

TITLE: Sjogren's Syndrome

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Definition

Sjogren's syndrome is defined as a syndrome of xerophthalmia (dry eyes) and xerostomia (dry mouth) due to immune destruction of endocrine glands, especially of the lacrimal and salivary glands.

Two types of Sjogren's disease

1. Primary Sjogren's syndrome- Sicca complex (dry eyes and dry mouth) and extra glandular symptoms without any additional connective tissue disorder
2. Secondary Sjogren's syndrome- Sicca complex that occurs with another autoimmune disorder such as SLE, RA, or scleroderma.

History

Henrick Sjogren was first credited for the discovery of the disease. As a resident on ophthalmology, he discovered women with rheumatism and corneal abrasion who could not produce tears when crying. He later published a paper, Keratoconjunctiva Sicca, describing this dysfunction. His paper did not receive a good report. However, he later did a series of 80 patients with the syndrome, the majority having arthritis. After which, Sjogren's syndrome received attention.

Incidence

1-2 million people in the US. Prevalence of 1-3% of the population. Sjogren's disease is in the top 3 of rheumatic diseases behind systemic lupus erythematosus and rheumatoid arthritis.

Primary Sjogren's disease has a ratio of 9:1 of women to men. Age range is from 40-60 with mean age of 52.7 yrs. However case reports have been seen in children.

Etiology

Pathogenesis of Sjogren's disease is believed to multifactorial. Known to be autoimmune, but studies have suggested that the disease process has been genetic, environmental and neuroendocrine.

HLA-DR genotype is the genetic predominance of Sjogren's disease. HLA-DR is a major histocompatibility complex, MHC class II cell surface receptor, that is found in antigen presenting cells. This genotype also produces an abnormal amount of chemokines compared to patients without the disease.

The trigger to Sjogren's has been postulated to be immunologic, environmental, or neuroendocrine. Environmental factors include links to Epstein-Barr virus, hepatitis C, HIV, and Human T-cell leukemia virus-1. Whatever the trigger, afterwards a glandular tissue autoimmune complex then becomes infiltrated with lymphocytes of CD4 cell type. These CD4 interact with the MHC class II receptors and initiate a cascade of events that include release of cytokine IL-1, TNF alpha, and interferon-gamma. Subsequent destruction of tissue and interference with acetylcholine release occurs, which leads to gland dysfunction.

Clinical Manifestations

Sjogren's disease, like any autoimmune disease has a multitude of symptoms which involve a multitude of organ systems. These include but not limited to

Glandular, ocular, oral, otological, laryngeal, thyroid, pulmonary, sinus, hepatobiliary, gastrointestinal, genitourinary, musculoskeletal, vascular, neurologic, and hematologic/lymphatic.

Ocular glandular manifestations include decrease lacrimal flow, Conjunctiva damage, dry eyes, foreign body sensation, irritation, photosensitivity, and ultimately visual impairment.

Now oral glandular manifestations include persistent salivary enlargement, tongue fissures, frequent mouth infections including fungal infections, and most commonly dental caries, especially at root and incisors.

Other manifestations include decrease hearing secondary to immune complexes in the stria vasularis. They may also have hoarseness secondary to bamboo node on the vocal cords, which are frequently seen in autoimmune disease. Also seen frequently are thyroid abnormalities such as Hashimoto's thyroiditis, which can be found in up to 1/2 pt. 10-15% of Sjogren's syndrome pt have hypothyroidism. It is important to evaluate every Sjogren's syndrome pt for routine thyroid function tests. Epistaxis, nasal crusting, xerotrachea, dyspnea, esophageal spasms and dysmotility, atrophic gastritis and celiac disease are also possible ENT manifestations of Sjogren's syndrome. Each must be worked up appropriately and treated symptomatically as there is no cure for Sjogren's syndrome.

One very serious and life threatening complication of Sjogren's syndrome is the risk of lymphoma. This typically shows up late in the disease, with an increase risk of 44 times greater than the general public. Lymphomas are classified as marginal B-cell lymphomas caused by chronic irritation, similar to H. pylori infections in gastritis.

Other non-ENT manifestations include vasculitis, palpable purpura, petechiae, subcutaneous nodules, renal involvement in up to 10% of patients, which includes renal tubular acidosis secondary to hyper-gammaglobulinemia, myalgias, arthralgias, fatigue, and malaise.

Clinical criteria for diagnosis

In 2002, an American-European consensus group was developed to create an international criterion for diagnosis. This was formed because US and European criteria differed so much that there were 10 times as many Europeans with Sjogren's disease than in US. This causes significant problems with clinical trials and publication reports. This new criteria included ocular symptom, oral symptoms, objective evidence of dry eyes and salivary gland involvement and lastly laboratory abnormalities.

For ocular symptoms at least one of the following must be present- persistent dry eye for 3 months, recurrent sensation of sand or gravel in eyes, or use of tear substitute for more than three times a day.

For oral symptom, again at least one of the following must be present- feeling of dry mouth every day for more than 3 months, recurrent swollen salivary glands as an adult, or need to drink liquids to swallow dry foods.

