

Ocular Manifestations of Sjögren Syndrome

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Sjögren Syndrome (SS) is one of the most frequent systemic autoimmune disorders, mainly involving the eye and mouth due to inflammation of lacrimal and salivary glands. Exocrine glands affected with a typical focal lymphocytic infiltration potentially lead to dry eyes and dry mouth. In addition to the known pathogenic mechanism of SS through autoimmunity, corneal neuropathy, as a peripheral neuropathy which is a relatively frequent extraglandular systemic manifestation of SS, recently draws attention as a possible pathogenic mechanism of ocular symptoms and dry eye induction. The diagnostic criteria of SS changed recently, proposed by the American College of Rheumatology/Sjögren's International Collaborative Clinical Alliance (ACR/SICCA) in 2012, and the ocular surface staining score is the only required test for ocular manifestation of SS. However, other diagnostic methods evaluating tear film status, though excluded from the new criteria, are still important for the staging and treatment planning, including direct observation of tear film, tear film break up time, Schirmer test, and measurement of the tear film levels of inflammatory mediators. Eye-specific symptoms and signs and ocular treatment options for SS including tear substitutes, secretagogue, topical anti-inflammatory therapy with corticosteroids and cyclosporine, punctal occlusion, autologous serum, and mucolytic therapy were summarized and discussed in this review article.

Key Words: Sjögren Syndrome; Dry Eye Syndrome; Corneal Neuropathy; Ocular Staining Score; Classification Criteria

INTRODUCTION

Sjögren's syndrome (SS) is a chronic, systemic autoimmune disorder which affects typically the exocrine glands associated with/without every other systemic autoimmune rheumatic disorder [1,2]. The ocular and oral dryness can be caused by a typical focal lymphocytic infiltration of the lacrimal and salivary glands [1]. Its wide clinical spectrum includes not only benign local exocrinopathy (dry eyes, dry mouth) but also systemic disorder that affects parenchymal organs (liver, kidneys, lung), lesions owing to immune complex hyperproduction and/or vasculitic involvement (glomerulonephritis, peripheral neuropathy, purpura), and lymphocytic malignancies which is known to occur in 5% of SS patients [3]. Thus, SS can be regarded as a heterogeneous autoimmune disease with both organ-specific and systemic features, and showing a wide va-

riety of clinical/serological abnormalities with scattered complications [4,5]. Due to such complexity, it has been difficult to identify a homogeneous group of patients sharing a common etiopathogenesis or prognosis and finally to develop classification/diagnostic criteria for the disease [1]. This also can be explained in the several different classification criteria sets for SS proposed by leading experts in the field over the years [6-8].

Among the extraglandular manifestations of SS, peripheral neuropathies (PN) are frequent with a reported prevalence from less than 2% to over 60% with variety of types including ataxic sensory neuropathy, nonataxic sensory neuropathy (including painful nonataxic sensory polyneuropathy, pure small-fiber neuropathy, and trigeminal neuropathy), and sensorimotor neuropathy (including sensorimotor polyneuropathy and multiple mononeuropathy) [9, 10]. Many studies suggest that PN is associated with benign glan-

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Received 3 June 2016
Revised 20 July 2016
Accepted 22 July 2016

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dular disease [11,12], while others considered the neuropathy to systemic manifestations, such as vasculitis, purpura, glomerulonephritis, low C4 complement factor and cryoglobulinemia [13,14].

This review aims to summarize current studies on the pathophysiology, recently proposed classification, clinical manifestations including ocular symptoms and signs, and evidence-based treatment options.

PATHOPHYSIOLOGY

As all other autoimmune diseases, the hypothesis that SS is a multifactorial disorder including genetic predisposition, hormonal and environmental factors has been strengthened by recent studies [3]. Although SS was considered as a T-cell mediated disease, tissue destruction is associated with the infiltration by mononuclear inflammatory cells including not only activated T cells but also activated autoreactive B cells together according to lesion severity [2]. Also, the key roles of epithelial cells, which are the targets of autoimmune responses in SS, have been enlightened in the regulation of the local inflammatory responses. The studies of minor salivary gland tissues and long-term cultured, non-neoplastic salivary gland epithelial cells elucidated that the epithelial cells of SS patients express increased immune-competent molecules of both innate immune response (TLRs, CD91) and acquired immune responses including lymphoid cell recruitment, homing, activation, differentiation, proliferation, and the expansion and organization of lymphoid infiltrates [3].

