

Review Article

SJOGREN'S SYNDROME: A REVIEW OF CLINICAL FEATURES, DIAGNOSIS AND TREATMENTS AVAILABLE

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ABSTRACT

Sjogren's syndrome (SS) (also known as "Mikulicz disease" and "Sicca syndrome") is a slowly progressive disease characterized by chronic inflammation of the exocrine glands. It is characterized by the Xerostomia, Keratoconjunctivitis sicca and B-lymphocytes hyperactivity. Salivary and lacrimal glands are the most affected, thus leading to mouth and eye dryness. Prevalence of primary-SS in the general population has been estimated to be around 1 to 3%. Nine out of ten Sjogren's patients are women and the average age of onset is late 40s, although Sjogren's occurs in all age groups in both women and men. In the majority of the patients, SS has an indolent or slowly progressive course with disease confined in exocrine glands. At presentation or during the course of the disease, almost one third of the primary-SS patients experience a more generalized disease, which does not usually evolve the failure of the affected organ. The most important complication is a 44-fold increase in the risk of developing non-Hodgkin lymphoma, compared with the general population. The treatment of Sjogren's syndrome is limited to symptomatic management, and involves the use of solutions to replace salivary secretion and afford a measure of hydration, cholinergic agents such as pilocarpine to stimulate the unaffected gland tissue and, recently, the administration of substances that act against surface antigens of the B lymphocytes, such as anti-CD20 and anti-CD22 antibodies. The present study provides an update on this disease, placing special emphasis on its odontologic implications.

Keywords: Autoimmune rheumatic diseases, exocrine glands, Primary Sjogren's syndrome, Secondary Sjogren's syndrome, xerostomia.

INTRODUCTION

Sjogren's syndrome is named after Henrik Sjogren (pronounced 'Shurgren'), the Swedish ophthalmologist who first described it in 1933¹. It is an autoimmune disorder, meaning the body's immune system, which usually fights infections, attacks the body's own tissues. The most common symptoms of the disease are dry eyes or a dry mouth (sometimes both together), and feeling very tired and aching. In addition, Sjogren's syndrome may cause skin, nose, and vaginal dryness, and may affect other organs of the body, including the kidneys, blood vessels, lungs, liver, pancreas, peripheral nervous system (distal axonal sensory motor neuropathy) and brain.

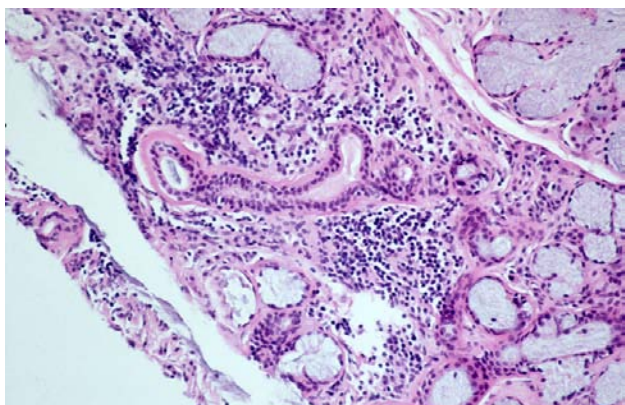


Figure 1: Histopathologic image of focal lymphoid infiltration in the minor salivary gland associated with Sjogren syndrome. Lip biopsy. H & E stain.

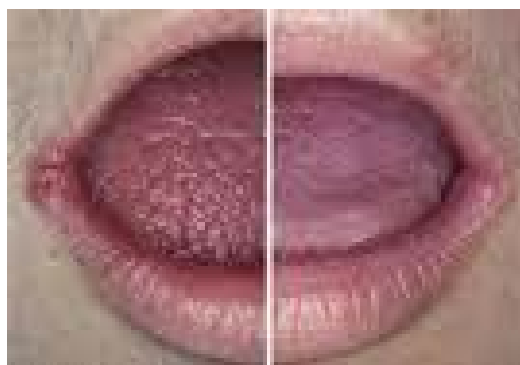


Figure 2: Chronic erythematous candidiasis on the dorsal surface of the tongue, and bilateral angle cheilitis.

