Review Article

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Sjogren's Syndrome: An Overview

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ABSTRACT

Background: As part of the triad of Sjogren's syndrome (SS), keratoconjunctivitis sicca (KCS) can be found in virtually all SS patients. The cause of the disease remains unclear. The syndrome develops slowly with progressive enlargement of salivary glands particularly the parotid gland bilaterally. There are multiple diagnostic procedures to diagnose Sjogrens syndrome. The early and accurate establishment of a correct diagnosis of SS can assist on the prevention and timely treatment of many complications associated with the disease's natural course. The treatment of the patient with Sjogrens syndrome is mostly supportive. This paper discusses the details of Sjögrens syndrome including its clinical manifestations diagnostic evaluation and treatment.

Keywords: Primary Sjogren's syndrome, Secondary Sjogren's syndrome, xerostomia, salivary glands, xeropthalmia.

INTRODUCTION

Sjögren syndrome is an autoimmune disease in which the mouth and eyes become extremely dry. Sjogren's syndrome is named after Henrik Sjogren (pronounced 'Shurgren'), the Swedish ophthalmologist who first described it in 1933[1]. The effects on the eye often are called keratoconjunctivitis sicca (sicca means "dry"), and the clinical presentation of both xerostomia and xerophthalmia is also sometimes called the sicca syndrome[2]. It is characterized by progressive lymphocytic infiltration that results in exocrine gland dysfunction. The cause of the disease remains unknown. It affects 1 in 2,000 persons, women in 90% of cases, and usually manifests between 35 and 50 years of age[3]. Sjogrens syndrome primarily affects peri- and post-menopausal women. The female to male ratio is 9:1.

Two forms of the disease are recognised[2]:

1. Primary Sjögren syndrome (sicca syndrome alone; no other autoimmune disorder is present)

2. Secondary Sjögren syndrome (the patient manifests sicca syndrome in addition to another associated autoimmune disease and dryness may affect other mucosal areas (nose, throat, trachea, vagina) and the skin and involve many organ systems (thyroid, lung, kidney, etc.) The cause of Sjögren syndrome is unknown. Although it is not a hereditary disease per se, there is evidence of a genetic influence. Examples of Sjögren syndrome have been reported in twins or in two or more members of the same family. Relatives of affected patients have an increased frequency of other autoimmune diseases[2].

CLINICAL MANIFESTATIONS:

Patients with sjogrens syndrome show complications resulting from dry mouth. Patients complain of dry mouth and a need to sip liquids throughout the day, this causes difficulty in chewing, swallowing and speaking. Additionally patients complain of dry and cracked lips, angular chelitis and burning sensation with spices, sensitive to heat and difficulty in wearing dentures.

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Intraorally, the mucosa appears pale and dry, friable, or furrowed. Salivary pooling is minimal and the saliva that is present tends to be thick, frothy and ropy. The tongue is often shows atrophy of papillae with fissures and is painful. Mucocutaneous candidal infections are common, particularly of the erythematous form. There is increased risk of caries and erosion due to decreased salivary flow.

Patients with Sjögren's syndrome may experience intermittent or chronic salivary gland enlargement. They are also susceptible to salivary gland infections and/or gland obstructions that present as acute exacerbations of chronically enlarged glands. There is diffuse, firm enlargement of major salivary gland and the swelling is usually bilateral, maybe non painful or slightly tender. Due to reduced salivary flow there are increased chances of retrograde bacterial sialadenitis. Parotid or major salivary gland enlargement occurs in 60% of primary Sjogren's syndrome patients[4]. Diminished tear production due to lacrimal gland involvement leads to the destruction of both corneal and bulbar conjunctival epithelium and a constellation of clinical findings termed keratoconjunctivitis sicca[4].

