ECRONICON OPEN ACCESS

EC OPHTHALMOLOGY
Review Article

Dry Eye Disease in Primary Sjogren's Syndrome: An Overview

Faten Frikha* and Zouhir Bahloul

Department of Internal Medicine Hedi Chaker Hospital, Medical University School of Sfax, Tunisia

***Corresponding Author**: Faten Frikha, Department of Internal Medicine Hedi Chaker Hospital, Medical University School of Sfax, Tunisia.

Received: May 24, 2017; **Published:** June 28, 2017

Abstract

Sjogren's syndrome (SS) is a chronic systemic autoimmune disease characterized by hypofunction of exocrine glands (mainly the lacrimal and salivary glands) with a wide spectrum of extraglandular manifestations that affect the skin, the lungs, the musculoskeletal system, the heart, the gastrointestinal, the renal and the peripheral nervous systems.

Keywords: *Primary Sjogren's Syndrome; Dry Eye; Tears; Management*

Abbreviations

SS: Sjogren's Syndrome; pSS: Primary Sjogren's Syndrome; ACR: American College of Rheumatology; EULAR: European League Against Rheumatism

Introduction

Sjogren's syndrome (SS) is a chronic systemic autoimmune disease characterized by hypofunction of exocrine glands (mainly the lacrimal and salivary glands) with a wide spectrum of extraglandular manifestations that affect the skin, the lungs, the musculoskeletal system, the heart, the gastrointestinal, the renal and the peripheral nervous systems [1,2]. Dry eyes and dry mouth are the most common complaints. Lymphoplasmocytic infiltration and destruction of the salivary and lacrimal glands is the histological hallmark of SS, leading to reduced lacrimal and salivary flow. SS is also characterized by the presence of rheumatoid factor, hypergammaglobulinemia, and autoantibody to Ro/ Sjogren's syndrome-related antigen A (anti-Ro/SSA) and La/Sjogren's syndrome-related antigen B (anti-La/anti-SSB) [1-3]. SS can be associated to other autoimmune diseases (systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), scleroderma, thyroiditis) called secondary Sjogren's syndrome (sSS), or occurs alone as the primary SS (pSS) [4].

Dry eyes diseases and their complications may be the first presenting symptoms of pSS and are commonly seen in Ophthalmology practices. This review provides a brief overview on primary Sjogren's syndrome and dry eye disease from the perspective of ophthalmology.

Primary Sjogren syndrome

Epidemiology

Primary SS has a worldwide distribution with an estimated incidence of 4 per 1000 patients per year [4] and a reported prevalence between 0.01% to 0.09% [5]. The disease affects mainly women, in the ratio of 9:1. The incidence peak is between 40 and 60 years of age, although pSS can occur at any age.

Etiopathogenesis

The etiology and pathogenesis of this connective tissue disease remain obscure. It has been suggested that genetic, environmental, viral and hormonal factors might contribute to the development of this auto-immune disorder. Activated B lymphocytes are a hallmark of

the disease with systemic production of autoantibodies (anti-SSA/Ro and anti- SSB/La) that interfere with muscarinic receptors. B cell activating factor (BAFF), a cytokine that promotes B cell proliferation, maturation and survival, is one of the key factors in this pathogenesis. Inflammatory cells involved in dry eye disease are T-lymphocytes, especially T-helper 17-subset (Th17), and many cytokines (interleukin (IL)-1, IL2, IL-4, IL-5, IL-6, IL-10, IL-17, IL-18, interferon (IFN)-gamma, tumor necrosis factor (TNF)- alpha, IL-1beta) and a chemokine (IL-8) [4,6].

Clinical Manifestations

The main symptoms in Sjogren's syndrome are keratoconjunctivitis sicca (dry eye) and xerostomia (dry mouth) due to lymphocytic infiltrates of lachrymal and salivary glands.

Other Symptoms of dryness may involve the skin (Xerosis) [4,7] or the vagina (in women with dyspareunia, and vulvar pruritus) [8].

