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REVIEW ARTICLE

Sjögren's syndrom – the review of the latest diagnostic guidelines essential for otolaryngologists

Zespół Sjögrena – przegląd najnowszych wytycznych diagnostycznych istotnych w praktyce otolaryngologa

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ABSTRACT: Sjogren's syndrome (SS) is a complex connective tissue disease with autoimmune background and high clinical, radiological and molecular heterogeneity. SS is typically manifested by sicca syndrome, characterized by dry eyes and dry mouth due to autoimmune-induced inflammation of the lacrimal and salivary glands. Complications of sicca syndrome are dental caries, oral candidiasis, dysosmia, dysgeusia, difficulties in swallowing and chewing. SS may coexist with other diseases of rheumatoid and autoimmune etiology. SS is linked to an 16-fold increased risk of non-Hodgkin lymphoma. Early diagnosis results in appropriate treatment and may slow down the course of the disease and limit extraglandular involvement. Due to diverse clinical phenotypes and symptomatology, establishing of the diagnosis is often difficult. In 2016 the American-European Consensus Group (AECG) and European League Against Rheumatism (EULAR) proposed a classification system that defines SS as a systemic disease. Diagnostic tools in establishing SS diagnosis are serological tests, ultrasonography, Schirmer's test, unstimulated whole saliva flow rate and Ocular Staining Score. The complete curing of SS is still not possible. As a complex multisystem disease, SS requires multidisciplinary cooperation and individual diagnostic and therapeutic approaches in patients. Therapy is focused on the treatment of symptoms and prophylaxis of complications. The laryngological treatment of oral cavity symptoms in SS include supervision of proper oral hygiene habits and adequate fluids supplementation. The EULAR Sjögren's syndrome disease activity index (ESSDAI) and Clinical Oral Dryness Score(CODS) are used to monitor disease progression and treatment effectiveness.

KEYWORDS: autoimmune sialadenitis, dry mouth, dryness syndrome, sicca syndromes, Sjögren syndrome

STRESZCZENIE: Zespół Sjögrena (ZS) jest złożoną chorobą tkanki łącznej o podłożu autoimmunologicznym i dużej heterogeniczności klinicznej, radiologicznej i molekularnej. Charakterystycznym jej obrazem jest tzw. zespół suchości (*sicca*, *dryness syndrome*), w którym suchość oczu i błon śluzowych jamy ustnej spowodowane są naciekami limfocytarnymi gruczołów ślinowych i łzowych. Wtórnie do zespołu suchości rozwijają się: próchnica zębów, zakażenia grzybicze, zaburzenie lub utrata węchu i smaku, problemy z mową i żuciem. ZS może współwystępować z innymi schorzeniami o etiologii reumatoidalnej i autoimmunologicznej. Ze względu na zróżnicowany przebieg choroby, jej rozpoznanie może stwarzać trudności. W 2016 American-European Consensus Group (AECG) i European League Against Rheumatism (EULAR) opracowały nowe kryteria rozpoznania ZS. Narzędziami diagnostycznymi stosowanymi w jej identyfikowaniu są: testy serologiczne, ultrasonografia ślinianek, test Schirmera, badanie niestymulowanego przepływu śliny, metoda Ocular Staining Score. Brakuje jednak jednego tzw. „złotego standardu". Całkowite wyleczenie ZS nie jest obecnie możliwe. Opisywana choroba ma charakter wieloukładowy, jej leczenie wymaga współpracy wielodyscyplinarnej oraz indywidualnego podejścia diagnostyczno-terapeutycznego u chorych. Terapia jest ukierunkowana na leczenie objawów i profilaktykę powikłań. Leczenie objawów ZS w zakresie jamy ustnej polega na wdrożeniu odpowiednich nawyków w zakresie higieny jamy ustnej oraz przyjmowaniu odpowiedniej ilości płynów. W monitorowaniu postępu i efektów leczenia choroby wykorzystuje się skalę ESSDAI (The EULAR Sjögren's syndrome disease activity index) oraz CODS (Clinical Oral Dryness Score).

