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Sjögren's syndrome – diagnosis and contemporary therapeutic possibilities

Oliwia Cwalina[1], Ada Pandey[1], Dominika Prokop[1], Kinga Czarnacka[1], Małgorzata Gawlak[1], Bartosz Kuźlik[1], Katarzyna Guzek[1], Ismael Alsoubie[1], Alicja Chmura-Hołyst[1], Anna Roszkowska[1, 2], Ilona Pawlicka[1, 2], Agnieszka Piskorz[1, 2], Maciej Kozak[1, 2]

[1] Faculty of Medicine and Health Sciences, Andrzej Frycz Modrzewski Academy in Krakow
Dean: Filip Gołkowski, MD, PhD

[2] Clinical Ophthalmology Department, Provincial Ophthalmology Hospital in Krakow
Head of the Department of Ophthalmology: prof. Anna Roszkowska, MD, PhD

HIGHLIGHTS

The complexity of the disease in Sjögren's syndrome as well as the dry eye symptom, which is a multifactorial and very widespread ailment, makes it much more difficult to make the correct diagnosis.

ABSTRACT

Dry eye syndrome is a group of medical conditions that can be caused by many factors, as a result of which there is an abnormality in moisturizing of the eye surface by a tear film. One of the causes of this disorder is Sjögren's syndrome, which is an autoimmune disease in which the body produces antibodies against its own proteins. The glands of external secretion, mainly lacrimal and salivary glands are damaged as a result of inflammation. Associated with this side effects, affect negatively and reduce the quality of life, which is why in the following article we present the available therapeutic options for patients suffering from ophthalmological manifestations of Sjögren's syndrome.

Key words: Sjögren's syndrome, dry eye syndrome, therapeutic options

INTRODUCTION

Sjögren's syndrome is an autoimmune disease, also called *sicca syndrome*, classified as a rheumatological disease. The disease is manifested by chronic inflammation and proliferation of lymphocytes in the endocrine glands (lacrimal, saliva, mucous), which leads to progressive impairment of their function [1]. Quick diagnosis and appropriate treatment make it possible to avoid serious consequences within the eye, as well as internal organs, such as lung and pancreatic involvement or the risk of developing malignant lymphoma [2]. It is estimated that 1 in 10 patients with clinically significant dry eye syndrome has Sjögren's syndrome. The lack of properly targeted diagnostics can significantly delay the diagnosis, and thus the correct treatment, which in turn can significantly worsen the course of the disease, as well as increase the percentage of complications [3].

SJÖGREN'S SYNDROME – DIAGNOSTICS

Sjögren's syndrome is a picture of dryness syndrome. Symptoms of this disease is dryness of the eyes, mucous membranes of the mouth and lymphocytic infiltrates of the salivary glands. The feeling accompanying patients is chronic dryness, which in addition to the mentioned may also affect the mucous membrane of the nasal cavity, vagina, as well as the skin [4]. The disease develops slowly and mildly, as many as 98% of patients report to the doctor with symptoms that have accompanied them for many months or even years. Therefore, most cases are diagnosed at an advanced stage of the disease. In 50% of patients there is swelling of the salivary gland (one or many) – these are most often parotid glands, less often sublingual and submandibular glands. The location of symptoms reported by patients is very different, but a large percentage indicates complaints appearing in the trachea, vagina, nasal mucosa or on the skin. Dry eyes are additionally associated with pain and, as a consequence, lead to corneal damage with subsequent chronic inflammation with scarring [4].

Diagnosis of a patient with suspected Sjögren's syndrome begins with laboratory tests. In the blood results, the picture of the disease is as follows: hypergammaglobulinaemia (in 80%), monoclonal gammapathy (4–22%), cryoglobulins (30%), ANA antibodies > 1: 80 (90%), anti-Ro (55%) and anti-La (40%), rheumatoid factor in high titre (60%), anemia (25%), leukopenia (10%).

