Understanding and Managing Sjögren Syndrome Dry Eye

Sjögren syndrome (SS) is a chronic autoimmune disorder that affects millions of people worldwide. The disease primarily targets the exocrine glands, leading to significant ocular and oral complications that can have a substantial impact on a patient's quality of life. The most common manifestations of SS are dry eyes and dry mouth. Early diagnosis and treatment are critical to prevent vision-threatening complications and systemic manifestations, so it's important for ophthalmologists to be familiar with the clinical features, diagnosis, and management of Sjögren syndrome dry eye (SSDE).

Classification of Sjögren Syndrome

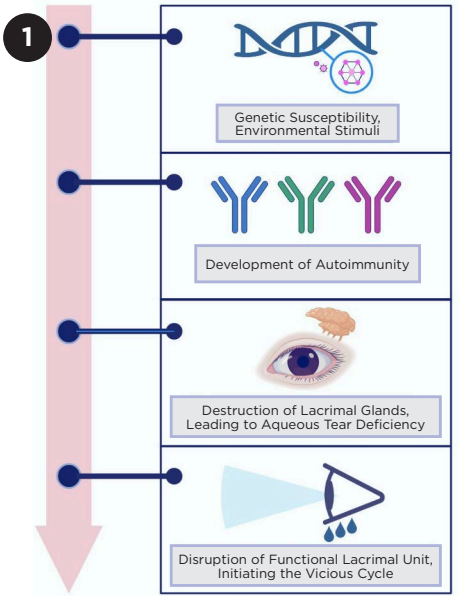
SS can be classified as either primary or secondary, depending on whether it occurs alone or in conjunction with another autoimmune disease. The most commonly associated autoimmune disorders are rheumatoid arthritis and systemic lupus erythematosus, although other diseases such as Raynaud disease, scleroderma, primary biliary cholangitis, and autoimmune hepatitis have also been reported.[1]

Prevalence

SS affects approximately 0.06% of the world's population, with women accounting for more than 90% of those affected. It has been reported that 10% of patients with dry eye disease (DED) have SS, but unfortunately, two-thirds of these cases are undiagnosed, with a median delay of 10 years to diagnosis.[2] This underdiagnosis can be attributed to several factors, including the high prevalence of dry eye and dry mouth, the nonspecific clinical manifestations of SS, and the insidious onset of the disease. In addition, patients with SSDE may be asymptomatic or only mildly symptomatic despite having significant ocular inflammation. Furthermore, there are few reliable and effective screening tools and algorithms to determine which DED patients should be worked up for SS. And physicians may underestimate the severity of SS's effect on quality of life and, thus, refer few patients for workup.

Pathophysiology

The pathogenesis of SS involves both genetic susceptibility and environmental exposure. Although the exact etiology is unknown, the pathogenesis of primary SSDE can be divided into four steps (Fig. 1). First is the interaction between genetic susceptibility and environmental exposure. This may trigger the second step, development of autoimmunity. The third step is the destruction of lacrimal glands, resulting in aqueous tear deficiency. Fourth is the dysfunction of the entire functional lacrimal unit, ultimately leading to a vicious cycle of DED. In the final stage, differentiating SSDE from other types of dry eye is challenging for clinicians. This is due to overlapping symptoms with general dry eye and the extensive damage to the lacrimal unit in SSDE, which is similar to other severe dry eye diseases.



SJÖGREN SYNDROME. *Four steps in pathogenesis of SS dry eye.*

Clinical Features and Presentation

Ophthalmic manifestations of SS. Ocular surface dysfunction can cause a range of symptoms, including blurry vision, foreign body sensation, burning sensation, photophobia, and red eyes. These symptoms can worsen due to prolonged visual effort and environmental factors such as low humidity and extreme cold. However, despite significant ocular inflammation, some

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patients may be asymptomatic or mildly symptomatic.

Physical examination typically reveals decreased meniscal height and decreased tear breakup time; occasionally, conjunctival hyperemia is also present. The use of rose bengal or lissamine green stain can reveal devitalized epithelium on the conjunctiva, and fluorescein can reveal punctate epithelial erosions on the cornea. However, in SSDE, the severity of symptoms does not always correlate with the severity of the signs of the disease. Advanced SSDE can lead to debris on the ocular surface, including discharge, filaments, and mucous plaques. In addition, keratinization of the cornea and conjunctiva and corneal calcification are sometimes observed.