SŁOWA KLUCZOWE: autoimmunologiczne zapalenie ślinianek, suchość jamy ustnej, zespół Sjögrena, zespół suchości

SS – Sjogren's syndrome
AECG – American-European Consensus Group
EULAR – European League Against Rheumatism
ESSDAI – EULAR – Sjogren's syndrome disease activity index
RA – rheumatoid arthritis
MCTD – mixed connective tissue disease
SLE – systemic lupus erythematosus
OSS – ocular staining score
FLS – focal lymphocytic sialadenitis
FS – focus score
SGUS – salivary gland ultrasonography
CODS – Clinical Oral Dryness Score

Sjögren's syndrome (SS) is a complex connective tissue disease with autoimmune background. The characteristic clinical presentation is the so-called sicca syndrome, which consists of dry eyes and oral mucosa, as well as lymphocytic infiltrates in the salivary glands. Dryness can also affect nasal or vagina mucosa and skin.

Pathological lesions in SS are not only confined to lacrimal and salivary glands. In 30–50% of SS patients, the clinical course is multi-systemic affecting blood vessels, joints, lungs, kidneys and pancreas [1]. SS increases the risk of Hodgkin's lymphoma [2]. It may coexist with other rheumatic and autoimmune diseases such as rheumatoid arthritis (RA), mixed connective tissue disease (MCTD), systemic lupus erythematosus (SLE), scleroderma, dermatomyositis, polymyositis and type 1 diabetes. When occurring together with another autoimmune disease, it is referred to as secondary SS [3].

SS is a disease with an unclear autoimmune profile, hence making a definitive diagnosis difficult. It is characterized by high clinical, radiological and molecular heterogeneity, which requires an individual diagnostic and therapeutic approach to patients [1].

CLINICAL COURSE

SS develops slowly and gradually. About 98% of patients present to the physician with a history of troublesome dryness lasting for many months or years. At the time of diagnosis, the disease is, in most cases, advanced due to its long and latent development [4].

In 50% of cases, patients present with swelling of one or more salivary glands. The parotid glands are most commonly affected, followed by submandibular and sublingual glands. Bilateral polycystic lesions in the parotid glands may be the first manifestation of the disease in some patients [5]. Many patients also report dryness of the nose, trachea, vagina and skin. It indicates that SS may affect various exocrine glands. Some patients, especially children and young adults, may experience constant, low-grade but well-tolerated fever, night sweats, fatigue, and weight loss. In such cases, absent or poorly expressed sicca symptoms result in delayed diagnosis. History of previous salivary gland swelling and abnormal test results (increased ESR, hypergammaglobulinemia, cytopenias) are the main factors indicating possible SS [5]. The first manifestation of SS can also be interstitial nephritis or non-specific neurological symptoms such as peripheral neuropathy.

The atypical course of the disease is characteristic for younger patients, in whom dryness symptoms are less pronounced or altogether absent. Subclinical dysfunction of the lacrimal and salivary glands in younger patients with end-organ symptoms of SS warrants further diagnostic investigation.

Dryness of the mouth can lead to complications such as dental caries, fungal infections, loss or abnormal olfaction and taste, impaired speech and chewing. In 35–70% of patients, xerostomia leads to dysphagia [3].

Dryness of the eyes causes pain and may lead to corneal dehydration with subsequent chronic inflammation and scarring.

As mentioned earlier, SS is associated with an increased incidence of lymphoma. The risk of non-Hodgkin's lymphoma is 16 times higher than in healthy population. For this reason it is crucial to introduce immunosuppressive therapy in order to slow down the progression of the disease [6].

The most common extraglandular manifestation of SS is arthralgia, which is present in about 50% of patients, usually resulting from polyarthritis without synovial erosions. Lung involvement in SS can manifest itself as interstitial lung disease or focal bronchiolitis developing after many years of active disease. Around 10% of patients also suffer from skin lesions, usually caused by inflammation of small- and medium-sized blood vessels of the lower limbs, clinically manifesting as livedo reticularis. Other less common lesions include annular erythema and vascular urticaria. Renal involvement can be observed in about 5% of patients, usually in the form of tubulointerstitial nephritis with type 1 renal tubular acidosis and hypokalemic muscular hypotonia. Glomerulonephritis is rare [4].

DIAGNOSIS

In 2016, new criteria were developed by the American-European Consensus Group (AECG) and the European League Against Rheumatism (EULAR), which combined and refined earlier classification systems [7]. The advantage of the previous systems was their simplified methodology, allowing for an easy diagnosis without any invasive tests. Ocular symptoms were evaluated by means of the Schirmer's test; the patient was further evaluated for xerostomia and anti-Ro antibody titer was obtained. The main limitation of those criteria was their low sensitivity in diagnosing SS at early stages.

