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The Risk of Infection in Dry Eye Syndrome Accompanying Primary Sjögren's Syndrome

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Additional information is available at the end of the chapter

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Abstract

Primary Sjögren's syndrome (pSS) is an autoimmune disease, which dominates the symptoms resulting from inflammatory infiltrates in exocrine glands. Frequently, patients complain of a feeling of sand under the eyelids, eye irritation, and red eye caused by a decrease in tear secretion. The ophthalmic examination beyond lowering the secretion of tears in Schirmer's test evaluation in cases with a significant intensification of dry eye disease (DED) can be visualized by measuring ocular staining score (OSS) using lissamine green and fluorescein staining. OSS can demonstrate the degree of damage to the corneal surface. It is known that keratoconjunctivitis sicca (KCS) in pSS is not only limited to the complaints of unpleasant feeling of sand under the eyelids but also can lead to serious corneal damage and decreased vision even to blindness. And between the others, complications of KCS in pSS must be replaced with an increased susceptibility to infection. We should also pay attention to possible co-infection with Epstein-Barr virus (EBV) virus and bacterial co-infections, e.g., *Chlamydia pneumoniae*, *Staphylococcus aureus*, or latent conjunctival infections *Chlamydia trachomatis*, *Mycoplasma hominis*, and *Ureaplasma urealyticum* in group of patients with DED, not only in pSS group. Another issue is simultaneous with hepatitis C virus (HCV) infection coexistence of clinical and laboratory features of Sjogrens syndrome and accompanying this situation clinical signs of KCS. To sum up symptoms of KCS in primary Sjögren's syndrome and in all patients with DED should be evaluated individually and should take into account the increased risk of infection among these patients.

Keywords: dry eye, infection, Sjögren's syndrome

1. Introduction

Primary Sjögren's syndrome (pSS) is an autoimmune disease in which the symptoms resulting from inflammatory infiltrates in exocrine glands dominate. Frequently, patients complain of

a feeling of sand under the eyelids, eye irritation, and red eye caused by a decrease in tear secretion. In pSS, other exocrine glands could be affected—among them: salivary glands, pancreas, vaginal mucous membranes, and glands of gastrointestinal tract or situated in bronchial tree. The patient may complain of dry mouth, dry vagina, and inflammation of the gastric and esophageal reflux. Dry cough may also occur. In the course of pSS interstitial changes in the lungs may occur with a progressive reduction of lung function and a failure of cardiovascular system (in conjunction with the development of right ventricular failure and pulmonary hypertension). Autoimmune inflammatory process may also involve peripheral and central nervous system, including cranial nerves, with symptoms of mixed sensory and motor neuropathy or multiple sclerosis (MS)-like symptoms. In pSS, B lymphocytes (B-cells) play a key role, with their hyperreactivity, leading to the overproduction of autoantibodies. Through the interaction between the cells, stimulation reaches T lymphocytes (T-cells), which are the first to form infiltrates in exocrine glands. The gradual destruction of the exocrine glands by the inflammation and by the autoimmune process causes the above- described symptoms [1].