Although SSDE originates as an aqueous tear deficiency, meibomian gland dysfunction and evaporative tear loss can also occur and may be accompanied by palpebral signs such as telangiectasias and meibomian gland obstruction and atrophy. Thus, in the absence of an SS diagnosis, there are no features that can clearly differentiate SSDE from non-SSDE.

Glandular manifestations of SS. The main glandular manifestation of SS is xerostomia (dry mouth). This can make eating, speaking, and swallowing difficult and may lead to dental caries, oral candidiasis, and chronic esophagitis. Enlargement of the salivary glands is a frequent finding in SS, often caused by sialadenitis due to lymphocytic infiltration. In contrast, enlargement of the lacrimal glands is relatively uncommon. Therefore, when enlarged lacrimal glands are present, it is essential to conduct further investigations to rule out any infiltrative diseases such as lymphoma, sarcoidosis, amyloidosis, and IgG4-related disease.

Extraglandular and systemic manifestations. SS can also involve multiple organs and systems. Arthralgia is fairly common, and pulmonary conditions such as bronchiolitis and interstitial lung diseases are less common but notable. Instances of liver and pancreatic disorders have been observed infrequently, as have neurological complications like sensory neuropathy, myelitis, and meningitis. Hematological disorders, although variable in prevalence, include anemia, leukopenia, thrombocytopenia, and hypergammaglobulinemia. In addition to these symptoms, patients show a higher propensity for certain conditions, such as Hashimoto thyroiditis, cardiovascular disease, and depression.

The disease is also linked to an increased risk of lymphoma, with a relative risk (RR) of 13.8 for non-Hodgkin lymphoma, as well as an RR of 1.5 for all malignant tumors, and an RR of 2.6 for thyroid tumors. Therefore, clinicians should consider the possibility of extraglandular and systemic manifestations when evaluating patients with SS to ensure prompt diagnosis and management of these potentially serious conditions.[3]

Ocular and Systemic Complications

Complications arising from SSDE can cause severe ocular damage such as neurotrophic keratitis. This condition can lead to corneal thinning, which in turn can result in corneal perforation. Additionally, SS can cause type III hypersensitivity reactions (i.e., immune-complex deposition) resulting in severe inflammation of other ocular structures, leading to scleritis, uveitis, optic neuropathy, or retinal vasculitis.[4]

In addition, the presence of SSDE may influence future ocular surgical decision-making. Both refractive surgery and blepharoplasty should be approached with caution in patients with SSDE.

Although SS tends to have a relatively benign systemic course, around one-third of patients may develop systemic complications leading to decreased quality of life, increased morbidity, and even mortality.

Diagnosis

The most widely studied and utilized system for diagnosing primary SS is the American College of Rheumatology/European League Against Rheumatism criteria established in 2016, which outlines the criteria and details regarding the diagnostic score for primary SS.[5]

When clinical suspicion is high for SS, the rheumatologic workup may include a panel of autoantibodies, including the following:

- Anti-Ro/SSA and anti-La/SSB are hallmarks of SS.
- Rheumatoid factor and antinuclear antibodies (ANAs) may also be present.
- Anticitrullinated peptide antibodies (ACPAs), commonly associated with rheumatoid arthritis, are found in approximately 10% of patients with SS.
- Anticentromere antibodies (ACAs) are present in around 7% of SS patients and are associated with Raynaud disease and scleroderma.
- Antimitochondrial antibodies (AMAs) are present in 7% of patients and are associated with primary biliary cholangitis.[1]

Management

The treatment approach for SSDE is like that of DED in general. First, patients should be educated on the importance of conservative measures that involve environmental control. These include maintaining optimal humidity levels at home, wearing goggles outside, and avoiding air blowing on the eyes from HVAC or wind.

Drops. Topical medications are the cornerstone for treating SSDE. Sometimes, topical treatments can be combined with interventional treatments like punctal plugs. Systemic administration of drugs, including pilocarpine or immunosuppressive or immunomodulatory agents, is rarely used as a first-line treatment for SSDE but may be used to address extraocular or systemic manifestations of SS.

Artificial tear substitutes. Artificial tear substitutes, available as gels, ointments, inserts, or drops, contain demulcents and emollients to reduce damage from desiccating stress. Preservative-free options can be considered if there are concerns about toxicity. Ointments reduce the need for frequent dosing but may cause blurred vision. For some patients, however, physical limitations such as hand tremors, impaired manual dexterity, and arthritis may make the process of instilling drops or applying ointments challenging, potentially affecting the consistency of dosing.