Despite developing new classification, there is still no clear indicator of the disease, so the diagnosis must still be based on recognizing a set of related symptoms. It is new, however, to look at SS as a systemic disease involving many organs and leading to B-cell hyperactivity, especially in cases with no exocrine gland dysfunction.

The following non-equivalent features were included in 2016 criteria for SS diagnosis:

1. focal lymphocytic infiltration [≥1 on FS scale] in labial gland biopsy – 3 points;

2. presence of anti-SS-A / Ro antibodies in serum – 3 points;

3. ocular staining score – 5 (or van Bijsterveld score 4) at least in one eye – 1 point;

4. positive Schirmer's test (≤ 5 mm / 5 min) at least in one eye –1 point;

5. total unstimulated salivary flow (≤ 0.1 mL / min) – 1 point.

The score of 4 points in the new classification allows to make the diagnosis of SS.

It is recommended to use this tool to diagnose patients who:

1. Have at least one of the following symptoms of eye or mouth dryness:

   - daily, persistent dry eye for a minimum of 3 months
   - persistent feeling of gritty eyes
   - use of artificial tears at least 3 times a day
   - daily feeling of dry mouth for a minimum of 3 months
   - the need to drink water while eating dry food

2. Scored at least 1 point in the European League Against Rheumatism Sjögren Syndrome Disease Activity Index (ESSDAI)

According to the new guidelines, to diagnose SS the following conditions must be excluded:

- previous radiotherapy of the head and neck
- active HCV infection
- AIDS
- sarcoidosis
- amyloidosis
- graft-versus-host disease
- IgG4-related disease

Also, patients taking anticholinergics should be evaluated after an appropriate period of drug withdrawal.

Unlike previous recommendations, lymphoma is no longer an exclusion criterion.

The 2016 criteria show high sensitivity (96%) and specificity (95%), even in cases where SS diagnosis was difficult due to limited symptoms.

TISSUE BIOPSY

Biopsy of labial salivary glands is a minimally invasive procedure performed under local anesthesia, which can demonstrate inflammation of the glands. The analysis of 1,700 biopsies showed a strong correlation between lymphocytic infiltration on microscopy with other test results such as anti-Ro antibodies, OSS (ocular staining score) and total unstimulated salivary flow ≤ 0.1 mL/min [8].

The salivary gland biopsy is recognized by both American College of Rheumatology and AECG as a very important component of SS diagnosis. Of all diagnostic studies the biopsy can be the most useful in patients not presenting typical symptoms and when clinical data have not been sufficient to make a diagnosis [9]. To ensure high diagnostic accuracy, an appropriate sample should be obtained. Usually, 4–6 lobules are considered sufficient, which corresponds to a fragment of at least 4 mm^2 (optimally 10-20 mm^2) [8, 10].

The presence of >50 lymphocytes / 4 mm^2 in the salivary gland is a sign of focal lymphocytic inflammation (FLS – focal lymphocytic sialadenitis). It is assigned 1 point for FS (focus score) and confirms the diagnosis of SS [6].

Another promising method is a needle biopsy of the parotid gland, although it is not widely used at present. This method allows to monitor the disease progression and to evaluate the treatment. The parotid gland biopsy is easy to perform, possible to repeat in the same salivary gland and compared to other studies such as ultrasound, sialography, scintigraphy and tomography [10].

False negative results are possible in patients on oral steroids due to their immunosuppressive effect, as well as in older patients with less pronounced inflammation.

False positive results can be observed at very early stages of the disease when the rest of the SS symptoms are absent and thus the diagnostic criteria cannot be met [8].

ANTIBODIES

Detection of anti-Ro antibodies may be used for early diagnosis of SS in the latent stage, which allows to promptly commence treatment [11]. Only anti-SS-A / Ro antibodies are crucial in the diagnosis of SS. The positive titer of antinuclear antibodies (ANA), rheumatoid factor (RF), anti-SS-B / La antibodies in the absence of anti-SS-A / Ro antibodies was omitted in the new criteria due to their low specificity [12].

Detection of anti-Ro 60 antibodies and anti-Ro 52 antibodies (Ro 52 and Ro 60 are SS-A antigen-forming subunits) has currently the highest positive predictive value, especially in young patients [12]. Anti-Ro 52 antibodies can be present in various autoimmune diseases, therefore only the combination of the above-listed antibodies has a positive predictive value [13].