Sjogren's syndrome causes increased levels of IL-1RA in CSF suggesting increased activity in the interleukin 1 system and that this is associated with increased fatigue through cytokine induced sickness behavior². Patients with secondary Sjogren's syndrome also have signs and symptoms associated with rheumatic disorder. Many patients also have IBS symptoms due to slow gastric transit.

CLINICAL FEATURES

Sjogren's disease usually runs an indolent course. Initial manifestations may be mild, and years may elapse from the initial manifestations to the full blown development and recognition of the syndrome.



Glandular manifestations

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 (KCS)³. Patients usually complain of a burning, sandy, or scratchy sensation under the lids, itchiness, redness, and mild photophobia. Physical signs include dilation of the bulbar conjunctival vessels, pericorneal injection, irregularity of the corneal image, and lacrimal gland enlargement. Xerostomia, or dry mouth, is the result of the decreased production of saliva by the salivary glands. Patients report difficulty swallowing dry food, inability to speak continuously, changes in sense of taste, a burning sensation in the mouth, an increase in dental caries, and problems in wearing complete dentures. Physical examination may show a dry erythematous sticky oral mucosa, poor dentition, scant and cloudy saliva from the major salivary glands, and atrophy of the filiform papillae on the dorsal tongue. Parotid or major salivary gland enlargement occurs in 60% of primary Sjogren's syndrome patients. The parotid gland enlargement may be episodic or chronic, unilateral or bilateral. 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.



Figure 3: Parotid gland swelling in a patient with Sjogren's Syndrome

Extraglandular manifestations

Approximately 50% of patients with the clinical picture of Sjogren's syndrome have systemic manifestations that can include general constitutional symptoms such as easy fatigability and low-grade fever, as well as specific organ involvement. There is debate whether many of these patients may actually have undifferentiated or overlap connective tissue diseases with prominent secondary Sjogren's syndrome, but this is an academic question, and patients should be treated according to their clinical problems and not according to putative diagnoses. Extraglandular manifestations are divided into two major groups. Periepithelial organ involvement (e.g., arthritis, interstitial nephritis, liver involvement, obstructive bronchiolitis) is the result of lymphocytic infiltration of affected organs. These features appear early in the

disease and usually have a benign course. In contrast, extraepithelial manifestations (e.g., palpable purpura, glomerulonephritis, and peripheral neuropathy) are caused by immune complex deposition disease secondary to the ongoing B cell hyper-reactivity. These features are usually observed late in the disease and are associated with increased morbidity and risk for the development of lymphoma¹⁶.

Respiratory tract Disease

Manifestations from the respiratory tract and the pleura are frequent but rarely dangerous. A nonproductive cough secondary to dryness of tracheobronchial mucosa (xerotrachea) or dyspnea due to small airway obstruction is relatively common¹⁷. High-resolution CT of the lungs often demonstrate wall thickening at the segmental bronchi, and bronchial biopsy shows peribronchial and/or peribronchiolar mononuclear inflammation. Interstitial lung disease in Sjogren's syndrome is less common. Pleural effusions are infrequently found in primary Sjogren's syndrome. Lymphoma should always be suspected when lung nodules or hilar or mediastinal lymphadenopathy are present in chest radiographs.

Musculoskeleton symptoms

Musculoskeletal manifestations can include polyarthralgias, polymyalgias, morning stiffness, intermittent inflammatory synovitis, and chronic polyarthritis. Despite myalgia and easy fatigue, frank myositis is unusual. Inflammatory arthritis is observed in 50% of patients but, in contrast to RA, there are usually no erosive changes. Rare cases of inflammatory myositis have been reported.