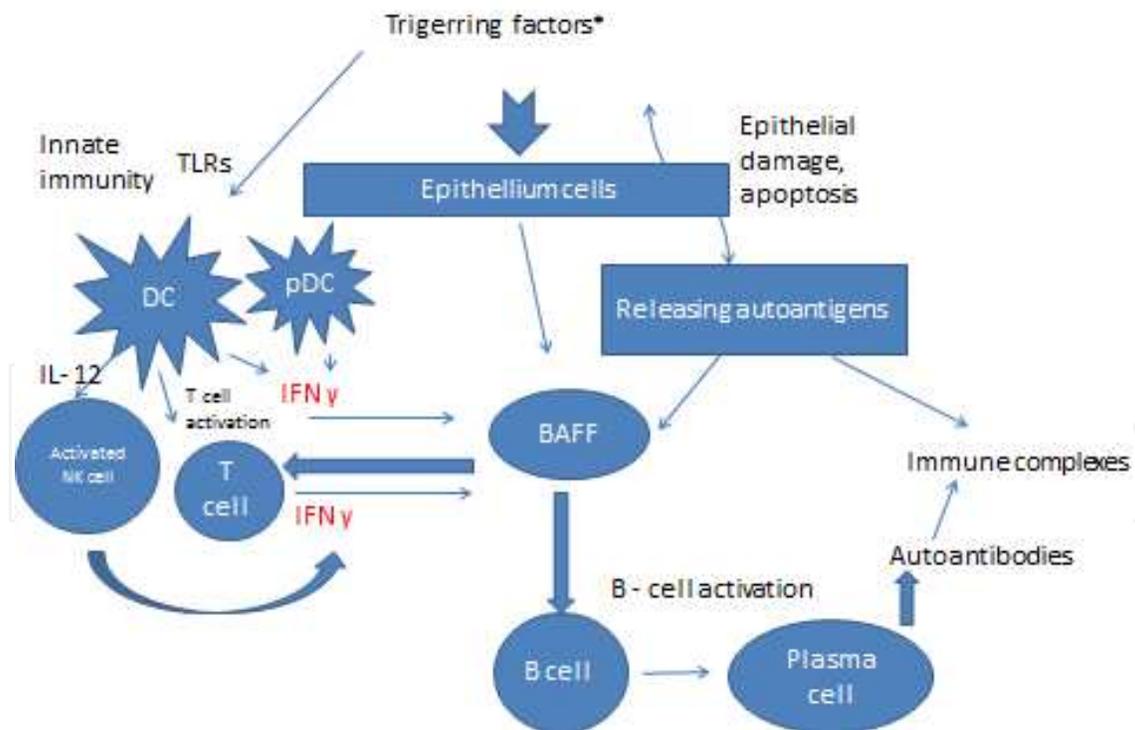
2. Epidemiology

The epidemiology data of dry eye symptom (DES) reveal that it affects from 5 to 35% of the population. Such discrepancy in the assessment of the frequency of the DES occurrence might be the effect of using different dry eye definitions in each of the studies, as well as the research being performed on different ethnic populations. The data given by the Women's Health Study indicate that Hispanics and Asians display greater predisposition to more severe symptoms of dry eye than Caucasians [2]. The incidence of Sjögren's syndrome, in which DES is a dominant symptom, may also be underestimated. There are no accurate records on the prevalence of this disease, with its milder course prone to be undiagnosed [3,4]. It is estimated that pSS occurs in 0.1–3.0% of the general population. The disease is more common for women (female/male ratio 9:1), affecting mainly individuals between the age of 40 and 60, with the disease most frequently occurring around 50 years of age [5].

3. Outline pathogenesis

The pathogenesis of the disease is not entirely clear and factors responsible for its development are still being sought. It is recognized that environmental or endogenous antigens trigger an inflammatory response in susceptible individuals. Among the environmental factors, several viral infections are considered as primary pSS cause: Epstein-Barr virus (EBV), human T-cell lymphotropic virus type-1 (HTLV-1), cytomegalovirus (CMV), and hepatitis C virus (HCV) [5–7]. These infections may result in the epithelial barrier damage and the release of autoantigens from the affected epithelial cells. In the case of individual genetic predisposition to pSS, the autoimmune process may develop, involving both mechanisms of innate and adaptive immunity. Genetic factors responsible for the predisposition to pSS development include the

presence of HLA-B8, HLA-DW3, HLA-DR3, and DRw52 genes; polymorphism of interferon regulatory factor 5 (IRF 5) gene may also play similar role [1,8]. The release of autoantigens triggers innate immunity through the activation of epithelial (EC) and dendritic cells (DC). DC stimulation promotes interferon I and II pathways; DCs also produce IL-12, which activates natural killer cells (NKCs) and stimulates Th1 cells. Both NKC and Th1 cells secrete interferon gamma (INF- γ), responsible for the tissue damage and stimulating the secretion of B cell activation factor (BAFF). BAFF is produced by T and B cells—both activated by DC; BAFF production is also strongly stimulated by interferon (IFN)- α , released by pDC (plasmacytoid dendritic cells). Moreover, the activation of innate response by Toll-like receptors (TLR-9, TLR-7) additionally increases the secretion of BAFF. This overproduction of BAFF can cause constant stimulation of B cells through different pathways and causes the loss of self-tolerance by T and B cells, overproduction of immunoglobulins, of autoantibodies (predominantly SS-A, SS-B) in particular, and the formation of germinal centres (GC) in the target organs. The affected tissues (especially the salivary glands) display the overexpression of cytokines such as tumor necrosis factor (TNF), lymphotoxin, CXC, and chemokines (ligand 13, 9, 21). This process can lead to the development of lymphoma. The occurrence of primarily marginal zone B-cell lymphoma (MZBCL) has been observed in about 8% of pSS patients—40-fold frequency of the MZBCL in the healthy population [9,10]. The scheme of pathogenesis of pSS is shown on figure1.