Although the prevalence and clinical manifestations of PN associated with SS are relatively well defined, the pathogenesis and the relationships with specific immunologic profiles are not well established [9]. The correlation between the PN and the newly developing SS autoantibodies against type-3 muscarinic acetylcholine receptors has been suggested but has not been proved yet [10]. Though there are variable opinions on the timing of the onset of PN, it may occur early when signs are mild and its serologic markers may be absent [10,15,16]. Symptoms of dry eye have been reported to follow or occur concurrently with clinical manifestations of PN in some of these patients [16,17]. Although symptoms of corneal dysesthesia have been generally considered as secondary to dry eye even without corneal epitheliopathy, the dry eye could be caused by the immunopathic pathogenesis of corneal neuropathy in early SS [18].

CLASSIFICATION CRITERIA

In 1993 the Preliminary European Classification criteria for SS were proposed and ever since they have been largely employed both in clinical practice and in observational and interventional studies for nearly ten years [8]. These criteria were subsequently reexamined in 2002, and their revised version, the American European Consensus Group (AECG) criteria set, has rapidly become the standard reference for SS [19]. However, due to its restrictive and stringent nature, new criteria have been proposed in 2012 based on the analysis of the Sjögren's International Collaborative Clinical Alliance (SICCA) cohort [20] and approved by the American College of Rheumatology (ACR) [21].

According to the ACR/SICCA criteria for SS diagnosis, at least 2 out of the following 3 are required: 1) a positive serum anti-Ro/SSA and/or anti-La/SSB or [positive rheumatoid factor and antinuclear antibody (ANA) $\geq 1:320$]; 2) Ocular surface staining score ≥ 3 (sum total score 0-12; 0-6 score for staining of the cornea with fluorescein, 0-3 score for staining of both the nasal and temporal conjunctivae with lissamine green, Fig. 1) [22]; and 3) focal lymphocytic sialadenitis defined by a focus score ≥ 1 focus/4 mm² in labial salivary gland biopsy samples [2,23]. Prior diagnosis excluding participation in SS studies or therapeutic trials is as follows: history of head and neck radiation treatment; hepatitis C infection; acquired immunodeficiency syndrome; sarcoidosis; amyloidosis; graft versus host disease; IgG4-related disease [23]. The differences from the previously used AECG criteria is that 1) they exclude subjective ocular and buccal symptoms and morphological or functional tests for salivary glands, 2) they use a new ocular staining score proposed by SICCA (Fig. 1) as the only evaluation for ocular

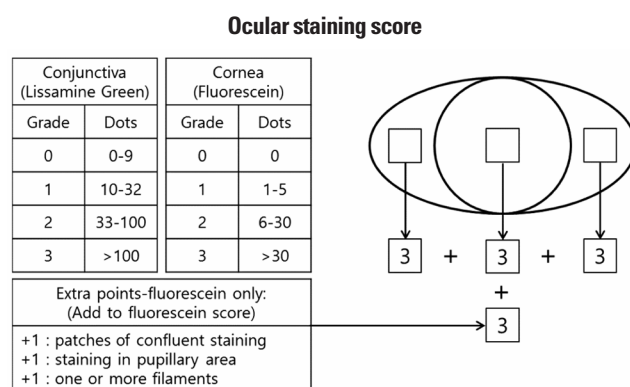


Fig. 1. SICCA Ocular staining score [22,25]. Total scores of 0 to 12 per eye assess the range of severity for dry eye.

involvement, and 3) they consider the association of RF positivity and ANA titer 1:320 as equivalent to anti-SSA/-SSB positivity [24].

Comparison of the Revised AECG and the ACR Classification criteria for SS are summarized in Table 1 [25].

Table 1. Comparison of the Revised American–European Consensus Group (AECG) Classification criteria and the American College of Rheumatology (ACR) Classification criteria for Sjögren's Syndrome [25]