Objective evidence of dry eyes includes at least one of the following- Schirmer's test or Rose-Bengal test. Schirmer's test consists of placing a small strip of filter paper inside lower eyelids, with eye closed for 5 minutes. The paper is removed and amount of moisture is measured. If less than 5 mm movement of moisture down the paper is measured, then this is positive for Sjogren's syndrome. Rose-Bengal dye is a stain of sodium salt that stains red any damage to conjunctiva or corneal cells. The amount of damage is measure and if found to be a significant amount, then the patient is positive for Sjogren's disease.

Another criterion for diagnosis includes salivary gland biopsy. A focal lymphocytic infiltrate in minor salivary gland, containing more than 50 lymphocytes per 4 mm of glandular tissue, is diagnostic positive.

Next, is the objective evidence of salivary gland involvement. A least one of the three must be positive

1. Salivary-gland scintigraphy which must show delayed uptake of technetium-99m
2. Parotid sialography or
3. Unstimulated whole sialometry, which is the measurement of total salivary production. If it is less than 1.5 ml in 15 minutes, then this is positive.

The last criterion is laboratory abnormality in which one must be present- Anti-SS-A (Ro), Anti-SS B (La), ANA, or IgM rheumatoid factor.

Both Sjogren's syndrome types have marked hyper-gammaglobulinemia of IgM, elevated protein and sedimentation rates, with persistent rheumatoid factors and low WBC counts. However, Anti-SSA/B antibodies are seen in approximately 60% of patients and have increased disease morbidity. All these tests are non-specific due to them being seen in other autoimmune diseases.

In order to be diagnosed with Primary Sjogren's one must have 4 of the 6 diagnostic criteria. For secondary Sjogren's syndrome, one must be diagnosed with an autoimmune disease and positive category 1 or 2, and be positive in 2 of the remaining 4 criteria.

Exclusion criteria do exist. If a patient had previous head and neck radiation, has Hep C, AIDS, a pre-existing lymphoma or sarcoidosis, a graft vs. host disease or using anticholinergic drugs, they cannot be diagnosed with Sjogren's syndrome.

Prognosis and Treatment

Sjogren's syndrome is slow in its course, as with all autoimmune diseases. Therapy is to treat symptoms. However, the risk of lymphomas is high, and a concern for mortality from the disease.

Symptomatic treatments include artificial tears, tear and salivary stimulators, immunosuppressive drugs, surgical procedures, salivary substitutions, humidification, PPI. One must also have frequent dental visits to care for dental caries, and treat infection of bacterial and fungal regularly.

Pilocarpine was the first FDA approved anti-muscarinic therapy proved useful for stimulation of tears and saliva. A next generation anti-muscarinic therapy Evoxac is also being used. It has less of the cardiac side effect of muscarinic therapy.

The systemic effects of all autoimmune diseases such as muscle pain, renal impairment and pulmonary involvement benefit from use of steroids and other immune modulators. However, these therapies have been proven not to help with the sicca symptoms of Sjogren's disease.

In conclusion, Sjogren's disease has many early ENT manifestations that may be encountered first by otolaryngologist. It is therefore important that the practicing otolaryngologist be aware of this disease and be able to diagnosis the disease. The otolaryngologist is also an important part of the multidisciplinary team by providing biopsies and aiding in treatment.

DISCUSSANT: Susan McCammon, MD:

That was very good Dr. Martinez. Thank you.

One of the reasons why Sjogren's is included in the area of our specialty is that we see many patients who have been told they have Sjogren's, or they have symptoms included in the syndrome, and they wind up in an ENT office.

I want to describe a couple of my own cases.

A 65 year old woman with a neck mass present intermittently for about a year in level one, sometimes in both sides of level one. It had been FNA'd by her primary care physician with nondiagnostic results.

Past medical history was significant for breast cancer treated on protocol with chemotherapeutic agents. She came to me for excision of the neck mass. We worked her up and it really felt like chronic submandibular sialadenitis.

We noticed during the exam that she did not have a dry mouth but she couldn't talk because she didn't have enough saliva to moisten her lips. But it wasn't until one or two visits later that I questioned her specifically about dry mouth and dry eyes and she admits to both conditions. We tested her and she ended up being positive for SS-A and SS-B and rheumatoid factor.

We must remember not to allow ourselves to become too tightly focused on the presenting complaint, such that we overlook obvious yet seemingly unrelated observations which may lead us to the correct diagnosis.

The other class of patients are those sent to me for a lip biopsy to confirm the diagnosis of Sjogren's syndrome.

There is a tendency to see the patient, do the biopsy, and send them home and since they are being seen by a rheumatologist, that's that. It is better, however, always to followup these patients yourself after educating them on self-examination of the parotid glands.

I always draw thyroid functions on these patients and I always do a good oral exam and I tell them about good oral care and to watch for any change in their saliva.

During my training I saw a localized carcinoma which had arisen in response to the bad oral hygiene in a typical Sjogren's patient.

These are just two examples of how these patients will present in your practice.

Occasionally I get requests for parotid biopsy but I never have found it necessary or advisable to do parotid salivary gland biopsies to confirm the diagnosis of Sjogren's.

Also, I get a steady stream of patients from Neurology here requesting lip biopsies in patients with absolutely no symptoms of Sjogren's syndrome, and it is unclear to me what neurological disorder they hope to uncover by this means. None of these biopsies have been positive.

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