Gastrointestinal and Hepatobiliary features

Patients with Sjogren's syndrome often report dysphagia due to either dryness of the pharynx and esophagus or abnormal esophageal motility. Nausea and epigastric pain are also common clinical symptoms. Gastric mucosa biopsy specimens show chronic atrophic gastritis and lymphocytic infiltrates similar to those described in minor salivary gland biopsy. Subclinical pancreatic involvement is rather common, with hyperamylasemia found in approximately 25% of patients. Patients often present with hepatomegaly (25%) and antimitochondrial antibodies (AMA) (5%). Liver biopsy generally reveals mild intrahepatic bile duct inflammation.

In patients with gastritis, helicobacter pylori infection should be sought because of its association with gastric mucosa-associated lymphoid tissue lymphomas¹⁸.

Lymphoproliferative disease

The prevalence of non-Hodgkin's lymphoma (NHL) in primary and secondary Sjogren's syndrome is 4.3%, representing a relative risk of 44-fold compared to age, sex, and race matched healthy individuals. Before the development of NHL, patients with primary Sjogren's syndrome may have monoclonal immunoglobulins or light chains in their serum and urine. Moreover, 20% of



patients have mixed monoclonal cryoglobulins (type II) containing an IgM monoclonal rheumatoid factor. Serial studies have shown that the presence of mixed monoclonal cryoglobulinemia correlates with lymphoma development in patients with primary Sjogren's syndrome. Persistent parotid gland enlargement, purpura, leukopenia, cryoglobulinemia, and low C4 complement levels are clinical manifestations that should raise the suspicion of lymphoma development. Most lymphomas are extranodal and low grade and are often detected incidentally upon the evaluation of labial biopsy. The median time between the initial diagnosis of Sjogren's syndrome and the diagnosis of lymphoma is 7.5 years. Constitutional "B" symptoms (i.e., fever, fatigue, and night sweats) are usually not present at the initial diagnosis of lymphoma in Sjogren's syndrome. Poor prognostic factors include the presence of "B" symptoms, lymph node size >7 cm, and high or intermediate histologic grade. NHL in Sjogren's syndrome is of B cell origin, and dysregulation of the p53 tumor suppressor gene has been suggested as an important contributing pathogenic factor.

Raynaud's phenomenon

As many as 35% of patients present with Raynaud's phenomenon that commonly precedes sicca manifestations by many years. Patients with Raynaud's phenomenon present with swollen hands but, in contrast to scleroderma, telangiectasias or digital ulcers are not typical. However, hand radiographs of these patients may show small soft tissue calcifications.

Renal involvement

Clinically significant renal disease is observed in approximately 5% of patients with primary Sjogren's syndrome, presenting with either interstitial nephritis or glomerulonephritis. Interstitial nephritis is usually an early feature and is characterized by an interstitial lymphocytic infiltration. Affected patients present with hyposthenuria and hypokalemic-hyperchloremic distal renal tubular acidosis (RTA). Distal RTA may be clinically silent, but untreated significant RTA may lead to renal stones, nephrocalcinosis, and compromised renal function. Glomerulonephritis is an uncommon late sequela. Membranous or membranoproliferative glomerulonephritis in Sjogren's syndrome has been described in a few patients. Cryoglobulinemia, associated with hypocomplementemia, is a consistent serologic finding in these patients.

Vasculitis

Vasculitis, found in approximately 5% of Sjogren's syndrome patients, affects small and medium-sized vessels and presents most commonly as palpable purpura, recurrent urticaria, skin ulcerations, and mononeuritis multiplex. Uncommon cases of systemic vasculitis with visceral involvement affecting kidneys, lungs, gastrointestinal tract, spleen, breasts, and reproductive tract have been described.

Cutaneous and Neurologic involvement

Cutaneous manifestations can include purpura, annular erythema, and pernio-like lesions. Flat purpura is usually seen in patients with hypergammaglobulinemia, whereas palpable purpura is a manifestation of dermal vasculitis^{19,20}. Annular erythemas have been described in patients with Sjogren's syndrome from Japan.