Extraglandular manifestations occur in approximately 50% of patients with involvement of diverse organ systems including the musculoskeletal system (arthritis/arthralgia, myositis), the skin (palpable purpura, annular erythema) [7], the pulmonary system (interstitial pneumonitis, follicular bronchiolitis), the hematologic system (leukopenia, neutropenia, thrombocytopenia) [9], neurologic system (peripheral neuropathy [10], myelitis), the vascular system (Raynaud, vasculitis) or the renal system (interstitial nephritis with renal tubular acidosis).

SS is also characterized by the presence of multiple related comorbidities, including depression and fibromyalgia that may influence the severity of patient symptoms [4].

Classification Criteria

The most commonly used classification criteria have been the American-European Consensus Group (AECG) criteria [11]. They include both symptoms (positive response to one of 3 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 3 times a day?) and signs (positive in one of two: Schirmer without anesthesia of ≤5mm/ 5 min or vital dye staining of the ocular surface ≥ 4 van Bijsterveld scoring system) of dry eye disease.

In 2012, new classification criteria developed using the NIH-funded Sjogren's International Collaborative Clinical Alliance (SICCA) registry were published [12].

Recently, a new approach has been developed by the American College of Rheumatology and European League Against Rheumatism (2016 ACR/EULAR Classification Criteria for Primary Sjogren's Syndrome). Those diagnostic criteria use two dry eye signs: Schirmer test of < 5 mm/5 min, and/or the presence of Ocular Staining (van Bijsterveld > 4 or Ocular Staining Score > 5) [13].

Dry eye disease in primary Sjogren's Syndrome

Dry eye disease (also called keratoconjunctivitis sicca) is defined by The Dry Eye Workshop (DEWS) as "a multi-factorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface" [14].

Causes of dry eyes [15]

Normally, the tear film is composed of three layers: a mucin layer that sits on the epithelial surface; a middle aqueous layer; and an outer lipid layer that plays a role in preventing tear evaporation.

Dryness is caused by aqueous tear deficiency related to diminished tear production (due to reduced aqueous secretion from lacrimal glands) or by excessive tear evaporation (due to a deficient lipid layer) [15,16]. Symptoms of dryness of the eyes are common among the

elderly and there are many causes for mucosal dryness. SS is an important diagnostic consideration particularly in older women presenting with dry eyes an dry mouth.

Aqueous Tear Deficiency related to decreased tear production

- Sjogren's syndrome
- Age-related dry eye
- Systemic medications (antihistamines, b-blockers, antispasmodics)
- Lacrimal gland duct obstruction
- Ocular sensory loss leading to reflex hyposecretion (diabetes mellitus, corneal surgery, contact lens wear, trigeminal nerve injury)
- Lacrimal gland infiltration (sarcoidosis, lymphoma, graft versus host disease, Human immunodeficiency virus infection and acquired immune deficiency syndrome (HIV/AIDS), IgG4-related disease).

Evaporative Tear Deficiency

- Meibomian gland dysfunction (posterior blepharitis)
- Exophthalmos, poor lid apposition, lid deformity
- Low blink rate
- Ocular surface disorders (e.g. vitamin A deficiency, toxicity from topical drugs/ preservatives, contact lens wear)
- Ocular surface disease (allergic conjunctivitis).

Evaluation of Dry Eye Disease

Evaluation of dry eye involves the assessment of ocular symptoms (burning, stinging, foreign body sensation, itching, or soreness), and the examination of several objective parameters (tear production, tear film stability, tear osmolarity, lid margin disease, and ocular surface damage).

There is discordance between signs and symptoms; in fact, some studies have shown that more than 40% of patients with objective evidence of dry eye disease are asymptomatic.

An objective evaluation is needed for the diagnosis, the determination of severity, and the evaluation of response to treatment for patients with dry eye disease.

There are many questionnaires which are used in clinical trials for the evaluation of symptoms: The Ocular Surface Disease Index (OSDI), the Standard Patient Evaluation of Eye Dryness questionnaire (SPEED), the Symptom Assessment in Dry Eye survey (SANDE) [17].

The assessment of dry eye requires multiple tests including the Schirmer test, the tear breakup time, the lissamine green staining test, and the corneal staining with fluorescein dye.

The Schirmer test is used to measure change in tear volume by observing wetting of a filter paper placed over the inferior eyelid. More than 10 mm of moisture on the filter paper after 5 minutes is a sign of normal tear production. The normal value for Tear breakup time is greater than 10 seconds. A short value is an indicator of tear instability.