AECG classification*	ACR classification†
Inclusion criteria	Inclusion criteria
I. Ocular symptoms: a positive response to at least one of the following questions: 1. Have you had daily, persistent, troublesome dry eyes for more than 3 months? 2. Do you have a recurrent sensation of sand or gravel in the eyes? 3. Do you use tear substitutes more than three times a day?	None
II. Oral symptoms: a positive response to at least one of the following questions: 1. Have you had a daily feeling of dry mouth for more than 3 months? 2. Have you had recurrently or persistently swollen salivary glands as an adult? 3. Do you frequently drink liquids to aid in swallowing dry food?	None
III. Ocular signs—that is, objective evidence of ocular involvement defined as a positive result for at least one of the following two tests: 1. Schirmer's I test, performed without anaesthesia (≤ 5 mm in 5 min) 2. Rose Bengal score or other ocular dye score (≥ 4 according to van Bijsterveld's scoring system)	Keratoconjunctivitis sicca with ocular staining score ≥ 3 (assuming that individual is not currently using daily eye drops for glaucoma and has not had corneal surgery or cosmetic eyelid surgery in the last 5 years)
IV. Histopathology: in minor salivary glands (obtained through normal appearing mucosa) focal lymphocytic sialoadenitis, evaluated by an expert histopathologist, with a focus score ≥ 1 , defined as number of lymphocytic foci (which are adjacent to normal-appearing mucous acini and contain more than 50 lymphocytes) per 4 mm ² of glandular tissue	Labial salivary gland biopsy exhibiting focal lymphocytic sialadenitis with a focus score ≥ 1 focus/4 mm ²
V. Salivary gland involvement: objective evidence of salivary gland involvement defined by a positive result for at least one of the following diagnostic tests: 1. Unstimulated whole salivary flow (≤ 1.5 mL in 15 min) 2. Parotid sialography showing the presence of diffuse sialectasias (punctate, cavitary or destructive pattern), without evidence of obstruction in major ducts 3. Salivary scintigraphy showing delayed uptake, reduced concentration and/or delayed excretion of tracer	None
VI. Autoantibodies: presence in the serum of the following autoantibodies: 1. Antibodies to Ro (SSA) or La (SSB) antigens, or both	Positive serum anti-SSA/Ro and/or anti-SSB/La or (positive rheumatoid factor and ANA titre $\geq 1:320$)
Classification rules	Classification rules
For primary SS: In patients without any potentially associated disease, primary SS may be defined as follows: A. The presence of any 4 of the 6 items is indicative of primary SS, as long as either item IV (histopathology) or VI (serology) is positive B. The presence of any 3 of the 4 objective criteria items (ie, items III, IV, V, VI) C. The classification tree procedure represents a valid alternative method for classification, although it should be more properly used in clinical-epidemiological survey	For SS: The classification of SS, which applies to individuals with signs/symptoms that may be suggestive of SS, will be met in patients who have at least 2 of the 3 objective features previously described
For Secondary SS: In patients with a potentially associated disease (for instance, another well-defined connective tissue disease), the presence of item 1 or item II plus any 2 from among items III, IV and V may be considered as indicative of secondary SS	Eliminated the distinction between primary and secondary forms of SS
Exclusion criteria	Exclusion criteria
1. Past head and neck radiation treatment 2. Hepatitis C infection 3. AIDS 4. Pre-existing lymphoma 5. Sarcoidosis 6. Graft versus host disease 7. Use of anticholinergic drugs (since a time shorter than 4-fold the half-life of the drug)	Prior diagnosis of any of the following conditions would exclude participation in SS studies or therapeutic trials because of overlapping clinical features or interference with criteria tests: 1. History of head and neck radiation treatment 2. Hepatitis C infection 3. AIDS 4. Sarcoidosis 5. Amyloidosis 6. Graft versus host disease 7. IgG4-related disease

*Revised AECG classification criteria [19]; †ACR criteria [21].
ANA, antinuclear antibodies.

Recently, other autoantibodies have been described in primary SS patients such as antibodies to alpha-fodrin, muscarinic receptors or carbonic anhydrase, but their clinical relevance remains to be elucidated [24].

SYMPTOMS

The initial diagnostic clue is often the symptoms of the patient including either eye discomfort and/or vision fluctuation. Most common symptoms of SS are sicca symptoms of eye and mouth, fatigue, and articular and muscular pain [26]. Several questionnaires have been developed for the assessment of symptoms of dry eye including the Ocular Surface Disease Index (OSDI), the McMonnies questionnaire, the Impact of Dry Eye on Everyday Life survey (IDEEL), the Standard Patient Evaluation of Eye Dryness questionnaire (SPEED), and the Symptom Assessment in Dry Eye survey (SANDE), but few have been validated for diagnosis or response to therapy [27]. A short symptom questionnaire which was used most frequently for clinical screening for dry eye in SS is recommended as follows [27,28]:

A patient reporting 'Yes' to any of the below questions needs a full ocular examination.

- How often do your eyes feel dryness, discomfort, or irritation? Would you say it is "often" or "constantly"? (Y/N)
- When you have eye dryness, discomfort, or irritation, does this impact your activities (e.g. do you stop or reduce your time doing them)? (Y/N)
- Do you think you have dry eye? (Y/N)

Of the diverse ocular symptoms, only two specific symptoms of dryness and irritation were reported to provide equivalent predictability as a longer 14-item questionnaire [29].