The occurrence of central nervous system and spinal cord involvement in Sjogren syndrome is estimated by various studies at 8-40%, with manifestations including myelopathy, optic neuropathy, seizures, cognitive dysfunction, and encephalopathy^{21,24,25}. Attempts must be made to distinguish other causes of these symptoms, including concomitant SLE, multiple sclerosis, cerebrovascular disease, and Alzheimer disease. Sensory, motor, or sensorimotor peripheral neuropathy, often subclinical, can be detected in up to 55% of unselected patients with Sjogren syndrome²². Symptoms of distal paresthesias may be present. Cranial neuropathies can develop particularly trigeminal neuropathy or facial nerve palsy. Mononeuritis multiplex should prompt a search for a vasculitis. Progressive weakness and paralysis secondary to hypokalemia due to underlying renal tubular acidosis can occur and is potentially treatable²³.

Other manifestations

Anti-thyroid antibodies and abnormal thyroid-hormone stimulation tests are common, but clinically overt autoimmune thyroiditis is not frequent. In a recent study, no significant has been observed in the prevalence of autoimmune and non-autoimmune thyroid disease between SS patients and controls⁴. Sensorineural hearing loss is reported to occur in 20-45% of the SS patients. Fertility, parity and sexual activity are not affected apparently, whereas insufficient vaginal lubrication causing dyspareunia appears to be correlated with atrophic vaginitis and perivascular infiltration. Elevated erythrocyte sedimentation rate is detected in approximately 70% of the patients.

DIAGNOSIS

Diagnosis of Sjogren's syndrome is based on an internationally approved set of criteria. The sensitivity and specificity of the diagnostic criteria exhibited good discrimination between patients and controls. Although lip biopsy for examination of minor salivary glands is the most common invasive diagnostic procedure for Sjogren's syndrome, the diagnosis is usually a clinical one based on the history and physical examination with support from laboratory data.

Serologic Testing

Anti-Ro (SSA) and anti-La (SSB) antibodies are included as part of the diagnostic criteria for Sjogren's syndrome and should be assessed in all patients considered for this diagnosis. Additional testing for autoantibodies (e.g., antinuclear antibodies, rheumatoid factor) can be helpful



in evaluating the possible presence of underlying disorders such as SLE or RA.

Lip Biopsy

Lip biopsy confirms lymphocytic infiltration of the minor salivary glands. Focal aggregates of at least 50 lymphocytes and plasma cells and adjacent to ducts and replacing acini are seen in patients with Sjogren's syndrome. However, the lymphocytic foci are not present in all minor salivary glands, and multiple glands should be examined to secure an accurate diagnosis⁵. This is the most accurate test available, though it is not essential for the diagnosis. When combined with sialometry, the diagnostic specificity is 95%²⁶. Sialometry takes as reference the total amount of saliva under resting and stimulated conditions – stimulation being carried out via a mechanical process such as chewing paraffin, or chemically in the form of 2% citric acid, for example. Abnormal values are considered to be less than 0.1 ml/min of saliva under baseline conditions and less than 0.7 ml/min with stimulation²⁷. The collection of saliva from a single gland (generally the parotid) is usually not performed.

When the lip biopsy proves inconclusive, sialometry and the presence of circulating auto-antibodies may provide the key to diagnosis⁵. Serology is used to establish the presence of anti-SS-A/Ro and anti-SS-B/La auto-antibodies, based on ELISA (enzyme-linked immune sorbent assay). Anti-SS-A/Ro antibodies can also be detected in other autoimmune processes such as rheumatoid arthritis and systemic lupus erythematosus; for this reason, anti-SS-B/La antibodies are considered to be more specific of SS²⁸. These antibodies concentrate in the nucleoplasm and cytoplasm of the acinar cells, with a diffuse or perinuclear distribution, and their presence is associated to prolonged duration of the disease, recurrent parotid gland enlargement, and florid extraglandular symptoms.

