LipiView is sold in conjunction with LipiFlow, a device which removes meibomian gland obstructions with direct heat and pressure applied to the eyelid. The LipiView system is based on interferometry which uses interference patterns of waves to make accurate measurements. Light passes through the tear film and into a camera via specular reflection. This creates an interference pattern, which is translated to a colored assessment of the tear film. LipiView measures the absolute thickness of the tear film lipid layer in nanometers. LipiView can help to determine if a patient has a lipid layer deficiency. The system may also help determine if the patient would be a good candidate for LipiFlow treatment.

The Oculus Keratograph Topography System (Oculus Corporation, Wetzlar, Germany) is a type of corneal topography that is a non-invasive assessment of tear meniscus height.[26] Tear meniscus height is an indicator of ocular surface tear volume. Topography measures the inferior tear meniscus height via imaging of the anterior ocular surface. It projects a small horizontal light that reflects off of the top of the tear meniscus and is able to

directly measure the height of the inferior tear meniscus in millimeters. The computer analyzes the reflected Placido ring mires and measures the breakup time throughout the surface measured. Time measures of localized tear breakup are recorded to the 0.10 of a second. Breakup times of greater than 14 seconds are considered normal. Between 13 and 8 seconds are considered borderline. Seven seconds and below are considered abnormal.

Oral tests for Sjögren's Syndrome

Salivary Flow measures the amount of saliva produced over a certain period of time. Salivary scintigraphy is a nuclear medicine test that measures salivary gland function. Salivary gland biopsy is typically performed in the lower lip and confirms inflammatory cell (lymphocytic) infiltration of the minor salivary glands. In Sjögren's Syndrome, autoantibodies are produced and lymphocytic aggregates are present in the salivary glands in approximately 25% of patients.[27]

Conclusion

As eyecare provides, we are about to apply novel testing for Sjögren's Syndrome.

With patient history, laboratory, blood tests, ocular testing and coordination with rheumatology and dentistry for salivary testing, we are able to detect Sjögren's Syndrome. Early detection and treatment of Sjögren's Syndrome is important to prevent lymphoma or other systemic complications. Coordination of care with rheumatology is useful if Sjögren's Syndrome is suspected.

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