*Trigerring factors as viral and bacterial infections, UVA (ultraviolet-A radiation), hormones, genetic predisposition
 DC-dendritic cell, pDC plasmacytoid DC cell, IFN- γ - interferon gamma, TLRs- Toll-like receptors, IL-12- interleukine 12, TH1-type1 helper cell, BAFF- B cell activating factor, NK-cell natural killer cell

Figure 1. Scheme of pathogenesis [1, 5]

The symptoms of primary Sjögren's syndrome are not homogenous. The autoimmune process involving the epithelium affects many systems and organs, so its manifestations can be very diverse. Symptoms can be divided into two primary groups: common ones, such as dry eyes and mouth, and less frequent symptoms, such as peripheral neuropathy with legs numbness and weakness—with reduced or without reflexes, dysesthesia, feeling of temperature, and vibration. Neurological symptoms may also indicate the seizure of the autonomic nervous system with cardiac arrhythmias or gastrointestinal motility disorder. In the pSS, trigeminal neuralgia and seizure of various nerves ("multiple mononeuropathy") may also occur. The central nervous system can also be involved in pSS therefore myelitis with weakness of limbs and disturbances of urination may occur. Neurological symptoms can also suggest MS, which leads to misdiagnosis. The types of symptoms in pSS are presented in Table 1.

Common symptoms	Less common symptoms/organ involvement
xerophthalmia	intestinal like disease (ILD)
xerostomia	bronchitis
troubles with swallowing	dysphagia, gastrointestinal reflux
dental caries	chronic gastritis
arthralgia	symptoms of PBC (primary biliary cirrhosis) and AIH
arthritis (non-erosive)	(autoimmune hepatitis)
myalgia	pericarditis
fatigue	pulmonary hypertension
general weakness	celiac-like diseases
weight loss	distal renal tubular acidosis (RTA type 1)
fever	nepritis/glomerulonephritis
Reynaud's phenomenon	chronic renal insufficiency
depression	vasculitis
anxiety	peripheral polyneuropathy, cranial neuropathy, mononeuritis multiplex sensorineural hearing loss SM-like syndrome

Table 1. Symptoms of pSS

Keratoconjunctivitis sicca (KCS) is the most frequent cause of complaints from the organ of sight of patients with Sjögren's syndrome, although it can be present in a number of other diseases [11]. KCS is caused by a decreased tear production or increased tear film evaporation. It manifests itself with a feeling of dryness— described as a sandy-gritty eye irritation— burning, stinging, and feeling of tired eyes. In severe cases, the patients suffer from pain, redness, or even decreased vision. The decreased tear production affects the overall reduction of tear secretin as well as limits the aqueous phase of the tears. The causes of DES and complications associated with KCS are presented in Tables 2 and 3.

Primary Sjögren's syndrome may be associated with other autoimmune diseases. Their simultaneous presence can influence both the course and the prognosis of the disease. The most common coexisting diseases are presented in Table 4.

The initial symptoms of an infection in dry eye syndrome—the eye pain, burning, eye redness—can be associated with symptoms of dryness and aseptic KCS, as well as with an incipient infection. However, when the pain and red eye are accompanied by a purulent excretion—a bacterial infection should be suspected. Viral infections primarily cause an eye pain and intense redness. These symptoms may also be associated with general symptoms of infections such as muscle pain, fever, and fatigue. The diagnosis and treatment are determined by the result of the ophthalmological examination.

Keratoconjunctivitis sicca symptoms – conditions and diseases

Environmental factors as dust, smoke, dry air, aircondition, Allergic conjunctivitis	
Behavior : working at the computer, watching television	Sarcoidosis
long - causing less frequent blinking	Lymphoma
Contact lenses	Graft versus host disease (GvHD)
Age - related dry eye (ARDE)	Autoimmune deficiency (AIDS)
Menopause (low level of estrogens)	Diabetes
Using drugs : antihistamines, β -blockers, diuretics,	Trachoma (cause chlamydia trachomatis)
antispasmodics,	VII cranial nerve damage
diuretics, psychotropic	Meibomian gland dysfunction
Vitami A deficiency	Reflex motor block (central damage of VII cranial nerve)
	Reflex sensory block (trigeminal nerve denervation)

Refractive surgery : laser assisted keratomileusis (LASIK); photorefractive keratoplasty (PRK)

Table 2. Keratoconjunctivitis sicca —not only symptom of pSS

Eye problems in primary Sjögren's syndrome

discomfort
 pain
 red eye
 conjunctivitis
 corneal erosions,
 filamentary keratitis,
 corneal ulcers
 decreased vision