Lissamine green, fluorescein, and rose bengal are vital dyes used to evaluate the ocular surface. Lissamine green is most commonly used to stain the conjunctiva and fluorescein the cornea. The presence of corneal and/or conjunctival staining with a vital dye is a clinical indicator of inflammation.

Abnormal Schirmer test and conjunctival staining were associated with a higher likelihood of having a positive labial salivary gland biopsy and immunology tests for SS.

Several imaging methods are used: interferometry, meibography, corneal topography, and ocular coherence tomography. They may characterize patients as evaporative or aqueous deficient.

Management of dry Eye disease

Management of dry eye disease is based upon it severity and the patient response to each therapy. All patients should try a series of approaches to find what treatment works best [18].

Many diagnosis and treatment guidelines have been developed, including the Delphi (the Dry Eye Preferred Practice Patterns of the American Academy of Ophthalmology and the International Task Force Delphi Panel on Dry Eye) panel treatment recommendations for dysfunctional tear syndrome (2006), the International Dry Eye Workshop (DEWS) (2007), the Meibomian Gland Dysfunction (MGD) Workshop (2011), and the updated Preferred Practice Pattern guidelines from the American Academy of Ophthalmology pertaining to dry eye and blepharitis (2013).

Foulks., *et al*. has explored recently the topic of treatment for dry eye disease specifically in SS patients [18]. Treatment of very severe dry eye disease related to Sjogren syndrome should be coordinated with an internist or a rheumatologist. In fact, dry eye in pSS is often severe and requires more aggressive treatment.

Artificial tears replacement

Artificial tears and ocular lubricants are usually the first line therapy for dry eyes.

There is a very wide range of available products with a wide variety of ingredients and viscosity (e.g. methylcellulose, propylene glycol, and glycerin).

Artificial tears with low viscosity are "light" and watery. They provide quick relief with no blurring of the vision. Artificial tears with high viscosity are more gel-like and can provide longer-lasting lubrication but they cause significant blurring of the vision.

Anti-inflammatory and immunomodulatory agents

Treatment with anti-inflammatory agents such as short course of topical corticosteroids and cyclosporine decreases the degree of associated inflammation.

Topical cyclosporine 0.05 % is a pharmacologic treatment which is approved by FDA to treat dry eye disease. It can reduce fluorescein staining, increase tear production, reduce expression of pro-inflammatory cytokine and decrease frequency of artificial tear use.

Lifitegrast ophthalmic solution 5% (Xiidra ®) has been recently FDA approved in the USA. It reduces the inflammatory response resulting from T-cell adhesion to endothelial cells.

Omega-3 supplementation [Eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and alpha linolenic acid (ALA)] can be also effective in treatment of dry eyes [19].

Combined with oral omega-3 therapy, Cyclosporine is effective and may be used chronically with minimal side effects compared with steroids.

Secretagogues

Oral pilocarpine and cevimeline are indicated for treatment of dry mouth in SS. They stimulate the secretion of tears and saliva. Two topical secretagogues: rebamipide and diquafosol tetrasodium are approved in Japan for dry eyes treatment.

Other treatment options

- Education and environmental (computer use, reading, schoolwork and other situations that may exacerbate dry eye disease) or dietary modifications should be considered.

- Some of other systemic medications used to treat SS such as Hydroxychloroquine or biologics drugs have not been demonstrated to be effective on dry eyes.

Hydroxychloroquine (HCQ), which is recommended as a first-line therapy for inflammatory musculoskeletal pain associated with pSS in the latest Sjogren's Syndrome Foundation Clinical Practice Guidelines [16], has no a significant effect in SS regarding to the subjective symptoms including dry eyes.

The results of studies regarding Rituximab, a chimeric monoclonal antibody anti-CD20 that leads to B cell depletion, are controversial. In a recent study, the treatment with a single course of Rituximab for patients with SS provides discrete effect for improving lacrimal gland function [20].

Other therapeutic options may be considered include the use of plugs that block the puncta. Temporary punctal occlusion may be accomplished with collagen (dissolvable) or silicone (permanent) plugs. Electrocauterization of the inferior puncta may be performed in patients with severe dry eye syndrome disease.