OCULAR SIGN & TEAR FUNCTION TEST

The simplest tests of tear function can be performed by direct observation. The corneal light reflex represents the luster and integrity of the tear film grossly. Irregularities of this reflex can be interpreted as either irregularities of the ocular surface or instability of the tear film [27]. Normally, the marginal tear strip is about 1 mm in height, but it is reduced in dry eye.

The fluorescein tear film breakup time (TFBUT) is the most common method for assessing tear film stability. After instilling small amount of fluorescein or applying a slightly moistened fluo-

rescein strip, the patient is asked to blink several times and then stop blinking. Then, the cornea is scanned by a wide slit lamp beam with cobalt blue filter. TFBUT is the time interval between the last complete blink and the first identified dark spot from the uniform greenish hue of the fluorescein in the tear film over the cornea [30]. TFBUT is usually greater than 10 seconds in the normal eyes and the shorter TFBUT represents tear instability which can be caused by dry eye and/or ocular surface irregularities.

The rate of tear secretion is most widely measured by the Schirmer test [30]. This test is performed by inserting a standardized size strip of filter paper (5 × 35 mm) over the lower lid margin into the cul-de-sac at the junction of the middle and lateral third of the eyelid. Keep it in place for 5 minutes with a closed eye and then measure the extent of wetting of the strip. With topical anesthesia in advance, it can measure the non-stimulated tear secretion ("basal" tear secretion test, so-called Schirmer II). Schirmer I test without topical anesthesia has become a standard method for assessing secretion of tears. The normal results of the Schirmer I test is greater than 10 mm, but cutoff values for aqueous tear deficiency have been recommended as 5 mm [30]. Some clinicians use a cutoff value of 7 mm for the Schirmer I test and 3 mm for the Schirmer II test.

Evaluation of the ocular surface is usually performed by instilling topical water-soluble dyes to evaluate the integrity of the epithelial cell layers of the cornea and conjunctiva [30]. Fluorescein dye is most commonly used and is conveniently observed after measurement of the TFBUT. Rose bengal and lissamine green are the two dyes most frequently used for the evaluation of the integrity of the conjunctiva [30]. Both dyes stain the disruptions in the protective healthy layer of mucin including filaments, mucus strands, and areas without normal mucin components. A classic pattern of interpalpebral staining including the medial and temporal conjunctiva, and cornea occurs in advanced dry eye, while early staining is located more often on the inferonasal cornea. Conjunctival staining usually precedes corneal staining, and medial conjunctival staining often precedes temporal staining [27].

Measurement of the tear film levels of inflammatory mediators is useful in identifying the contribution of inflammation and determining the severity of dry eye disease [27]. Interleukin (IL)-1 and interferon gamma (IFN- γ) promote conjunctival squamous metaplasia which leads to decreased number of goblet cells that produce mucins in the conjunctiva [31,32]. IL-17 stimulates production of proteases that can cause damage to the superficial corneal epithelium, leading to a poorly lubricated and irregular cor-

neal surface [33,34]. Increased activity and production of matrix metalloproteinase (MMP)-9 has been reported in dry eye disease and other ocular surface disorders [35].

OCULAR MANAGEMENT

1. Topical tear substitutes and lubrication

The first line of treatment for dry eye has been tear volume replacement and lubrication using artificial tears. However, the composition of these “artificial” tears is far from human tears. The ingredients are designed to add volume to the tear film and to increase the residence time on the ocular surface. The lubricants can also cushion the ocular surface, decreasing friction between globe and lid, and offer additional comfort [27]. Preservatives in the artificial tear affect the health of the ocular surface; EDTA and Benzalkonium chloride have potential toxicity on the ocular surface. The toxic effect of preservatives can be augmented in dry eye patients by increased frequency of administration, decreased tear volume, and increased susceptibility. Therefore preservative-free unit dose vials are recommended when artificial tears are planned for more than 4-6 times a day [27].

2. Secretagogue therapy

Oral pilocarpine is a lacrimal and salivary gland secretagogue which stimulates secretion of tears (lacrimal gland fluid) and saliva. Oral pilocarpine (Salagen[®]) improves dry eye symptoms at dosages of 10-30 mg/day [27]. In the largest clinical trial enrolling 373 subjects, a significantly higher proportion of subjects who was given 5.0 mg of oral pilocarpine every 6 hours experienced improvement of dry eye symptoms compared with the placebo group (42% vs 26%, $P = 0.009$), but not in the 2.5 mg group [36]. Human conjunctival goblet cells also express muscarinic receptors and oral pilocarpine has been reported to increase the number of goblet cells in patients with SS [37]. In summary, oral pilocarpine has been effective in reducing dry eye symptoms and in improving objective findings but these medications are more effective on dry mouth symptoms compared with dry eye symptoms [27,36]. The predominant side effect is sweating [36].