Anti-Ro / SS-A or La / SS-B antibodies are present in 71% of patients with SS and are fundamental for the diagnosis, but are nonspecific. They can also be detected in SLE, systemic sclerosis, mixed connective tissue disease, primary biliary cirrhosis, RA [13].

According to the new guidelines, patients with symptomatic SS and positive antibodies do not require confirmation by tissue biopsy.

ULTRASOUND

Salivary gland ultrasound (SGUS) is a non-invasive and commonly used diagnostic method. The characteristic image of SS includes

heterogeneity of the salivary gland parenchyma resulting from the presence of hypoechogenic areas resembling fluid-filled cysts, blurred gland borders, gland enlargement, parenchymal calcifications and increased vasculature on color doppler [14].

The ultrasound evaluation of the salivary glands has not been included in the new guidelines, although many studies point out that it can be a good alternative to salivary gland biopsy. Moreover, the SGUS image correlates very well with the results of sialography and sialoscintigraphy. The meta-analysis of SGUS in SS diagnosis showed that the sensitivity and specificity are 69% and 92% respectively [14]. Both large and small salivary glands can be involved in SS. Ultrasound of large salivary glands correlates well with the small salivary gland biopsy results [14].

The results of ultrasound evaluation of the submandibular and parotid glands strongly correlate with the anti-Ro / SSA titre and are inversely proportional to the salivary flow [14].

The fist parenchymal lesions are present in submandibular and sublingual salivary glands, which are responsible for basal salivary secretion. Later on, as the disease progresses, the parotid glands are involved, which are responsible for stimulus-induced salivary secretion. Ultrasound evaluation of the parotid glands has greater specificity, while sublingual and submandibular salivary gland evaluation shows higher sensitivity. Ultrasound evaluation of all large salivary glands is recommended to maximize the validity of this method [14].

SGUS is considered very promising for the diagnosis of SS, but it requires unification and standardization of the tested parameters to be included in the guidelines.

The new guidelines also draw attention to the immunological component of the disease, i.e. systemic activation of B-cells and a number of associated biomarkers. Their assessment is included in the ESSDAI questionnaire and allows for early detection of the disease that has not yet presented with sicca syndrome.

ESSDAI is also useful in clinical practice to assess the disease activity during follow-up visits. Sjögren Syndrome Responder Index (SSRI) is another tool used to evaluate the response to treatment [7].

There is still no single tool that serves as the ‚gold standard' of diagnosis. The new criteria apply to primary SS. Their use in secondary SS requires further confirmation and research.

TREATMENT

Total cure from SS is currently impossible. It is a multi-system disease and treatment requires multidisciplinary cooperation.

Therapy is focused on relieving symptoms, preventing complications and immunosuppression in selected patients.

In the otolaryngologist's practice, complications of SS are important and include dental caries, cheilitis, oral ulcers, salivary gland inflammation, oral candidiasis, dysarthria, dysphagia and dysgeusia [15].

Medical treatment includes monitoring fluid intake (recommended 2–2.5 liters per day), avoiding tobacco and caffeine. Aggravating agents include diuretics, beta blockers, antidepressants and anxiolytics.

Patients should be educated to avoid dry and air-conditioned rooms, staying in the wind, as well as eye-straining activities such as using a computer or reading for a long time. It is recommended that patients use air purifiers.

Supplementation of omega-3 acids may be helpful in fighting dry eye, however, the evidence for the efficacy of such treatment is inconclusive [16].

Oral hygiene is of upmost importance, involving restricting sugar consumption and acidic products, because neutral oral pH can prevent caries. It is recommended to drink lots of water, chew xylitol-containing gum, avoid toothpaste with sodium lauryl sulfate (SLS) and alcohol-based mouthwash; also, regular dental checkup every 3-6 months is recommended.

It is recommended to use fluoride-rich toothpaste twice daily. SS patients require higher fluoride concentration to compensate for its deficiency due to insufficient saliva production. The usual fluoride concentration in toothpaste is 500-1,500 ppm; however, 5,000 ppm pastes are also available, e.g. Colgate Duraphat. Also, chlorhexidine-based products are also available, such as e.g. Curasept.

Artificial saliva can temporarily alleviate xerostomia. Such product should have a neutral pH, contain fluoride and other electrolytes, imitating the composition of natural saliva. Artificial saliva is available as spray, gel and mouthwash (e.g. Xerostom, Mucinox, Bioxtra) [17].

Products with neutral pH and fluoride should be used by patients with preserved dentition. Products of acidic pH, with or without fluoride, can only be used by patients who no longer have their own teeth.