Punctal plugs. Punctal occlusion is

a safe and quick procedure that reduces tear drainage and improves aqueous retention. It has been shown to provide significant improvement in the markers for aqueous and evaporative dry eye (i.e., tear osmolarity).[6] Punctal cautery is another treatment option, which may be more effective than plugs, especially in patients with severe aqueous deficiency. However, it is crucial to control any ocular inflammation before either method of punctal occlusion, as inflammatory mediators on the ocular surface may interfere with the success of punctal occlusion.

Topical corticosteroids. A limited course of topical steroids is often used to suppress inflammation in SSDE, and patients may need them for several weeks in gradually tapered doses. Long-term use of steroids can cause ocular complications such as ocular hypertension and cataracts. Therefore, they are generally limited to treatment of acute symptoms or as pretreatment for delayed-onset therapies.

Cyclosporine A. Cyclosporine A (CsA) can be an effective treatment for mild, moderate, and severe cases of SSDE and has a better safety profile than corticosteroids. It reduces inflammation by inhibiting T-cell activation and cytokine release. The therapeutic effect of CsA has a delayed onset of four to 12 weeks and requires consistent dosing. It may cause short-term ocular pain and irritation but is well tolerated when bridged with corticosteroids. CsA is available as 0.05% and 0.1% eyedrops and in a new nanomicellar 0.09% formulation.[7]

Lifitegrast. Lifitegrast is a topical integrin antagonist that inhibits the inflammatory cascade by preventing helper T-cells from binding to vascular endothelial cells. Its therapeutic onset is more rapid than that of CsA, improving symptoms within two to four weeks, and it can be used for dry eye ranging from mild to severe.[8]

Autologous serum eyedrops. Serum derived from the patient's blood contains nutrients and factors that promote wound healing and regeneration. It has anti-inflammatory properties that may be beneficial in managing severe disease. However, the preparation, cost, storage requirements, and need for frequent dosing of autologous serum eyedrops limit their widespread use.

Platelet-rich plasma eyedrops. Platelet-rich plasma (PRP) eyedrops, also derived from the patient's own blood, contain a concentration of growth factors, vitamins, and cytokines that resemble natural tears and can facilitate the recovery of damaged ocular surface tissues. The similarity of PRP to the pH and osmolarity of natural tears, along with its absence of preservatives, stabilizers, or additives, makes it an effective lubricant for DED. The preparation maintains the integrity of the platelets and allows for their activation at the injury site, potentially leading to a more biologically relevant response.

Amniotic membrane. Prepared patches or grafts of amniotic membrane obtained from human placental tissue provide mechanical support and growth factors that promote wound healing and reduce pro-inflammatory cytokines. When applied to the ocular surface, these membranes have been reported to be effective in treating refractory and severe SSDE, although foreign body sensation and blurred vision are associated with their use.[9]

Advances in Therapy and Diagnostics

In recent years, a variety of innovative treatment modalities have emerged that hold promise for improving SSDE management, particularly in the area of drug delivery to the ocular surface. Recent advances include the use of contact lenses for drug delivery, such as the silicone hydrogel lens for CsA, and the use of nano-based drug delivery systems, such as the recently FDA-approved 0.09% nanomicellar topical formulation of CsA.[10]

New diagnostic modalities are also available or in development. These include use of tear and saliva proteomics and exosomal biomarkers.

Conclusion

Sjögren syndrome is a complex autoimmune disease with multisystemic implications beyond just dry eyes. SSDE is frequently underdiagnosed, and rheumatologic workup for early diagnosis and appropriate management is crucial, as the condition can progress insidiously and without a correlation to disease severity. Collaboration between interdisciplinary teams is necessary in managing the underlying condition. With new diagnostic tools and emerging therapeutic approaches under investigation, it is increasingly important for clinicians to stay up to date with developments in the field.

1 Selmi C, Meroni PL, Gershwin ME. *J Autoimmun.* 2012;39(1-2):34-42.
2 Qin B et al. *Ann Rheum Dis.* 2015;74(11):1983-1989.
3 Brito-Zerón P et al. *J Hematol Oncol.* 2017;10(1):90.
4 Akpek EK et al. *Ophthalmology.* 2015;122(1):56-61.
5 Shiboski CH et al. *Arthritis Rheumatol.* 2017;69(1):35-45.
6 Liu T et al. *Front Med (Lausanne).* 2022;9:849700.
7 Mandal A et al. *Pharm Res.* 2019;36(2):36.
8 Li JX et al. *J Clin Med.* 2022;11(17):5014.
9 Shafer BM et al. *Digit J Ophthalmol.* 2019;25(1):21-25.
10 Wu KY et al. *Pharmaceutics.* 2022;15(1):147.

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