Evaluation of Xerostomia

Various tests of salivary gland function have been developed. These include direct measurement of salivary flow (sialometry), radiocontrast assessment of salivary ductal system (sialography), and functional evaluation of the rate and density of salivary gland uptake of ⁹⁹Tc^mpertechnetate (scintigraphic isotope scanning). These tests are primarily used in clinical trials, rarely to confirm the diagnosis in routine clinical practice.

Evaluation of Xerophthalmia

Ocular involvement leading to keratoconjunctivitis sicca is a major glandular manifestation of Sjogren's syndrome. All tests for the evaluation of this condition are very sensitive but not specific for Sjogren's syndrome.

Schirmer's Test

The tip of a strip of filter paper 30 mm long is slipped beneath the inferior lid, with the remainder of the paper hanging out. After 5 minutes, the length of paper wetted

is measured. Wetting of less than 5 mm is a strong indication of diminished tearing.

Rose Bengal Staining

Rose bengal is an aniline compound that stains the devitalized or damaged epithelium of both the cornea and conjunctiva. In Sjogren's syndrome, slitlamp examination after rose bengal staining shows a punctate pattern of filamentary keratitis.

Tear Break-up Time:

A drop of fluorescein is instilled into the eye, and the time between the last blink and appearance of dark, nonfluorescent areas in the tear film is measured. An overly rapid break-up of the tear film indicates an abnormality of either the mucin or the lipid layer.

TREATMENT AND MANAGEMENT

Prevention and treatment of sicca and constitutional symptoms are among the primary objectives of management of Sjogren's syndrome. These objectives can generally be accomplished without rheumatology consultation, because Sjogren's syndrome is a chronic disease with a broad clinical spectrum, patients should also be regularly followed for significant functional deterioration and evidence of disease complications such as extra glandular involvement or lymphoma; if these occur, specialty consultation is appropriate.

Treat of Sicca Symptoms

A preventive measure for sicca manifestations is very important. Lubrication of dry eyes with artificial tear drops and ocular ointments should be done as often as necessary, even hourly if required. A variety of commercially available preparations differ primarily in viscosity and type of preservative. Patients usually test several different preparations to determine which is most suitable for their individual needs. Bicarbonate-buffered electrolyte solutions, which mimic the electrolyte composition of human tears, have shown promising results. Avoidance of windy and/or low humidity indoor and outdoor environments is helpful. Cigarette smoking and drugs with anticholinergic side effects such as phenothiazines, tricyclic antidepressants, antispasmodics, and anti-Parkinsonian agents should be avoided. Oral pilocarpine 5 mg four times daily has been shown to reduce the ocular symptoms of Sjogren's syndrome without serious adverse effects^{6,7}. Topical administration of cyclosporine 0.05% has been shown to be moderately effective in a placebo-controlled clinical trial and is now FDA approved for keratoconjunctivitis sicca⁸. In severely dry eyes, punctal cauterization should be used. When corneal opacification or perforation occurs, corneal transplantation is recommended.

Commercially Available Preparations of Artificial Tears and Ocular Ointments

- Hydroxyethyl cellulose (Adsorbotear)
- White petrolatum (Duratears, Lacrilube)



- Polyvinyl alcohol (HypoTears, Liquifilm Forte, Tears Plus)
- Polyethylene glycol (AquaSite)
- Hydroxypropyl methylcellulose (Bion Tears, Tears Naturale)
- Methylcellulose (Murocel)
- Carboxymethylcellulose (Refresh Plus)

