

What Ophthalmologists Should Know About Sjögren's Syndrome

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Abstract

About one-quarter of patients with dry-eye syndrome (DES) have an underlying rheumatic condition, most commonly Sjogren's syndrome (SS). SS is a common, frequently underdiagnosed cause of dry eye with multisystemic involvement. The immunological background of SS involves activation of both innate and acquired immune systems. According to the 2002 American and European classification systems, presence of any four of the six criteria (i.e. symptoms of dry eye, symptoms of dry mouth, ocular signs of dry eye, objective salivary gland involvement, typical histopathology findings in minor salivary gland biopsy specimens and presence of serum autoantibodies) as long as either the biopsy or serology is positive or presence of any three of the four objective criteria is considered diagnostic of SS. The main goal of treatment of ocular involvement is the alleviation of dry-eye symptoms with replacement therapy, stimulation of tear secretion and supportive surgical procedures to conserve tears. Preservative-free tear substitutes, topical steroids, cyclosporine A, autologous serum eye-drops and punctal plugs are commonly used for this purpose.

Keywords

Sjögren's syndrome, dry eye, serology

Disclosure: Canan Asli Utine has no conflicts of interest to declare. Esen K Akpek has received research grants from Allergan Inc., Pfizer Inc. and Inspire Pharmaceuticals Inc. and is the recipient of the Mary Greve scholarship from Research to Prevent Blindness.

Received: 17 May 2010 **Accepted:** 10 June 2010 **Citation:** *European Ophthalmic Review*, 2010;4:77–80 DOI: 10.17925/EOR.2010.04.01.77

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Epidemiology of Dry Eye and Sjögren's Syndrome

Dry-eye syndrome (DES) is a common ocular disorder, affecting an estimated 25% of patients presenting to general ophthalmology clinics.¹ The incidence of DES varies significantly depending on the age of the population studied and the signs and/or symptoms considered for making the diagnosis. Recent studies suggested that over nine million Americans suffer from a clinically significant form of DES and many more millions are thought to have either a milder form of the disease or intermittent manifestations.² The prevalence of DES was found to be 11% in the general population ≥40 years of age, with a significant increase in prevalence after 60 years of age in women and after 70 years of age in men.³ Overall, the frequency of DES is thought to be on the rise owing to multiple factors including ageing of the population, changing lifestyles (particularly artificial lighting and air conditioning) and widespread use of contact lenses and computers.³

DES is regarded as an inflammatory disorder of the ocular surface whether from a systemic autoimmune disease or as an isolated local autoimmune event. In a retrospective study, we noted that about one-quarter (25.9%) of 220 patients with DES had an underlying rheumatic condition, most commonly primary Sjögren's syndrome (SS).⁴ Interestingly, only one-third of the patients with SS carried a diagnosis prior to presenting to the ophthalmology clinic with dry-eye symptomatology.

An SS-like clinical condition was first mentioned by Mikulicz, who described a 42-year-old man with bilateral enlargement of the parotid and lacrimal glands associated with small round-cell infiltrate in 1892.⁵ However, the Danish ophthalmologist Sjogren is credited with first elaborating the clinical and histological findings in 19 women with dry mouth and dry eyes.

SS is one of the most common autoimmune diseases, with an incidence of 0.1–3% in the US,⁶ 2.7% in Sweden, 0.6% in Greece, 1% in Slovenia⁷ and 0.16% in Turkey.⁸ In Japan, approximately 17,000 new SS patients are diagnosed yearly.⁹ However, due to the heterogeneity of clinical manifestations it is likely that the disease remains undiagnosed in the majority of patients.¹⁰

SS is more common in females, with a female:male ratio of 9:1.^{11,12} Although SS can be seen in all age groups, it is most commonly encountered in the fourth and fifth decades of life.⁶ Over 90% of SS patients are females in their mid-50s, around the age of menopause.¹³ Signs and symptoms of the disease do not vary significantly between the genders.¹⁴