Imaging tests that are worth performing are: sialography (irregular enlargements and narrowing of the glandular ducts), salivary gland scintigraphy (delayed uptake, reduced accumulation and delayed excretion of the marker after stimulation) and ultrasonography (the possibility of assessing salivary glands – size, structure, as well as pathological structures, e.g. cysts or lymphadenopathy). Tests such as X-rays and computed tomography of the chest can additionally be used to reveal features of interstitial pneumonia. Ophthalmic examinations recommended in the diagnostic process are primarily the Schirmer test, by means of which we assess the secretion of tears, as well as a test with blush Bengal (or other dye) to assess the condition of the cornea (method of Whitcher et al., van Bijsterveld method). To assess salivation without stimulation, you can use the method of Navazesh and Kumar. Histological examinations in the course of diagnostics are based on the collection of a section of the salivary labial gland and its assessment in terms of the number of lymphocyte infiltrates and the resulting reproduction centers [5]. In assessing the result of eye staining using fluorescein, it is very helpful to use the standard Oxford scale – it allows you to interpret the results obtained and assign the appropriate degree of eye damage [6].

DRY EYE SYNDROME AND SJÖGREN'S SYNDROME

Dry eye syndrome is an ailment with which approx. 8% of the more than 108 million Americans over 50 years old, and approx. 1 in 10 of these cases is based on the Sjögren syndrome. According to available research, undoubtedly the biggest diagnostic problem is the time from the beginning of the onset of symptoms to diagnosis – it is approx. decade [7].

The complexity of Sjögren's syndrome, as well as the dry eye symptom, which is a multifactorial and very widespread complaint, makes it very difficult to identify patients. There is currently no management algorithm or screening to identify dry-eyed patients who need to be diagnosed for Sjögren's syndrome [8].

Dry eye syndrome associated with Sjögren's syndrome is a progressive condition that significantly affects the quality of life of patients. Patients struggle with significant fluctuations of vision with blinking, blurred vision, eye strain and reading difficulties – these symptoms occur despite often excellent visual acuity. Undoubtedly, these symptoms negatively affect the productivity at work of patients – primarily office workers. Patients whose condition is related to Sjögren's syndrome have higher scores on the eye surface staining scale, but less severe symptoms of eye discomfort than patients with dry eye not associated with Sjögren's syndrome. The cause of this situation is unknown, it can be concluded that reduced ocular discomfort may be associated with reduced corneal sensation, which occurs in advanced dryness of the eye surface and in case of inflammation. A study conducted in a group of patients with dry eye associated with Sjögren's syndrome showed that they rated dry eye as significantly more problematic than dry mouth. Patients often experience inflammation of the eye surface, e.g. conjunctivitis, non-healing corneal ulcers, inflammation of other parts of the eye – uveal membrane.

Therefore, it is necessary to include general treatment as soon as possible to improve the quality of life of patients, but also to avoid ocular consequences such as visual impairment or even blindness [3].

Treatment

Dry eye syndrome is treated with non-pharmacological and pharmacological methods. The former include: hygiene of the eyelid edges, the use of tear point plugs depending on the severity of symptoms, as well as avoiding factors that may cause irritation. The pharmacological component uses artificial tears, topical glucocorticoids, cyclosporine A [9], serine protease inhibitors (in the research phase) and rituximab and oral tetracycline therapy.

Eye drops containing hyaluronic acid

Hyaluronic acid (HA) or sodium hyaluronate is a linear biopolymer of glycosaminoglycan disaccharide consisting of repeating alternating sequences of N-acetylglucosamine and glucuronate [10]. Topical application of HA is aimed at increasing the secretion of water and mucin on the surface of the eye [11]. Hyaluronic acid is commonly used to treat dry eye syndrome. A meta-analysis of studies on the effectiveness of this substance shows that HA eye drops (used since the early 1990s), including saline and artificial tears (AT), significantly improved tear production compared to non-HA eye drops, but more research is still needed to assess efficacy by age, duration of treatment, disease severity, and optimal doses [12].

Own serum drops

Artificial tears prepared from own serum are particularly considered in people who do not respond to treatment with cyclosporine A (CsA) or do not tolerate it in the form of eye drops. This preparation is nothing more than the patient's blood collected and properly centrifuged. For this purpose, from 150 ml to 300 ml of blood is taken, which is then prepared and portioned to minims [13]. An important advantage of autologous artificial tears over other pharmaceutical counterparts is the fact that they contain such ingredients as: epidermal growth factor (EGF), vitamins A (retinol) or transforming growth factor (TGF-β, transforming growth factor β), which are also found in the natural film lacrimal. Numerous studies have shown that they play an important role in regulating the proliferation and maturation of the superficial epithelium of the eye, which in Sjögren's syndrome is systematically damaged. Therefore, the main and prerequisites for the use of autologous artificial tears are its regeneration, stabilization of the tear film and substitution of important components of tears, which are clearly missing in patients suffering from Sjögren's syndrome. The advantage of using serum is also that it does not contain preservatives, which with prolonged use can cause a number of side effects, such as: allergies, redness, pinching or destabilization of the tear film itself, which may be associated with increased evaporation of tears or even inflammation on the surface of the eye caused by it. The serum itself contains many antibacterial substances, such as IgG, lysozyme or complement components, which have bacteriostatic properties, so the potential risk of infection when using them is minimized. This method of treatment is primarily designed to alleviate the symptoms of dry eyes, through long-term hydration of the corneal and conjunctival epithelium, as well as – what is associated with it – reducing eye discomfort and pain. Therapy with serum drops is safe for patients and intended for chronic use.