Treatment of Xerostomia

Treatment of xerostomia is difficult. No single method is consistently effective, and most efforts are aimed only at palliation. Stimulation of salivary flow by sugar-free highly flavored lozenges is helpful. Various artificial saliva preparations are available, but they tend to be not highly liked by patients. Conscientious oral hygiene after meals is a prerequisite for prevention of dental disease. Topical treatment with stannous fluoride enhances dental mineralization and retards damage to tooth surfaces. In cases of rapidly progressive dental disease, the fluoride can be directly applied to the teeth from plastic trays that are used at night. Two muscarinic agonists, pilocarpine hydrochloride (Salagen) and cevimeline (Evoxac), have recently been approved for the treatment of symptoms of xerostomia in Sjögren's syndrome. These agents stimulate the M1 and M3 muscarinic receptors present on salivary glands, leading to increased secretory function (9). 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 hours⁶. Cevimeline (30 mg three times daily) has also been shown also to increase the salivary flow¹⁰. Pilocarpine and cevimeline can cause transient hemodynamic changes and arrhythmias and should be used with caution in patients with cardiovascular disease. Side effects such as flushing, headache, and sweating are uncomfortable but usually mild.

Commercially Available Preparations of Artificial Saliva and Oral Lubricants

- Salivart
- Biotène Mouthwash
- MouthKote
- Xero-Lube
- Saliment

MEDICATIONS

(a). Nonsteroidal Anti-Inflammatory Drugs (NSAIDs): This group of medications, which includes aspirin, helps relieve both pain and inflammation. Side effects may include indigestion and stomach bleeding. Therefore, always take NSAIDs with food. Prescription NSAIDs can provide higher doses and more potency than over-the-counter types of NSAIDs.

(b). Corticosteroids: These medications reduce inflammation and may slow joint damage. In the short term, corticosteroids can make the patient feel

dramatically better. But when used for many months or years, they may become less effective and also cause serious side effects. Side effects may include easy bruising, thinning of bones, cataracts, weight gain, a round face, diabetes and high blood pressure.

(c). Hydroxychloroquine (Plaquenil): This antimalarial drug may be useful if the patient have inflamed joints, as with rheumatoid arthritis. It's not usually effective for the dryness caused by Sjogren's syndrome.

(d). Pilocarpine (Salagen): Pilocarpine prescribes if the patients have dry-mouth symptoms caused by Sjogren's syndrome

(e). Cevimeline (Evoxac): For Sjogren's syndrome this prescription medication is used to relieve symptoms of a dry mouth. The medication works by causing certain mouth glands to produce more saliva. Common side effects may include excessive sweating, nausea, and a runny or stuffy nose.

(f). Cyclosporine: Eye drops containing cyclosporine (Restasis) is recommending to treat symptoms of Sjogren's syndrome that affect your eyes.

(g). Immunosuppressant: These medications, such as cyclophosphamide (Cytoxan), methotrexate (Rheumatrex), mycophenolate (CellCept) and azathioprine (Imuran), suppress the immune system¹¹.

DRUG THERAPIES

Hydroxychloroquine

Hydroxychloroquine 200-400 mg/day can be effective in a subgroup of patients complaining of arthritis/artralgias, myalgias, and constitutional symptoms¹².

Methotrexate

An open trial of weekly methotrexate 0.2 mg/kg for the treatment of primary Sjogren's syndrome resulted in subjective improvement in symptoms of xerophthalmia and xerostomia, dry cough, and purpura, but there was no beneficial effect on objective measures of dry eyes and mouth¹³. Some of the musculoskeletal symptoms may respond to methotrexate, but the overall role of this drug in Sjogren's syndrome remains to be determined.

Systemic Corticosteroids and Cytotoxic Agents

Severe extraepithelial disease (e.g., diffuse interstitial pneumonitis, glomerulonephritis, vasculitis, peripheral neuropathy) requires high-dose systemic corticosteroid therapy (starting at prednisone 0.5-1.0 mg/kg daily or equivalent) and/or immunosuppressive therapy with agents such as cyclophosphamide. The duration of corticosteroid and/or immunosuppressive therapy is dictated by the severity of the disease manifestation. Typically, corticosteroid tapers are not initiated until control of the acute problem is achieved and then are conducted gradually over weeks to months with careful monitoring for disease relapses. When immunosuppressants are required, they are usually



maintained at least 6 months after a remission is obtained before they are tapered or discontinued. The impact of these agents on the natural course of Sjogren's syndrome is not well established.