Clinical Findings of Sjögren's Syndrome

SS is a chronic autoimmune disorder characterised by immune-mediated destruction and malfunctioning of the salivary and lacrimal glands, with subsequent development of xerostomia (dry mouth) and keratoconjunctivitis sicca (dry eye). SS may present as a primary

disorder or can be secondary to other well-defined autoimmune diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), polyarteritis nodosa, Wegener's granulomatosis, systemic sclerosis, primary biliary sclerosis, mixed connective tissue disease or occult thyroid eye disease.^{15,16} SS is known to occur in 30–50% of patients with RA and 10–25% of patients with SLE.¹⁷

SS is a multisystemic disorder with varying clinical presentations.¹³ Systemic manifestations of SS are subdivided into non-visceral (skin, arthralgia, myalgia) and visceral (lung, heart, kidney, gastrointestinal, endocrine, central and peripheral nervous systems). Skin manifestations of small vessels include palpable and non-palpable purpura in association with cryoglobulinaemia and hyperglobulinaemia. Necrotising vasculitis involving medium-sized vessels as well as venous and arterial thrombotic lesions may also occur. Joint and muscle involvement lead to symmetrical arthralgia and arthritis as well as myalgia and symptoms of fatigue. Interstitial pneumonitis and tracheobronchial sicca are the most common presentations of pulmonary involvement. Pericarditis and pulmonary hypertension can also occur. Renal manifestations of SS include interstitial nephritis, hypokalaemic paralysis, renal calculi or osteomalacia. The main gastrointestinal manifestation is dysphagia, which is due partly to xerostomia but mostly to oesophageal dysfunction. Coeliac sprue has also been reported in association with SS. Hypothyroidism seems to be common in SS, and SS is present in about 10% of patients with autoimmune thyroid disease. Neurological manifestations are reported in about 20% of patients with SS and can include central nervous system involvement, cranial neuropathies, myelopathy and peripheral neuropathies.¹³ Psychiatric disorders, including depression and anxiety, have also been described in association with SS.

Lymphoproliferative disease is a particular concern in SS. The risk of lymphoma is 44 times higher in patients with SS than in the general population.¹⁸ Lymphoma appears to occur in approximately 5% of primary SS patients, and the risk increases with disease duration.¹⁷ Most lymphomas associated with SS are marginal-zone B-cell lymphomas that arise in diverse extra-nodal and nodal sites, and generally are not associated with viruses.¹⁹ Reportedly, about 20% of deaths among primary SS patients are attributed to lymphoma.²⁰

DES is the main ocular manifestation of SS and results from impaired lacrimal gland function from inflammatory tissue damage.²¹ Initial symptoms of SS-related DES include irritation, a gritty feeling, burning and discomfort in the eyes. After the initial stage of the disease, ocular surface inflammation with conjunctival hyperaemia and corneal epithelial drop-out leading to functional impairment of vision will follow. Other ocular findings include squamous metaplasia of the ocular surface epithelium, corneal epitheliopathy, filamentary keratitis, sterile infiltrates, follicular conjunctivitis, scleritis and, in more severe cases, poor epithelial integrity, recurrent erosion and persistent corneal ulceration, vascularisation, opacification and, infrequently, perforation.^{10,22–24} Sterile corneal melt leading to spontaneous perforation and loss of vision in previously unrecognised SS patients is well known,²³ and has been reported after cataract surgery, conductive keratoplasty and, more recently, endothelial keratoplasty.²⁵ The ocular surface complications of SS may necessitate extensive surgeries, including corneal transplantation or keratoprosthesis implantation for the restoration of vision. However, all of these interventions will have only limited success if the underlying DES has not been promptly and adequately addressed.