Table 3. Eye complications associated with KCS

The diseases coexisting with p SS

Autoimmune Thyroid Disease (AITD) - Haschimoto disease
 Intestinal Lung Disease (ILD)
 Primary Biliary Cirrhosis (PBC)
 Autoimmune hepatitis (AIH)
 Cryoglobulinemia
 Autoimmune pancreatitis (AIP)
 Distal renal tubular acidosis (RTA)
 Sclerosis-multiplex like syndrome

Table 4. The diseases coexisting with p SS

4. Risk of eye infections in KCS

The conjunctivitis and changes in the cornea in the pSS are aseptic, yet coexisting infections that may play a part in the development and course of the pSS, KCS in particular. Due to the large differences in estimating the incidence and prevalence of dry eye syndrome (from 5 to 35%) and due to differences in the frequency of recognition of Sjögren's syndrome, it is difficult to accurately estimate the rate of incidence of sicca syndrome associated with eye infections. However, impaired humidification of the eye and related development of KCS undoubtedly significantly increase the risk of bacterial contamination, compared with the normal population.

Among viral infections, EBV plays an important role, which is not limited to the above-mentioned impact on the immune system and lymphocytes. The EBV may be a separate, independent cause of the dry eye syndrome because the infection affects mucosal surfaces and lymphoid tissues. The EBV presence persists in ocular surface epithelia, following primary infection and may cause dacryoadenitis, which leads to abnormal tear secretion [12,13]. Although no direct link between the occurrence of KCS and EBV infection has been established, the influence of EBV on patient's immune status could cause the development of symptoms of dryness. Apart from EBV, other viral infections, which may contribute to the occurrence of KCS and clinical picture of Sjogren's disease, include in particular HCV, human T-cell lymphotropic virus (HTLV), Human (HSV-1), and HIV [7,14]. HCV infection may be responsible for the incidence of ocular symptoms in the course of pSS, such as KCS retinopathy, scleritis, and keratitis. In HSV-1 infection, besides KCS, keratitis, blepharitis, conjunctivitis, uveitis, and retinitis may develop [15]. Viral agents involved in pathogenesis of pSS, EBV in particular, can be simultaneously responsible for causing KCS, conjunctivitis, and reducing resistance of the corneal epithelium.

Although viruses play a significant role in the pathogenesis of pSS, the importance of bacterial co-infections, e.g., *Chlamydia pneumonia* in the course of pSS should not be underestimated [16]. It is known that a tear film has antimicrobial properties, whereas the normal ocular surface contains bacterial flora, including *Staphylococcus epidermidis*, *S. aureus*, and diptheroides (e.g.,

Corynebacterium diphtheriae and *Propionibacterium acnes*). However, in patients with DESs and treated with immunosuppressants, such therapy, along with dryness and cornea damage, results in increased susceptibility to common bacterial infections. In the diagnosis of ocular symptoms, bacterial keratitis should come under consideration. This may more likely be caused by *S. aureus*, *Haemophilus influenzae*, *Streptococcus pneumoniae* and, in the case of use of contact lenses, more often *Pseudomonas aeruginosa*. Hori et al. [17] showed that infections with bacteria resistant to fluoroquinolones (*Staph. sp. Staph. aureus*) are more common in patients with dry eye syndrome, although among dry eye patients, regardless of use of punctal plugs or topical steroids, there were no differences in bacteria isolated from conjunctiva.

In the diagnosis of pSS, it must also be considered that some of the commonly known infections, such as HIV, tuberculosis, leprosy, spirochetes, hepatitis A, B, or C, parvovirus B19, Dengue fever, malaria, subacute bacterial endocarditis, and HIV can mimic Sjögren's syndrome with symptoms of eye dryness. Prognosis for the infection occurring in the course of a dry eye in Sjögren's syndrome is more serious compared to the infection cases with no additional risk factors present. This results from the, pre-existing in Sjögren's syndrome, surface damage and use of immunosuppressive therapy in this disease. Therefore, patients with Sjögren's syndrome and a coexisting bacterial infection of the eye belong to a group in which immediate antibiotic therapy should be considered.