Another advantage of xylitol-containing gum, in addition to stimulating saliva production, is the anticaries effect of xylitol. Research proved that xylitol added to toothpaste at 10% concentration and used for 2.5–3 years is 13% more effective in preventing caries than fluoride-based toothpaste [17]. An example of a xylitol-containing toothpaste available on the market is Neobio. Some foods may stimulate salivation, e.g. yogurts.

Chlorhexidine is an effective antiseptic that inhibits the development of plaque, which is useful in managing gingivitis. It is available as a toothpaste (Curasept, Eldygium) or a mouthwash (Curasept).

Muscarinic receptor agonists are commonly used in SS. Pilocarpine at a dose of 5 mg (applied once daily, with a gradually increased dosage to 5 mg q.i.d.) is used to treat dryness of the mouth and eyes. However, side effects are common and are dose-dependent. Those include excessive sweating, diarrhea and bradycardia.

Cevimeline has a higher affinity to muscarinic receptors in the lacrimal and salivary glands, and its side effects are milder compared to pilocarpine [17]. Anhydrous crystalline maltose is another salivation stimulant [17].

Oral candidiasis is a very common problem in patients with SS. Proper oral hygiene does not entirely prevent fungal infection. Candidiasis can manifest itself in two ways: either as white plaques or redness of the mouth and tongue. In the first case, nystatin solution (1 mL 5 x day for 7 days) is recommended for mouthwash; in the latter, fluconazole orally (50 mg for 10 days) should be administered. If infections occur frequently, you can repeat the weekly nystatin treatment every 8 weeks. In cheilitis it is recommended to use miconazole locally for 2 weeks [17].

Some patients with SS may complain of recurrent or chronic salivary gland swelling, especially during exacerbations of the disease or due to obstruction caused by constriction, stones or thickened secretions. If the inflammation is acute and is not accompanied by symptoms of a bacterial infection, a short course of oral prednisolone or methylprednisolone is recommended. Systemic therapy for recurrent salivary inflammation with low-dose glucocorticoids has low efficacy and is associated with a number of side effects.

Salivary gland massage may be helpful in treatment, however, it is not highly effective. Patients who do not respond to medical therapy may benefit from sialoendoscopy. It is a minimally invasive procedure that allows visualization of salivary ducts and administration of drugs or widening salivary ducts. Its effectiveness in reducing the frequency of salivary inflammation episodes has been well-documented. Irrigation of salivary ducts with saline and glucocorticoids reduces the severity of symptoms in patients with sicca syndrome [18]. Managing extra-glandular symptoms falls within competence of the rheumatologist. Such patient also need ophthalmologist consultation.

MONITORING

The ESSDAI score (EULAR Sjögren's syndrome disease activity index) was created to measure the activity of the primary SS. Currently, it is the gold standard for monitoring disease activity used in clinical trials. However, it can also be successfully used by clinicians, helping them in diagnosis and evaluation of treatment [19].

The part of ESSDAI questionnaire devoted to ENT symptoms includes swallowing of parotid, submandibular and lacrimal glands. They should be assessed on physical examination. Submandibular gland swelling < 2 cm is considered moderate, while > 2 cm – as significant. Swelling of the lacrimal gland <1 cm is considered moderate and > 1 cm - significant. The CODS (Clinical Oral Dryness Score) scoring system is used for fast, simple and objective evaluation of salivary gland function based on clinical symptoms of sicca syndrome [20]. It is a 10-point scale, where points are assigned for each feature of the sicca syndrome:

1. The dental mirror sticks to the buccal mucosa;

2. The dental mirror sticks to the tongue;

3. The presence of foamy saliva;

4. Lack of saliva at the oral cavity floor;

5. The disappearance of lingual papillae;

6. Abnormal gums (smoothened);

7. Glassy appearance of the oral mucosa (especially the palate);

8. Cobbled or lobular tongue surface;

9. Active or cured dental caries within the last 6 months;

10. Cobbling of the hard palate.

The sum of points determines the severity of sicca syndrome, which can be classified as mild, moderate or severe.

- Mild (1–3 points) – Conservative treatment is recommended, such as chewing sugar-free gum twice daily and maintaining water balance.
- Moderate (4–6 points) – It is recommended to stimulate salivation and using fluoride-rich toothpaste.
- Severe (7–10 points) – Artificial saliva, regular dental check-ups and rheumatology consultation are recommended.

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