Pathogenesis and Immunological Basis of Sjögren's Syndrome

The immunological background of SS involves activation or apoptosis of glandular epithelial cells in genetically predisposed individuals and subsequent immune activation, resulting in the expression of autoantigens that initiate a self-perpetuating T-cell-dependent autoimmune response. After excitation of glandular cells by environmental factors, such as a viral illness,²⁶ the human leukocyte antigen DR-1 (HLA-DR)-independent (innate) immune system becomes activated. Interferon (IFN) I production by plasmacytoid dendritic cells might be triggered, inducing apoptosis or necrosis of glandular epithelial cells. IFN- α upregulates the major histocompatibility complex (MHC) class I and II (HLA-DR) molecules and the co-stimulatory molecules CD80 and CD86, expressed on the antigen-presenting cells, and at the same time promotes production of the cytokines and chemokines that control the attraction of leukocytes to tissues, thereby activating the inflammatory process. The induced apoptosis or necrosis in turn reveals autoantigens including cytoplasmic/nuclear ribonucleoprotein particles containing uridine-rich fragments of RNA (i.e. Sjögren's-specific antibody A [SSA]/anti-Ro and Sjögren's-specific antibody-B [SSB]/anti-La). The cellular function of these autoantigens remains unknown, although the SS-B has been reported to take part in the maturation process and to act as a termination factor for RNA polymerase III transcripts. Inability to suppress the immune response results in compromised function, but with persistence of the inflammation permanent tissue damage to the glands occurs.²⁸

Interleukins such as IFN- γ , interleukin (IL)-6, IL-10 and IL-15 are important for sustained activation of the immune system. Production of IL-12 and tissue growth factor (TGF)- β from dendritic cells drives proinflammatory (Th1 and Th17) and restrains inhibitory (Treg) pathways. Tumour necrosis factor (TNF)- α and IL-6 have been implicated in the resultant tissue injury.

Salivary gland analysis of SS patients revealed that the chemokines CXCL-13 and CCL-21 operate in the organisation and maintenance of immune cell aggregates.²⁹ CXCL-12 also has a key role as a 'molecular bridge' between autoimmunity by antibody-secreting plasma cells and B-cell lymphoid malignancy development. The potent T-cell chemoattractant CXCL-11 was shown in the ductal epithelium adjacent to lymphoid infiltrates in the SS salivary glands, and is thought to be involved in the development of glandular lesions in SS.¹³ In an animal model, the macrophage-derived chemokine (MDC) was shown to be present on infiltrating lymphocytes throughout the lacrimal gland, whereas thymus-activation-regulated chemokine (TARC) was shown to be present in lacrimal gland ductular cells.²⁷ Additionally, in the glandular tissue abnormal distribution of aquaporin 5 (AQP5) cell membrane transporter and a defect in AQP5 trafficking, increased B-cell-activating factor (BAFF, also known as B-lymphocyte stimulator) and the matrix metalloproteinases (MMP), especially the gelatinases (MMP-2 and MMP-9), were found to be related to tissue damage in SS.^{26,30,31}

Immunological markers in the sera of patients with SS other than anti-SSA/SSB antibodies include antinuclear antibody (ANA), rheumatoid factor (RF), cryoglobulinaemia and low complement levels. In addition, autoantibodies directed against α -fodrin and M3 muscarinic receptors have been implicated in the immunopathogenesis of SS.³²

The neuroendocrine system also has a profound impact on lacrimal gland structure and function. A central role of androgens was

documented in the support of lacrimal gland functions.³³ Androgens have potent anti-inflammatory properties,³⁴ whereas oestrogens and prolactin are known to possess pro-inflammatory properties.³⁵ A decline in androgens might play an important role in the susceptibility of the lacrimal gland to inflammation, and reduced levels of circulating androgens were found in SS patients.³⁶

Diagnosis of Sjögren's Syndrome Among Dry-eye Patients

Commonly, DES is the presenting symptom of SS. Initially, these patients seek help in ophthalmology clinics for several years prior to final diagnosis of SS.²¹ Additionally, DES is frequently the symptom causing the greatest morbidity and impairment of quality of life early in the course of SS. Therefore, it is very important for ophthalmologists to determine who is at risk of having SS.