Glucocorticoids

If the first choice treatment with artificial tears and/or moisturizing ophthalmic gels does not bring improvement or has ceased to be effective with long-term use, glucocorticoids may be considered. More and more of research indicates that dry eye syndrome is associated with inflammation of the eye surface, based on an immune response induced by inflammatory mediators. The pathomechanism of this phenomenon is that cytokines stimulate nerve endings that mediate pain and itching; cytokines were found in a tear film in patients with dry eye syndrome [14]. Glucocorticoids are effective anti-inflammatory drugs widely used in inflammation controlling. There is no doubt that they bring significant improvement and quickly alleviate dry eye complaints in patients even within a week of starting treatment [15]. However, it is recommended that they should be used in short-term therapy (maximum 2–4 weeks), because long-term treatment is associated with a number of side effects, such as: increased risk of bacterial or fungal infection, intraocular pressure jumps or cataract formation. Some studies indicate that glucocorticoid reduces not only the symptoms of eye irritation, but also the central staining of the cornea with fluorescein and alleviates corneal fibrillusitis [14]. The choice of the right glucocorticoid for the patient is determined by three main features: tolerance, potency and side effects. Preservatives found in some preparations may exacerbate the symptoms of dry eye syndrome, therefore they will not be recommended in such patients. Dexamethasone is a very potent glucocorticoid, while it penetrates into tissues worse and has a strong side effect profile. Almost as strong is prednisolone, which penetrates well into the tissues of the eye. Other glucocorticoid – such as loteprednol etabonate and fluorometholone – are weaker in action and safer, because compared to dexamethasone and prednisolone they have a lower incidence of complications [14]. Alternatively or as an adjunct therapy, cyclosporine A may also be used, which does not have as rapid anti-inflammatory effects as glucocorticoids, but is safer in long-term therapy. Due to the complementary

profiles of both drugs, physicians often decide to initiate combination therapy [14]. The use of loteprednol etabonate suspension in exacerbations allows for faster control of the inflammatory process and may relieve burning, probably caused by the use of cyclosporine A. This method allows to obtain immediate anti-inflammatory action which causes a glucocorticoid and long-term control of inflammation with cyclosporine. Mutual immunomodulation of both these drugs, acting at different stages of the inflammatory cascade, is aimed at acting faster and more effectively in combination than separately – in monotherapy [14].

Cyclosporine A

CsA is an anti-inflammatory drug belonging to calcineurin inhibitors, widely used in the treatment of inflammation of the eyes in various diseases [16]. Its action is based on the inhibition of the activity of T lymphocytes and the co-occurring inflammatory cascade. CsA binds to cytophylline, and this complex reduces calcineurin activity, which in turn reduces the transcription of IL-2, necessary for T cell replication [9]. Numerous publications emphasize many months of therapy with a relatively small number of adverse local and systemic side effects. There are numerous benefits, such as limiting the amount of topical glucocorticoids and artificial tear preparations. However, it is impossible to completely discontinue other topical medications. The use of CsA may be an alternative anti-inflammatory treatment in patients with elevated intraocular pressure caused by glucocorticoid use. Patients developing dry eye syndrome after cataract surgery may also benefit from CsA treatment [9].

Topically administered CsA may increase the number of goblet cells of the conjunctiva, however, current evidence does not support that better production of conjunctival mucus (by increasing the number of goblet cells of the conjunctiva) translates into an improvement in symptoms or parameters of the ocular surface and tear film. Well-planned, long-term, large clinical trials are still needed to better assess CsA in the long term [16].