TNF Inhibition

In a recent single-center, open-label pilot study, 16 patients with primary Sjogren's syndrome received three infusions of infliximab, a chimeric human-mouse anti-TNF-monoclonal antibody, at a dose of 3 mg/kg, at 0, 2, and 6 weeks¹⁴. There was statistically significant improvement in all clinical and functional parameters, including global assessments (patient's global assessment, patient's assessment of pain and fatigue, physician's global assessment), erythrocyte sedimentation rate, salivary flow rate, Schirmer's test, tender joint count, fatigue score, and dry eyes and dry mouth indices. However, a subsequent multi-center, randomized, double-blind, placebo-controlled study of 103 patients with primary Sjogren's syndrome did not demonstrate any efficacy for infliximab over 22 weeks¹⁵.

CONCLUSION

Sjogren's syndrome is frequently difficult to diagnose as it often overlaps with other diseases such as lupus, Rheumatoid Arthritis, Scleroderma and Polymyositis. People with Sjogren's syndrome may be more susceptible to drug allergies and care is needed to monitor their condition if medication is required. Drugs such as antihistamines and antidepressants can cause mucosal dryness and should only be taken in consultation with your doctor. It is important to remember that air-conditioning dries you out, and dust and smoke are irritating - avoid these wherever possible. Like all chronic diseases it is important to have regular contact with your doctor and eye specialist to monitor your condition. Regular dental checkups are essential. Although Sjogren's syndrome is not life threatening, careful attention to the problems it causes can help minimise the "nuisance" aspect of this condition and assist in a more relaxed way of living.

REFERENCES

- Sjogren H. Zur kenntis der keratoconjunctivitis sicca (keratitis filiformis bei hypofunktion der tranenduser). *Acta Ophthal*. 1933;2:1-151.
- Harboe E, Tjensvoll AB, Vefring HK, Gøransson LG, Kvaløy JT, Omdal R. (2009). Fatigue in primary Sjogren's syndrome--a link to sickness behaviour in animals? *Brain Behav Immun*.23(8):1104-8.
- Manoussakis MN, Moutsopoulos HM: sjogrens syndrome : autoimmune epithelitis. *Baillieres Best Pract Res Clin Rheumatol*; 14:73-95,2000.
- Ramos-Casals M, Garcia-Carrasco M, Cervera R, et al.: Thyroid disease in primary sjogrens syndrome. Study in a series of 10 patients. *Medicine (Baltimore)*; 79:103-108, 2000
- Soto-Rojas AE, Kraus A. The oral side of Sjogren syndrome. Diagnosis and treatment. A review. *Arch Med Res*. 2002;33:95-106.
- Vivino FB, Al-Hashimi I, Khan Z, et al. Pilocarpine tablets for the treatment of dry mouth and dry eye symptoms in patients with Sjogren syndrome: a randomized placebo-controlled, fixed dose, multicenter trial. P92-01 Study Group. *Arch Intern Med*. 1999;159:174-81.
- Tsifetaki N, Kitsos G, Paschides CA, et al. Oral pilocarpine for the treatment of ocular symptoms in patients with Sjogren's syndrome: a randomized 12 week controlled study. *Ann Rheum Dis*. 2003;62:1204-7.
- Sall K, Stevenson OD, Mandorf TK, Reis BL. Two multicenter, randomized studies of the efficacy and safety of cyclosporine ophthalmic emulsion in moderate-to-severe dry eye disease. CsA Phase 3 Study Group. *Ophthalmology*. 2000;107:631-9.
- Fox RI, Konttinen Y, Fisher A. Use of muscarinic agonists in the treatment of Sjogren's syndrome. *Clin Immunol*. 2001;101:249-63.
- Fife RS, Chase WF, Dore RK, et al. Cevimeline for the treatment of xerostomia in patients with Sjogren's syndrome. *Arch Intern Med*. 2002;162:1293-1300.
- Talal, N.: Sjogren's syndrome: historical overview and clinical spectrum of disease. *Rheum Dis Clin North Am* 1992 Aug; 18(3): 507-15.
- Tishler M, Yaran I, Shirazi I, Yaron M. Hydroxychloroquine treatment for primary Sjogren's syndrome: its effect on salivary and serum inflammatory markers. *Ann Rheum Dis*. 1999;58:253-6.
- Skopouli FN, Dafni U, Ioannidis JP, Moutsopoulos HM. Clinical evolution, and morbidity and mortality of primary Sjogren's syndrome. *Semin Arthritis Rheum*. 2000;29:296-304.
- Steinfeld SD, Demols P, Salmon I, et al. Infliximab in patients with primary Sjogren's syndrome: a pilot study. *Arthritis Rheum*. 2001;44:2371-5.
- Mariette X, Ravaud P, Steinfeld S, et al. Inefficacy of infliximab in primary Sjogren's syndrome: results of the randomized, controlled Trial of Remicade in Primary Sjogren's Syndrome (TRIPSS). *Arthritis Rheum*. 2004;50:1270-6.
- Tzioufas AG, Voulgarelis M. Update on Sjogren's syndrome autoimmune epithelitis: from classification to increased neoplasias. *Best Pract Res Clin Rheumatol*. Dec 2007;21(6):989-1010.
- Constantopoulos SH, Tsianos EV, Moutsopoulos HM. Pulmonary and gastrointestinal manifestations of Sjogren's syndrome. *Rheum Dis Clin North Am*. Aug 1992;18(3):617-35.