Conclusion

Dry eye disease is a multifactorial disease. It is related to the volume of tears production, the rate of tear evaporation and the presence or absence of inflammation. Early detection and appropriate treatment of dry eye disease may help prevent severe complications such as corneal ulcers. The chronic nature of the disease emphasizes the importance of patient's regular follow-up.

Bibliography

1. Ferro F., *et al*. "One year in review 2016: Sjogren's syndrome". *Clinical and Experimental Rheumatology* 34.2 (2016): 161-171.

2. Baldini C., *et al*. "Primary Sjogren's syndrome as a multi-organ disease: impact of the serological profile on the clinical presentation of the disease in a large cohort of Italian patients". *Rheumatology (Oxford)* 53.5 (2014): 839-844.

3. Mackay F., *et al*. "An important role for B-cell activation factor and B cells in the pathogenesis of Sjogren's syndrome". *Current Opinion in Rheumatology* 19.5 (2007): 406-413.

4. Both T., *et al*. "Reviewing primary Sjögren's syndrome: beyond the dryness - From pathophysiology to diagnosis and treatment". *International Journal of Medical Sciences* 14.3 (2017): 191-200.

5. Qin B., *et al*. "Epidemiology of primary Sjögren's syndrome: a systematic review and meta-analysis". *Annals of the Rheumatic Diseases* 74.11 (2015): 1983-1989.

6. Nocturne G and Mariette X. "Advances in understanding the pathogenesis of primary Sjogren's syndrome". *Nature Reviews Rheumatology* 9.9 (2013): 544-556.

7. Fox RI and Liu AY. "Sjogren's syndrome in dermatology". *Clinics in Dermatology* 24.5 (2006): 393-413.

8. Lehrer S., *et al*. "Gynecologic manifestations of Sjogren's syndrome". *American Journal of Obstetrics and Gynecology* 170.3 (1994): 835-837.

9. Ramos-Casals M., *et al*. "Primary Sjogren syndrome: hematologic patterns of disease expression". *Medicine* 81.4 (2002): 281-292.

10. Pavlakis PP., *et al*. "Peripheral neuropathies in Sjogren's syndrome: a critical update on clinical features and pathogenetic mechanisms". *Journal of Autoimmunity* 39.1-2 (2012): 27-33.

11. Vitali C., *et al*. "Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group". Annals of the Rheumatic Diseases 61.6 (2002): 554-558.

12. Shiboski SC., *et al*. "American College of Rheumatology Classification Criteria for Sjögren's Syndrome: A Data-Driven, Expert Consensus Approach in the SICCA Cohort". *Arthritis Care and Research (Hoboken)* 64.4 (2012): 475-487.

13. Shiboski CH., *et al*. "2016 American College of Rheumatology/European League Against Rheumatism classification criteria for primary Sjögren's syndrome: A consensus and data-driven methodology involving three international patient cohorts". *Annals of the Rheumatic Diseases* 76.1 (2017): 9-16.

14. "The definition and classification of dry eye disease: report of the Definition and Classification Subcommittee of the International Dry Eye Workshop (2007)". *Ocular Surface* 5.2 (2007): 75-92.

15. Baer AN and Walitt B. "Sjögren Syndrome and Other Causes of Sicca in Older Adults". *Clinics in Geriatric Medicine* 33.1 (2017): 87-103.

16. Vivino FB., *et al*. "New Treatment Guidelines for Sjögren's Disease". *Rheumatic Disease Clinics of North America* 42.3 (2016): 531-551.

17. Kuklinski E and Asbell PA. "Sjogren's syndrome from the perspective of ophthalmology". *Clinical Immunology* (2017).

18. Foulks GN., *et al*. "Clinical Guidelines for Management of Dry Eye Associated with Sjögren Disease". *The Ocular Surface* 13.2 (2015): 118-132.

19. Rosenberg ES and Asbell PA. "Essential fatty acids in the treatment of dry eye". *Ocular Surface* 8.1 (2010): 18-28.

20. Souza FB., *et al*. "Rituximab Effectiveness and Safety for Treating Primary Sjögren's Syndrome (pSS): Systematic Review and Meta-Analysis". *PLoS One* 11.3 (2016): e0150749.

Volume 7 Issue 2 June 2017