Rituximab

Rituximab is a genetically engineered, chimeric monoclonal antibody directed against the transmembrane phosphoprotein CD20 present on the surface of almost all B cells except stem cells, pro-B cells and plasma cells, which are therefore not treated. In autoimmune diseases, rituximab is usually given as a cycle of two infusions at a dose of 1000 mg with an interval of 2 weeks or four infusions at a dose of 375 mg/m^2 at weekly intervals. It is a drug recognized in the treatment of diseases such as rheumatoid arthritis or systemic lupus erythematosus [17].

In contrast, the role of rituximab in the treatment of Sjögren's syndrome remains undetermined due to controversial assessments of its effectiveness published in recent years. In several case reports of rituximab in the treatment of Sjögren's syndrome and associated with lymphoma have shown an improvement in the symptoms of this disease. Given the central role of B cells in the pathogenesis of the disease, this is an indisputably legitimate treatment to consider. From the available data, it can be concluded that rituximab at least stabilizes the symptoms of dryness in patients with residual exocrine function of the glands and reduces the total number of infiltrating B cells in the salivary glands, including the number of FcRL+ B cells, belonging to the group of intraepithelial B lymphocytes, which are considered precursors of MALT lymphoma. Rituximab is generally safe in use, with reported adverse reactions from studies including infusion-related reactions, less commonly infections, respiratory symptoms and gastrointestinal symptoms [18].

Serine protease inhibitors

Serine proteases play an important role in conditions accompanied by chronic inflammation, which is why they have attracted attention as therapeutic targets in diseases such as keratitis, arthritis, vasculitis, asthma, cancer and multiple sclerosis [19]. They demonstrate the ability to promote the expression of inflammatory proteins and affect the degradation of extracellular matrix components, loss of epithelial barrier function and activation of MMP-9 (metalloproteinases 9) [20]. Due to the fact that these abnormal processes also occur in inflammation associated with dry eye syndrome, attempts are underway to use serine protease inhibitors to treat it. In a study published in "Science Report", *A novel serine protease inhibitor as potential treatment for dry eye syndrome and ocular inflammation*, we read about the effects of using a potent serine protease inhibitor, UAMC-00050, to treat dry eye syndrome in animal models. In this study, a positive effect of UAMC-00050 on tear volume was observed, however, these results were not statistically significant. The reason for this may have been the induction method used, i.e. the procedure to remove the lacrimal gland from the eye socket, performed to induce dry eye syndrome. The results of this study suggest the involvement of serine proteases in dry eye syndrome and inflammation of the eye. The concept of trypsin-like serine protease inhibitors as a potential therapeutic target has been proven, but further experimentation is needed to gain better insight into the biochemical and immune pathways involved in this process [20].

CONCLUSIONS

A patient who struggles with dry eye syndrome and the associated deterioration of visual acuity on a daily basis, as well as if it is combined with additional ailments from oth-

er systems, should undergo a deeper diagnosis, because he may suffer from Sjögren's syndrome. The earlier the disease is detected, the sooner appropriate treatment can be implemented, which is associated with stopping the progression of the disease and reducing the associated ailments.

CORESSPONDENCE
Oliwia Cwalina, MSc
Faculty of Medicine and Health Sciences, Andrzej Frycz Modrzewski Academy in Krakow
30-705 Kraków, ul. Gustawa Herlinga-Grudzińskiego 1
e-mail: oliwia.cwalina97@gmail.com

ORCID
Ada Pandey – ID – http://orcid.org/0000-0001-9467-1005
Alicja Chmura-Hołyst – ID – http://orcid.org/0000-0003-0733-1542
Dominika Prokop – ID – http://orcid.org/0000-0001-7318-7716
Oliwia Cwalina – ID – http://orcid.org/0000-0002-7071-0273
Ismael Alsoubie – ID – http://orcid.org/0000-00020974-3025
Bartosz Kuźlik – ID – http://orcid.org/0000-0001-8028-5525
Katarzyna Guzek – ID – http://orcid.org/0000-0003-1790-8667
Kinga Czarnacka – ID – http://orcid.org/0000-0002-6889-6507
Małgorzata Gawlak – ID – http://orcid.org/0000-0003-4573-1379
Maciej Kozak – ID – http://orcid.org/0000-0001-7993-2588
Ilona Pawlicka – ID – http://orcid.org/0000-0003-1556-7678
Katarzyna Sajak-Hydzik – ID – http://orcid.org/0000-0002-1973-2717
Agnieszka Piskorz – ID – http://orcid.org/0000-0003-4553-0497
Anna Roszkowska – ID – http://orcid.org/0000-0002-8083-3437

Piśmiennictwo

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