According to the 2002 American European classification system for SS, six criteria are considered for diagnosis of SS: symptoms of dry eye, symptoms of dry mouth, ocular signs of dry eye (i.e. decreased aqueous tear secretion as measured with Schirmer's test and conjunctival staining as determined with vital stains such as rose bengal or lissamine green), objective salivary gland involvement (determined by whole salivary flow, sialography or salivary scintigraphy), typical histopathology findings in minor salivary gland biopsy specimens and presence of serum autoantibodies (i.e. SSA and/or SSB). Presence of any four of these six items, as long as the antibody testing or histopathology is positive, or presence of any three of the four objective criteria is diagnostic of primary SS. Exclusions include previous radiotherapy to the head and neck, lymphoma, sarcoidosis, graft-versus-host disease, infection with hepatitis C virus, human T-lymphotropic virus type I or HIV. ANA and RF were removed from the list of serological components after 1996 because they provided no increase in sensitivity and specificity compared with the 1993 European criteria.^{12,37} One problem is that serological testing for SS is known to have high specificity but low sensitivity values,^{38,39} with only 26–56% positivity rates for SSA and/or SSB in the rheumatology literature.^{38,40} Histopathological examination of minor salivary glands yields better diagnostic results. The histological hallmark of primary SS is focal lymphocyte aggregates in the exocrine glands (i.e. lacrimal and salivary glands), which initially surround the ducts but later extend to the acinar epithelium and eventually result in a net loss of acinar cells and acinar-cell atrophy.¹⁷

Treatment of Sjögren's Syndrome

Non-visceral manifestations such as arthralgia, myalgia and lymphadenopathy are generally managed with salicylates, non-steroidal anti-inflammatory agents and hydroxychloroquine.^{41,42} For visceral involvement, such as pneumonitis, neuropathy and nephritis, corticosteroids are frequently used. However, their use is limited by their usual side effects.¹³ Systemic immunomodulatory therapy with cyclophosphamide, methotrexate, azathiopurine and nucleoside analogues has been used to help taper the corticosteroids, with conflicting results.^{43,44} Biologics have also been tried in the treatment of SS. Two randomised controlled trials – one with infliximab and the other with etanercept – showed a lack of efficacy of these TNF antagonists.^{20,45} By contrast, rituximab, an anti-CD20 monoclonal antibody for B-cell depletion, has shown efficacy in the treatment of three open-label studies and one randomised controlled trial.^{46–48} Reduced lymphocytic infiltrate with a decreased B:T-cell ratio and partial disappearance of germinal centres in parotid gland biopsy specimens were noted.

Patients reported improvement in fatigue, dry mouth, dry eyes, dry vagina and number of tender joints.⁴⁹ Of note, patients with a short disease duration showed greater improvements compared with patients with chronic disease.⁴⁹ Similarly, another open-label phase I-II trial with a humanised monoclonal anti-CD22 antibody, epratuzumab, revealed improved lacrimal flow (71.4%) and salivary flow (35.7%) along with clinical improvement in dry eyes (58%), dry mouth (36%), fatigue (65%) and tender joints (100%) in patients with primary SS.⁵⁰ These findings indicate that B-cell modulation might be a promising new treatment strategy for SS. The most important side effects of treatment with biological agents are related to the infusions themselves, in the form of serum-sickness-like disease.⁵¹

Treatment of Sjögren's-syndrome-related Dry-eye Syndrome

The main goal of treatment of ocular involvement in SS is the alleviation of dry-eye symptoms with replacement therapy, stimulation of tear secretion and supportive surgical procedures to conserve tears.²¹ Additionally, use of medications that exacerbate DES such as anticholinergics, antihistamines and diuretics, as well as contact with dust and cigarette smoke, must be discouraged.²¹ Maintenance of a humid environment, use of spectacles with side shields and taking regular breaks and blinking while performing near tasks should be recommended.⁵² Preservative-free tear substitutes are the first step in medical management. Short-acting preparations are based on carboxy-methylcellulose or polyvinyl alcohol, whereas longer-acting tear substitutes contain aqueous carbomer gels or paraffin. A preservative-free 0.5% hydroxypropyl methylcellulose formula was found to be effective in improving DES symptoms in both SS and non-SS DES patients, with a significant improvement in conjunctival and corneal staining scores and break-up times.⁵³ Also, sodium hyaluronate eye drops are known to be effective in promoting corneal re-epithelisation,⁵⁴ and were found to be more effective in the treatment of subjective and objective findings of dry eye compared with the vehicle⁵⁵ and carbomer lubricants⁵⁶ in randomised, double-masked clinical trials.