5. Cicatrizing conjunctivitis as complication of dry eye disorders

In course of pSS, a slow progressive cicatrizing conjunctivitis (PCC) may also develop with complications such as an impairment of vision (and even blindness), pain, and corneal damage. Cicatrizing is a type of scarring, which can occur as a complication of dry eye accompanied by autoimmune diseases like Sjögren's syndrome or ocular cicatrical pemphigoid. Chronic conjunctival cicatrization (CCC) can also occur as an effect of thermal and chemical burns, postinfectious conjunctivitis, ocular rosacea, atopic keratitis, graft versus host disease, and Stevens-Johnson syndrome (in the latter case prognosis being particularly poor) [18,19]. The presence of cicatrizing conjunctivitis predisposes to microbial keratitis, especially in Sjögren's syndrome. Ormerod et al. [20] described that almost 50% of studied Sjögren's syndrome patients had microbial keratitis as a complication of sterile ulcerations and were subject to recurrent infections. Most common infection in that group was Gram-positive bacteria such as *S. aureus*. It was also noted that patients with conjunctival cicatrization (CC) in the course of Sjögren's syndrome had higher complication rate compared to those in which CC was caused by other factors; such complications included corneal perforation, endophthalmitis, and descemetocele. Interestingly, the authors also point out that a long-term therapy with topical corticosteroids and application of bandage contact lenses used in refractive surgery enhanced a risk of microbial keratitis.

Treatment strategies in CC depend on the cause of the underlying disease. In case of microbial keratitis, topical antibiotic use is recommended.

6. Diagnosis criteria of Sjogren's syndrome

Over the years (since 2002), pSS recognition has been based on the criteria set by American-European Consensus Group (AECG) in which both Schirmer's test and tear break-up time (BUT) results are assessed. According to former pSS criteria, the examination of salivary secretory function was assessed by measuring minute salivation and evaluation in sialography. From 2012, the American College of Rheumatology (ACR) has proposed new diagnostic criteria that are presented in Table 5 [21–23].

Sjögren's Syndrome criteria ACR 2012

1. Positive serum anti-SSA/Ro and/or anti-SSB/La or positive rheumatoid factor and ANA titer 1:320
 2. Labial salivary gland biopsy exhibiting focal lymphocytic sialadenitis with a focus score 1 focus/4 mm²
 3. Ocular staining score 3 proving keratoconjunctivitis sicca *
-

Exclusions:

Head and neck radiation treatment
 Active Hepatitis C infection
 Acquired immunodeficiency syndrome
 Sarcoidosis
 Amyloidosis
 Graft versus host disease (GVHD)
 IgG4-related disease (IgG4-RD)

*Excluding the patients using daily eye drops for glaucoma and who has had corneal surgery or cosmetic eyelid surgery in the last 5 years

Table 5. Diagnostic criteria of Sjögren's syndrome

It was found that most changes associated with KCS can be demonstrated using the Lissamine green and fluorescein stainings. Both stainings are used for establishing ocular staining score (OSS), determined for each eye separately and used to identify the degree of change in the conjunctiva (Lissamine green) as well as the damage to the cornea (fluorescein) [21]. The slit lamp examination reveals damage to the cornea, but using staining allows for a quantitative and qualitative assessment of these changes. Another test which can be useful in the evaluation of dry eye is a tear osmolality test. However, this test is not included in the criteria for pSS diagnosis [24,25].

The newly proposed criteria also apply to the early stage of diagnosis, when no evidence of the presence of autoantibodies for ribonucleoproteins anti-Ro (SS-A) and anti-La (SS-B) is available. In such a case, the mutual presence of rheumatoid factor (RF) and of antinuclear antibody (ANA, the latter in titer of no less than 1: 320) proves the diagnosis [25].

The important part of establishing pSS diagnosis is confirming the presence of typical changes in histopathology material from minor salivary gland biopsy (MSGB)— mononuclear inflammatory cells form focal infiltrates of more than 50 cells in 4 mm² of glandular section. The so-called focus score (FS) is based on the assessment of number of such changes in the tested

material. The presence of one or more foci is considered as a positive result. Primary Sjögren's syndrome may be accompanied by other than SS-A, SS-B, or RF autoantibodies [26,27]. Most common pSS-specific antibodies, also associated with other autoimmune diseases, are presented in Table 6.

Autoantibodies in pSS

diagnostic hallmark:

Anti SS-A (Ro)

Anti-SS-B (La)

Autoantibodies in pSS and other autoimmune diseases:

Antinuclear antibodies (ANAs)

Rheumatoid factors (RF)

Anti-centromere antibodies (ACA) (systemic sclerosis)

Anti-mitochondrial antibodies (AMA) - Primary biliary cirrhosis

Anti-cyclic citrullinated peptide antibodies (anti-CCP)

anti-smooth muscle antibodies (ASMA) Autoimmune hepatitis

dsDNA (systemic lupus erythematosus)

Anti- thyroglobulin (anti TG) – autoimmune thyroiditis

Anti-thyroid peroxidase (anti-TPO)- autoimmune thyroiditis

Novel autoantibodies:

Anti-M3R antibodies

Anti- β fodrin

Anti - protein 1 (SP-1),

Anti - carbonic anhydrase 6 (CA6)

Anti-parotid secretory protein (PSP)

Table 6. Autoantibodies in pSS

Several laboratory tests prove helpful in the diagnosis of pSS, although they do not constitute a part of the present diagnostic pSS criteria. In particular, the deviations in the composition of blood cells and proteins occur and the increased erythrocyte sedimentation rate (ESR) with normal or low concentrations of CRP (a similar situation may exist in multiple myeloma) may be present. Laboratory findings in pSS are presented in Table 7.

Laboratory findings in pSS

Elevated erythrocyte sedimentation rate (ESR),

leucopenia,

anemia

low platelet count

Hypergammaglobulinemia (polyclonal),

ANAs, RF, anti-Ro/SS-A, anti-B/SSB,

decreased level of complement component C4

Table 7. Laboratory findings in pSS

Lissamine green (conjunctiva)		Fluoresceine (cornea)	
grade	dots	grade	dots
0	0-9	0	0
1	10-32	1	1-5
2	33- 100	2	6- 30
3	> 100	3	> 30

eye

Temporal area

Nasal area

For fluoresceine staining the extra points could be added :

- + 1 for patches on confluent staining
- + 1 for staining in pupillary area
- + 1 for one or more filaments

Figure 2. Sicca ocular staining score [25]

7. Prognosis

The emergence of pSS carries an increased risk (by 40 times – comparing to the normal population) of lymphoma development. This imposes necessity of regular monitoring and assessment in pSS of factors/markers determining patient's total capacity for developing lymphoma, including the emergence of cryoglobulins, rheumatoid factor (if previously not present) or of monoclonal proteins, chronic enlargement of the salivary glands, or persistent presence of general symptoms, such as weight loss, fever, and lymphadenopathy.

7.1. Eye examinations for the diagnosis of KCS and pSS

The ophthalmic examination includes first of all a well-known Schirmer's test used to evaluate the extent of decrease in the tear secretion.

In the case of significant intensity of dry eye syndrome, the damage to the cornea can be visualized by applying lissamine green and fluorescein staining [28]. This scoring system has been proposed for the evaluation of KCS in Sjögren's syndrome, but applies in general to the changes in the course of dry eye.

The scoring rules are illustrated in Figure 2, and photographs of eye examination in Figures 3 and 4.

The maximum score for each eye is 12. Scoring more than 3 and higher indicates KCS.

The previous AECG pSS diagnosis criteria consisted, in addition to the Schirmer's test, in other tests confirming the presence of KCS and lacrimation disorder, with Bengal rose staining among the most frequently used. This test allows for the assessment of scaly, dead cells of the corneal epithelium, and conjunctiva as well as mucus particles (filaments) fixed to the corneal

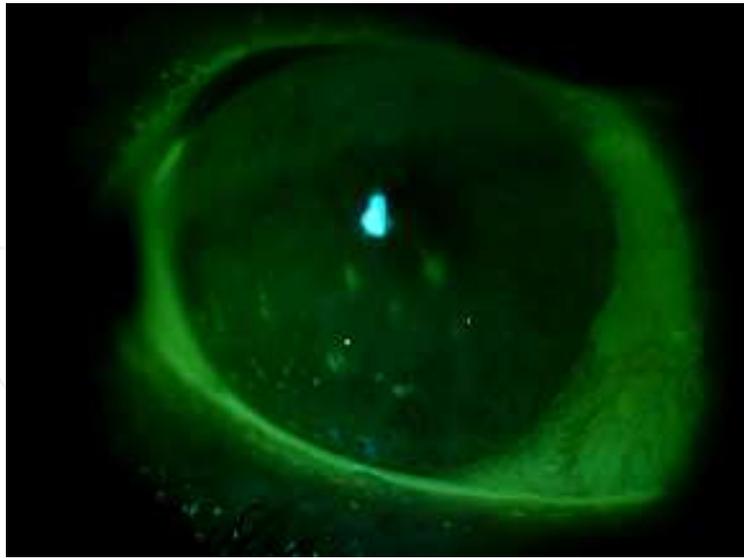


Figure 3. Fluorescein staining



Figure 4. Lissamine green staining

surface, associated with the dry eye syndrome. The results of rose Bengal staining, however, are dose-dependent and cause phototoxicity. The lissamine green dye is less irritating and thus considered better for such use. The quality and quantity of the tear film can be evaluated using tear film break up time (T-BUT)—assessing the time interval between the last complete blink and the first appearance of a dry spot or of disruption of the tear film, observed in the slit lamp. The extension of this test uses fluorescein (F-BUT) staining. The diagnosis of DES is established with BUT result ≤ 5 seconds. The limitations of this test are eye irritation and increased blink after fluorescein application as well as difficulty in meeting the condition that the patient can blink freely [28].