3. Anti-inflammatory therapy

Recent studies have revealed that in dry eye, inflammation is present on the ocular surface [31-33]. Controlled inflammatory reaction can relieve the signs and symptoms of dry eye and this pro-

vides the reason for considering anti-inflammatory medication in the management of patients with SS with moderate to severe dry eye [27].

Several studies have demonstrated the clinical value of topical steroids for a short period in managing dry eye [27]. Two controlled and 1 prospective studies investigated different topical steroids. The first controlled study showed that patients treated with topical fluorometholone had lower scores of dry eye symptom severity compared to artificial tears ($P = 0.03$) and flurbiprofen ($P = 0.03$), and lower fluorescein and rose bengal staining scores compared to the flurbiprofen group ($P = 0.02$ and $P = 0.046$, respectively) [38]. The second controlled study found that 0.5% loteprednol etabonate and placebo did not show significant differences in a combined corneal staining score [39]. The prospective study showed significant improvement in ocular tests scores following treatment with topical 1% methylprednisolone with respect to baseline [40]. Two to four weeks of preemptive topical steroids may relieve the burning and stinging sensation related to topical cyclosporine [41].

Cyclosporine, a calcineurin inhibitor, has been studied in patients with aqueous tear-deficient dry eye disease. Besides the ability to suppress activation of T-lymphocytes which was initially expected as a primary mechanism of action, further study has found that it has multiple inhibitory potential, including inhibition of apoptosis in other cell types [42]. Patients treated with topical cyclosporine 0.05% emulsion showed superior improvement in blurred vision, reduced punctate corneal fluorescein staining, decreased frequency of artificial tear use, and increased tear production [43, 44]. Topical cyclosporine treatment also induced immunohistological improvement of the ocular surface with reduced apoptotic cells in the conjunctiva and reduced markers of activated T-lymphocytes [45,46]. Topical cyclosporine treatment also decreased pro-inflammatory cytokine expression and increased goblet cell densities in the conjunctiva of dry eye patients [45,46].

4. Punctal occlusion

Punctal occlusion blocks the normal tear drainage system and it helps maintain natural or instilled artificial tears longer. Punctal occlusion has been strongly suggested by its capability of decreasing the symptoms and signs associated with dry eye in more than 70 reports, though there are no prospective controlled, large scale studies [47]. As compared with artificial tears, punctal plugs significantly increased Schirmer test scores and TFBUT in the patients with SS and keratoconjunctivitis [48].

5. Autologous serum

Topical autologous serum is used to treat severe ocular surface damage which has not responded to conventional dry eye treatments with intensive lubricant and anti-inflammatory therapy. Autologous serum of 20% concentration is most frequently used clinically in a variety of patients with ocular surface disease including SS with preferable results which is supported by numerous reports [49]. Autologous serum contains vitamin A, fibronectin, cytokines, growth factors, and anti-inflammatory substances [27]. Though there is no clear evidence yet on which constituent is most effective, significant improvement in symptoms, staining scores, and TF-BUT has been reported in comparisons with artificial tears [50].

6. Mucolytic therapy

Mucus strands or filaments on the cornea can induce severe irritation, so that therapy with topical mucolytic solutions can be applied to resolve them [27]. Topical N-acetylcysteine can be prepared usually as 10-20% solutions by only compounding pharmacies and topical application three times a day would resolve filaments within 2 weeks. Patients can complain about an odor of sulfur or burning sensation on instillation, which can usually be accommodated within 2-4 weeks of therapy [27].

CONCLUSION

SS is a multifactorial disorder that genetic predisposition, hormonal and environmental factors are thought to be implicated. For the ocular manifestation of SS, corneal neuropathy has recently drawn attention as a possible pathogenic mechanism of ocular symptoms and dry eye induction in addition to the known autoimmune pathogenesis through the lacrimal gland. The diagnostic criteria of SS has been changed recently, accompanied by the changes in the required evaluating methods for the ocular manifestation. However, other diagnostic methods evaluating tear film status are still worthy for the staging and treatment planning for dry eye, including direct observation of tear film, TF-BUT, Schirmer test, and measurement of the tear film levels of inflammatory mediators. Proper choice of the ocular treatment options according to the grade of dry eye, including tear substitutes, secretagogue, topical anti-inflammatory therapy including corticosteroids and cyclosporine, punctal occlusion, mucolytic therapy, and autologous serum, would be helpful in improving dry eye symptoms and clinical outcomes.

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