Topical steroids target the inflammatory component of DES in a non-specific manner. Given the high risk of complications with chronic use, this therapy can be considered as a short-term 'pulse' for the inflammatory exacerbations of the disease.⁵⁷ A potent steroid with a long duration of action and low potential for intraocular pressure rise might be considered in patients with significant ocular surface inflammation.⁵⁸

Cyclosporine A is an immunomodulator that specifically inhibits T-lymphocyte proliferation and IL-2 production by activated helper T cells. Topical cyclosporine 0.05% is approved by the US Food and Drug Administration (FDA) for DES treatment.⁵⁹ Oral secretagogues are FDA-approved for use in SS (mainly in dry-mouth symptoms). Although a few studies have demonstrated the efficacy of oral secretagogues in the treatment of SS-related DES, the common occurrence of side effects such as diarrhoea and sweating limits their clinical use.

Autologous serum eye-drops (ASEs) and punctal plugs are also commonly used based on the severity of dryness and presence of associated ocular surface complications. ASEs have similar biochemical properties to normal tears and provide the ocular epithelia with components such as epithelial growth factor, fibronectin, vitamin A and TGF- β , which support their normal proliferation and differentiation.⁶⁰ Punctal occlusion using plugs,

surgery or cauterisation for the preservation of the tear film is mostly reserved for more severe disease.⁶¹ However, it is important not to pursue this approach in the active inflammatory stages of the disease, since this therapy may cause retention of the proinflammatory mediators and cytokines on the ocular surface and promote increased inflammation and desensitisation of the cornea.⁶²

Although hydroxychloroquine seems to be the most commonly used drug for SS, particularly for extraglandular and non-visceral inflammation, its efficacy on oral or ocular sicca has yet to be demonstrated.^{63,64}

For the proper management of SS-related sicca findings, it is important to diagnose the disease in the early stages and start topical or local anti-inflammatory treatment before irreversible damage occurs in the secretory glands. Therefore, screening of DES patients for the presence of SS should always be considered by ophthalmologists caring for dry-eye patients. ■



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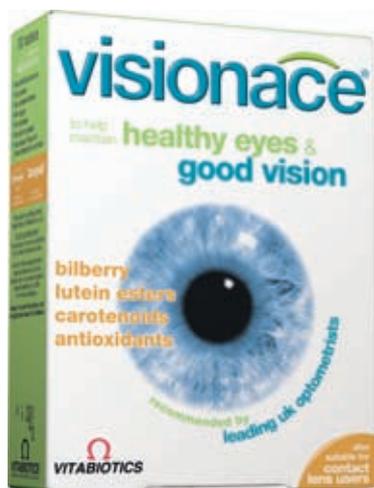


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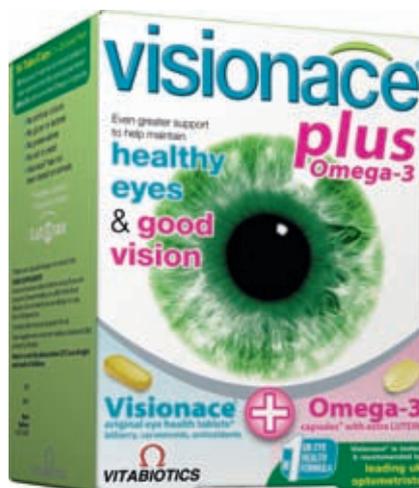
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