7.2. Own research

In our study, 30 patients—22 females (73%), 8 males (27%) in mean age of 52 years (from 22 to 85)—diagnosed with pSS revealed stronger correlation of the Schirmer's test results with FS than with OSS. The correlation coefficient of OSS with ANA, anti-SS-A, RF was higher than that of Schirmer's test with anti-SS-A and RF. OSS correlated negatively with Schirmer's test results ($r = -0.54$; $p = 0.007$). There were no differences between female and male subjects in the Schirmer's test, a group of male patients presented more pronounced symptoms of ocular dryness in the evaluation of staining scores. Our results suggest that the Schirmer's test reflects the intensity of ocular gland infiltration by inflammatory cells, whereas immunostaining proposed in the new Sjögren's syndrome criteria is more closely associated with the immunoactivity and autoantibodies production. It is obvious that the observed correlation requires further support and analysis of research performed on a more numerous group of patients.

7.2.1. Statistical analysis

Correlation analyses were performed with the Spearman correlation coefficient (because of the non-normal distribution of variables). The study was approved by the Bioethics Commission of the Institute of Rheumatology; the subjects have signed written informed consent statements. The study was supported by National Science Center (Narodowe Centrum Nauki) —grant no. 2012/05/N/NZ5/02838. The correlations are shown in Table 8.

Correlations	Correlation coefficient (Spearman test) N=30
OSS mean– SS-A	0,17
OSS mean– SS- B	0,00
OSS mean – FS	0,13
OSS mean – RF	0,04
OSS mean – ANA	-0,16
Schirmer's test mean – SS-A	-0,10
Schirmer's test mean – SS-B	0,14
Schirmer's test mean – FS	0,07
Schirmer's test mean – RF	0,20
test Schirmera średnia – ppj	-0,01
SA-A – SS-B	0,56
OSS mean – Schirmer's test mean	-0,54
Ro – FS	0,04
Ro – RF	0,20
Ro – ppj	0,25
La – FS	0,07
La – RF	0,20
La – ppj	0,27

Table 8. Correlations in patients group with pSS

The data were presented at the 3rd International Congress on Controversies in Rheumatology and Autoimmunity in 2014 [29]. Toker et al. [30] also studied the presence of anti-SS/A and anti-SS/B antibodies in tears and serum as well as assessed the correlations between subjective and objective clinical score of dry eye (then performed Schirmer's test, TBUT test, and rose Bengal staining). This study demonstrated that serum titer of anti-Ro/SSA and anti-La/SSB correlated positively with DESs and negatively with tear production.

7.3. Treatment of pSS

1. Systemic treatment of Sjogren's syndrome

The therapy of autoimmune diseases, such as pSS, is based on the elimination of inflammation and inhibition of stimulation of the immune system. Initially, immunosuppressant drugs, such as corticosteroids, methotrexate, cyclosporine A, and azathioprine are applied. For years, the effectiveness and relevance of applying antimalaria drugs for the treatment of pSS have been debated [31–33]. A number of studies confirm beneficial effects of this drug on the symptoms of dryness and the reduction of BAFF in patients with pSS without significant internal organ involvement [32–34]. In severe cases with life threatening organ involvement, the use of cyclophosphamide, infusions of immunoglobulins, and plasmapheresis are considered necessary.

In the case of renal tubular acidosis, sodium and/or potassium are administered. Considering the role of B cells in pSS, monoclonal anti-CD20 (rituximab RTX) antibodies seem to be a favorable option for therapy. RTX has already shown efficacy in the treatment of rheumatoid arthritis, SLE, and vasculitis [35–37]. The full effectiveness of other biologic drugs causing the depletion of B cells—such as Belimumab (BLyS/BAFF inhibitor) and epratuzumab (humanized anti-CD22 monoclonal antibody)—has not yet been confirmed in pSS treatment [38]. The purpose of the therapy could also be the inhibition of interferon alpha and gamma (IFN- α and IFN- γ) involved in the stimulation of B cells, but this course of therapy requires further study.

Currently, the use of mesenchymal stem cell (MSC) transplantation as a method of treatment of various autoimmune diseases, including Sjogren's syndrome, is also being contemplated [39].