The lacrimal inflammation causes a decrease of the aqueous layer of the tear film; however, mucin production is normal and may result in a mucoid discharge. Patients often complain of a scratchy, gritty sensation or the perceived presence of a foreign body in the eye. Vision may become blurred, and sometimes there is an aching pain. The ocular manifestations are least severe in the morning on wakening and become more pronounced as the day progresses. Dryness of the upper respiratory tract or the oropharynx causes hoarseness, recurrent bronchitis, and pneumonitis. Loss of exocrine function may also lead to loss of pancreatic function and hypochlorhydria. Patients may also experience dermal dryness and loss of vaginal secretions[4]. There is an increased risk of patients with Sjogrens syndrome developing malignant lymphoma, most commonly mucosa- associated B-cell lymphomas (MALT lymphomas) involving the salivary glands[4].

DIAGNOSIS:

The early and accurate establishment of a correct diagnosis of SS can assist in the prevention and timely treatment of many complications associated with the disease's natural course. Even though minor salivary gland biopsy has been traditionally considered the gold standard for the diagnosis of SS, the diagnosis of SS is based on an internationally approved set of criteria and is usually a clinical one based on the history and physical examination with support from laboratory data.

Evalution of xeropthalmia:

SS shows involvement of ocular gland and a method to test decreased tear production is Schrimmers test. A standardized strip (with 5 mm width and 35 mm length) of sterile filter paper is placed over the margin of the lower eyelid, between the medial and lateral third of the lid of the unanesthetized eye, so that the tabbed end rests just inside the lower lid. By measuring the length of wetting of the filter paper, tear production can be assessed. Values less than 5 mm (after a 5-minute period) are considered diagnostic of keratoconjunctivitis sicca.

Alternatively, positive ocular surface Rose Bengal or other ocular dye score, (i.e., fluorescein vital staining, lissamine green, etc.) can also be conducted. These tests are most commonly used for the evaluation of ocular surface epithelial damage, since these vital stains mark cells, on the surface of the eye, that are not fully coated by the mucin layer of tear fluid and/or are damaged. The Rose Bengal score, a quantified version of the original. Rose Bengal test, is commonly used to quantify the degree of staining[5,6]. The test is conducted by the application of a 1% solution of Rose Bengal, within the inferior fornix of both eyes. The patient should be following asked to make one or two full blinks. The examiner uses white light to assess the amount of staining, in the two exposed conjunctival zones (medial and lateral) and cornea. Each section is scored up to 3 points, according to the Van Bijsterveld score: 1, sparsely scattered spots; 2, densely scattered spots; and 3, confluent spots). While the maximum score is 9, a score of 4 or more, or 3 or more, was considered diagnostic of SS, according to the International classification criteria, or Japanese criteria for SS, respectively. In patients with SS, Rose Bengal staining can cause the eyes to sting and the test may be painful. Scoring with lissamine green stain is less painful, but more difficult to evaluate[5,6].

The tear break up time (BUT) test aims to measure the quality of the tear fluid[5]. It is defined as the

interval between a complete blink and the appearance of the first randomly distributed drys pots. Usually, a 1% fluorescein solution is carefully placed in the inferior fornix of both eyes. The patient is then asked to blink a few times, and then, it is examined how long the tear film remains evenly distributed over the surface of the cornea[6]. The tear film normally remains intact for 10 seconds or longer, being highly abnormal in SS-affected individuals[7].

Histopathological analysis:

Minor salivary gland biopsy remains a highly used diagnostic procedure for the salivary component of SS. This is usually performed on the internal face of the lower lip on normal- appearing mucosa. Under local anaesthesia an incision of around 1.5 to 2 cm is made between midline and the commissure, through the mucosa with penetration of the epithelium. With this procedure, usually 5 or more minor salivary glands are excised. A grading system exists for quantifying the salivary histologic changes seen in the minor glands, as follows:

— the numbers of infiltrating mononuclear cells are determined, with an aggregate of 50 or more cells being termed a focus;

— the total number of foci and the surface area of the specimen are determined;

— the number of foci per 4 mm2 is calculated. this constitutes the focus score.

The range is from 0 to 12, with 12 denoting confluent infiltrates. A focus score of 1 is considered positive for salivary involvement consistent with Sjögren's syndrome.