18. Wotherspoon AC. Gastric MALT lymphoma and Helicobacter pylori. *Yale J Biol Med.* Jan-Feb 1996; 69(1):61-8.
19. Soy M, Piskin S. Cutaneous findings in patients with primary Sjogren's syndrome. *Clin Rheumatol.* Aug 2007; 26(8):1350-2.
20. Fox RI, Liu AY. Sjögren's syndrome in dermatology. *Clin Dermatol.* Sep-Oct 2006;24(5):393-413.
21. Ng KP, Isenberg DA. Sjögren's syndrome: diagnosis and therapeutic challenges in the elderly. *Drugs Aging.* 2008;25(1):19-33.
22. Gøransson LG, Herigstad A, Tjensvoll AB, Harboe E, Mellgren SI, Omdal R. Peripheral neuropathy in primary sjogren syndrome: a population-based study. *Arch Neurol.* Nov 2006;63(11):1612-5.
23. Ramachandiran N. Apparently persistent weakness after recurrent hypokalemic paralysis: a tale of two disorders. *South Med J.* Sep 2008;101(9):940-2.
24. Delalande S, de Seze J, Fauchais AL, Hachulla E, Stojkovic T, Ferriby D, et al. Neurologic manifestations in primary Sjögren syndrome: a study of 82 patients. *Medicine (Baltimore).* Sep 2004;83(5):280-91
25. Mori K, Iijima M, Koike H, Hattori N, Tanaka F, Watanabe H, et al. The wide spectrum of clinical manifestations in Sjögren's syndrome-associated neuropathy. *Brain.* Nov 2005;128:2518-34
26. Liquidato BM, Soler Rde C, Bussoloti Filho I. Evaluation of the concordance of sialometry and salivary glands scintigraphy in dry mouth patients. *Braz J Otorhinolaryngol.* 2006;72:116-9.
27. Von Bültzingslöwen I, Sollecito TP, Fox PC, Daniels T, Jonsson R, Lockhart PB, et al. Salivary dysfunction associated with systemic diseases: systematic review and clinical management recommendations. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2007;103:S57.e1-15
28. Nakamura H, Kawakami A, Eguchi K. Mechanisms of autoantibody production and the relationship between autoantibodies and the clinical manifestations in Sjögren's syndrome. *Transl Res.* 2006;148:281-8.