2. Topical treatment—the fight against dryness

Apart from the systemic treatment, no less important for pSS patients is local treatment and alleviation of dryness symptoms. Firstly, in the case of dry eye, the influence of exacerbating factors, such as dryness, dust, long hours of working with computer, and smoking, should be limited. It is recommended to use artificial tears during the day and lubricant ointment at night. Agents used as preservatives in medical drops, even those in moisturizers—among them: benzalkonium chloride (BAK) and disodium (EDTA) pose another problem [40]. The use of over-the-counter (OTC) drops with a higher dose of preservatives increases the symptoms of dryness [41].

The wide array of medications is being used in topical treatment: eye lubricants and moisturizers, such as drops, gels, ointments containing tear substitutes, oils and petrolatum, acrylic

acid, hyaluronic acid, glycerin, erythritol, levocarnitine, hydroxymethylcellulose, carboxymethylcellulose, or glycol. The preparations without preservatives that replace tears include, e.g., Refresh (Allergan), TheraTears, Soothe (Bausch + Lomb), and System (Alcon) [41].

Ocular lubricants and moisturizers are designed to supplement the shortage of tears, osmolarity, and to improve tear film stability and act protectively. A patient with severe DES both in the course of PSS and from other causes, however, should consult the use of these substances with an ophthalmologist. Increasing the amount of tears can be achieved by permanent occluding of nasolacrimal channel and by the use of biological tear substitutes, namely a drop of the patient's own serum. The inflammatory process in the course KCS also requires anti-inflammatory therapy with cyclosporine drops and topical glucocorticoids. Research is being conducted on the use of pimecrolimus and tacrolimus as immunomodulatory drugs in drops. Also drugs stimulating tear secretion with cholinergic agonists are being used and two of them, namely pilocarpine and cevimeline, are used widely. Currently, studies are being carried out on other stimulants, among others diquafosol (P2Y2 receptor agonist) and rebamipide [42,43].

Tetracyclines (minocycline, tetracycline) might also be considered as important drugs for pSS therapy, showing both antibacterial and immunomodulating effect. They have greater than just antimicrobial effect on inflammation by inhibiting the proinflammatory cytokines as TNF or interleukin-1 (IL-1) and also inhibiting angiogenesis. They have been applied to treat eye infections, ocular and skin manifestations of acne rosacea and are used in the case of meibomian gland dysfunction [44]. In the case of complications of bacterial infection in the course of KCS, typical antibiotics covering the activities of most common pathogens are being used. These include aminoglycosides (e.g., Tobramycin), macrolides, fluoroquinolones, sodium sulfacetamide, or trimethoprim/polymyxin. While wearing contact lenses is as a possible cause of dry eye, in the treatment of DES contact lenses made of special materials such as silicone rubber and highly oxygen permeable materials may protect the eye from drying [45,46].

The surgical treatment, including placement of punctual plugs (collagen or silicone) and cauterization of the puncta, is used in cases of severe corneal injuries and at a risk of a loss of vision. The transplantation of minor salivary glands is an interesting and promising method, but so far with limited use as a therapeutic option [47]. The salivary glands are transplanted as a complex graft to the posterior lamella of the eyelids to increase an ocular surface lubrication and reduce a discomfort in dry eyes.

Frequent blinking is also important for the prophylaxis and complementary action treatment for symptoms of dry eye; avoiding situations that increase the evaporation of the tear film (e.g. wind, air conditioning, and smoking) is recommended as well. The patients with pSS and symptoms of dry eye should be controlled both by a rheumatologist and an ophthalmologist. Routine check of a dry eye should take place at least once every 3 months. However ophthalmologic monitoring frequency will depend on the severity of DESs and the presence of dry eye complications, such as infections. In the latter case, the control should be performed every few days until the infection is cured. The aim of the topical therapy is to eliminate symptoms of dryness and to directly protect mucous membranes. The systemic treatment is directed at achieving a remission—the inhibition of the disease progress, changes in internal organs, and inflammation and infiltration of exocrine glands.

8. Summary

The Sjögren's syndrome is one of the most common rheumatic diseases with predominant symptoms of dryness, particularly of the eye. Therefore, the knowledge on dry eye disease or KCS symptoms is essential not only for ophthalmologic but also for rheumatologic practice. The above section certainly does not exhaust the problem of Sjögren's syndrome, its intricate and still uncertain pathogenesis and a differentiated clinical picture. The author's intention was primarily to draw attention to the problem of DESs and associated complications, including infections.

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