A false negative result ranges from around 20 to 40% and also positive biopsy results have been found up to 10% of healthy individuals[8]. There are factors that affect the focus score determination like presence of autoimmune diseases, density of infiltrate etc.

Serological tests:

A positive rheumatoid factor (RF) is found in approximately 60% of cases, regardless of whether the patient has rheumatoid arthritis. Elevated RA factor more than 1:320 is a dingostic criteria for SS as per San Diego diagnostic criteria.

Antinuclear antibodies (ANAs) are also present in 75% to 85% of patients, and elevated ANAs more than 1:320 is diagnostic of SS as per San Diego diagnostic criteria. Two particular nuclear autoantibodies—anti-SS-A (anti-Ro) and anti- SS-B (anti-La)—may be found, especially in patients with primary Sjögren syndrome. Anti-SS-A antibodies have been detected in approximately 40% of patients, whereas anti-SS-B antibodies have been discovered in about 25% of these individuals. Occasionally, salivary duct autoantibodies also can be demonstrated, usually in secondary Sjögren syndrome.

Salivary gland testing:

Sialometry aims to measure the saliva flow function. The saliva collected can be whole saliva or saliva obtained from a specific gland which maybe or unstimulated saliva. The no obvious correlations of oral dryness with the measurements of saliva function are however unclear. There are various methods to collect saliva and depending upon the amount collected hypo salivation can be determined thereby determining xerostomia. The presence of xerostomia alone does not confirm a positive Sjogrens syndrome.

Sialography is one of the oldest modality to study the ductal system of the salivary gland described by Carpy. The technique involves a radiopaque dye injected into the ducts of the gland following which a radiographic image is obtained. Sialography studies may show presence of globular, punctuate or cavitary pseudo sialectases in the gland that are filled with radiopaque dye. The appearance is because of the extravasation of the dye and not due to dilatation of the ductules, typically demonstrating a "fruit-laden, branchless tree, cherry blossom" pattern.

Scintigraphy or radioisotope scanning is a procedure in which radiopharmaceutical agent is injected. The functional changes taking place are then recorded as the agents emit radiation that is detected on special scintillation cameras. Scintigraphic studies in patients with SS show delayed appearance of tracer in the oral cavity due

to reduced salivary secretion. The test reports a high sensitivity but a low specificity in SS diagnosis.

MRI and USG:

MR imaging (MRI), MR sialography and Ultrasonography (USG) are noninvasive methodologies that allow the imaging of salivary glands in their physiological state without artefacts induced by intraductal contrast media or biopsy procedures. These imaging modalities allow a reduction in the inconveniences and risk of complications to the patient[9]. Recent advances in technical equipment allowed for the yield of such a definitive picture of the glandular structural changes that they are promising alternatives to conventional examinations[7].

MR imaging was shown to provide a reliable imaging procedure to evaluate glandular alterations. A salt and pepper appearance on the MRI scan is highly suggestive of Sjogrens syndrome. Characteristically, in SS, MRI reveals an inhomogeneous internal pattern on both T1 and T2 sequences, with multiple hypo- and hyper-intense nodules of different sizes[9]. The signal intensity in T1-weighted parotid MR images was found to increase proportionally to the severity of the disease[10]. Other MR modalities in the SS assessment have also been used,

including MR sialography, functional MR sialography, and dynamic contrast-enhanced MRI. The latter and tracer kinetic modelling were used to quantify the altered microvascular pathophysiologic features of salivary glands in SS. SS-affected patients were shown to report a great differentiation and an increased heterogeneity in microvascular parameters, comparing to controls[11].

USG is more effective on the parotid gland and less helpful in the assessment of other salivary glands. Moreover, it is a technique highly operator-dependent. Characteristic USG features of SS include an inhomogeneous structure of the gland (early stages), with scattered multiple small, oval, hypoechoic or anechoic areas of lymphocytic infiltrates (intermediate stages), and the presence of echogenic lines - fibrosis - that converge into a glandular reticular pattern (late stages) usually well defined. Other features, though more uncommonly found, may include the dilatation of the main duct, increased parenchymal blood flow (accessed by Doppler), pseudo masses, irregular cystic masses, and intraparotid lymph node enlargement[12].

TREATMENT:

The treatment of the patient with Sjögren syndrome is mostly supportive. Preventive measures should be taken before the manifestation of the sicca. The dry eyes are best managed by periodic use of artificial tears. Use of artificial tear drops and ocular ointments for lubrication of dry eyes as often as necessary. The suitable preparation differs from patient to patient and are tested by the patient as per their needs. Attempts can be made to conserve the tear film through the use of sealed glasses to prevent evaporation. Sealing the lacrimal punctum at the inner margin of the eyelids also can be helpful by blocking the normal drainage of any lacrimal secretions into the nose. A number of factors can also increase the dryness of eyes like the use of certain drugs like anti- Parkinsonian agents, tricycle antidepressants, antispasmodics etc. which should be avoided. There are a number of commercially available preparations of artificial tears and ocular ointments namely HypoTears, Tear Plus (polyvinyl alcohol), AquaSite (polyethylene glycol), Adsorbotear, Hydrxy-E-Cel (Hydroxyethyl cellulose), Duratears (white petrolatum).

A minor procedure to seal the tear ducts that drain tears from your eyes (punctal occlusion) might help relieve your dry eyes. Collagen or silicone plugs are inserted into the ducts to help preserve your tears[13]. Management of the oral consequences of salivary dysfunction is not different from those in other causes of secretory damage. However, the treatment of xerostomia may be difficult. The primary treatment in xerostomia is use of artificial saliva, sugarless candy or gum or other secretagogues to keep the mouth moist. Drying of mouth should be prevented by avoiding smoking and use of drugs that can cause xerostomia like anti-Parkinsonian agents, antihypertensives, antispasmodics etc. and the use of nasal sprays have shown reduced dryness of mouth and thereby prevent mouth breathing. Symptoms often can be relieved by the use of oral hygiene products that contain lactoperoxidase, lysozyme, and lactoferrin. Sialagogue medications, such as pilocarpine and cevimeline, can be useful to stimulate salivary flow.

Increased salivary flow rate can occur within 15 minutes of oral-dose pilocarpine hydrochloride 5 mg (generally administered four times daily) and can last for at least 4 hours[14]. Cevimeline (30 mg three times daily) has also been shown also to increase the salivary flow[15]. Frequent sipping of water and use of artificial saliva like wet mouth, xerolube show symptomatic relief. Moisturising agents such as paraffin oil or vaseline or cold cream can be applied to cracked lips for symptomatic relief. Because of the increased risk of dental caries, daily fluoride applications may be indicated in dentulous patients. Antifungal therapy often is needed to treat secondary candidiasis.

Secondary Sjogrens syndrome that may include autoimmune diseases have to be treated with the use of NSAIDs, corticosteroids, hydroxychloroquine that will help in treating the joint pain and inflammation as with rheumatoid arthritis.

Another approach has been to modify the inflammatory cytokine pathway, specifically targeting tumor necrosis factor a (TNF-α). anti-TNF-α agents, including etanercept, in- fliximab, and thalidomide, have shown no significant efficacy for dry mouth symptoms or salivary function in randomized controlled trials in Sjögren's syndrome[16].

CONCLUSIONS

The diagnosis of sjogrens syndrome is often delayed as the symptoms overlap other autoimmune diseases such as scleroderma, rheumatoid arthritis, systemic lupus erythromatosus. Proper patient identification is essential in order to avoid complications from untreated sicca symptoms, and to treat morbidity from internal organ manifestations and associated autoimmune diseases. Since there is no validated and simple test for the diagnosis of SS, a straighter forward and easy test for assessment for diagnosis of SS is highly demanded. The use of all the available diagnostic methods helps reduce the time needed for the diagnosis of SS and thereby can improve the quality of life of patients with SS.

CONFLICTS OF INTEREST

The authors declare they have no potential conflict of interests regarding this article.

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