Sjögren's Syndrome – Pathophysiology, Symptoms in Various Organs, Diagnosis, Treatment, and Prognosis

Authors:

1. **Agnieszka Suszek**
   Medical University of Silesia, Poniatowskiego 15, 40-055 Katowice, Poland
   ORCID: https://orcid.org/0009-0002-4640-8143
2. **Monika Suszek**
   Medical University of Silesia, Poniatowskiego 15, 40-055 Katowice, Poland
   ORCID: https://orcid.org/0009-0000-4794-4410
3. **Angelika Złotnik**
   Medical University of Silesia, Poniatowskiego 15, 40-055 Katowice, Poland
   ORCID: https://orcid.org/0009-0004-5142-6199
4. **Małgorzata Filak**
   Independent Public Health Care Facility, Municipal Hospitals Complex in Chorzów, 11 Strzelców Bytomskich Street, 41-500 Chorzów
   ORCID: https://orcid.org/0009-0009-9099-5083
5. **Agata Zabierowska**
   Medical University of Silesia, Poniatowskiego 15, 40-055 Katowice, Poland
   ORCID: https://orcid.org/0009-0002-1149-0108
6. **Agnieszka Walus**
   Medical University of Silesia, Poniatowskiego 15, 40-055 Katowice, Poland
   ORCID: https://orcid.org/0009-0000-5903-633X
7. **Maciej Bulwa**
   Medical University of Silesia, Poniatowskiego 15, 40-055 Katowice, Poland
   ORCID: https://orcid.org/0009-0007-2661-0797
8. **Adrianna Lysko**
   Healthcare Centre Beskidzka, Beskidzka 3, 41-500 Chorzów, Poland
   ORCID: https://orcid.org/0009-0001-5854-7135
9. **Julia Surowaniec**
   Medical University of Silesia, Poniatowskiego 15, 40-055 Katowice, Poland
   ORCID: https://orcid.org/0009-0008-5469-7727
10. **Natalia Wieczorek-Durdzińska**
    Regional Blood Donation and Transfusion Center in Raciborz, Henryka Sienkiewicza 3A, 47-400 Racibórz
    ORCID: https://orcid.org/0009-0005-6115-1640

Corresponding author:

Agnieszka Suszek

Abstract

Introduction:

Sjögren’s syndrome, or SS, is this long-lasting autoimmune disorder that mostly hits the exocrine glands. Often, people with SS have these autoantibodies floating around, which isn’t surprising given the immune system’s role here. Now, sometimes it shows up on its own what folks call primary SS but it can also tag along with other autoimmune issues like rheumatoid arthritis or lupus. The story of SS dates back to 1933 when Henrik Sjögren, a Swedish eye doctor, gave the first thorough description. He noticed the classic trio of symptoms: dry eyes, dry mouth, and arthritis and that pretty much set the stage for identifying the disease.

Purpose:

This review aims to enhance the understanding and management of Sjögrent's syndrome by summarizing current guidelines and providing practical compensations for clinical practice.

Material and methods:

In this article, we present a comprehensive discussion of Sjögren's syndrome. By examining current research, we present the main features of the disease, such as its signs, causes, testing techniques, treatment plans, and prospects.

Discussion:

Sjögren's syndrome remains a major medical problem because of its unclear and variable progression, which includes common symptoms such as dry eyes and dry mouth, often appearing during the course of the disease and progressing gradually. Its vague symptoms cause delays in identifying the condition, potentially causing permanent organ damage and a serious deterioration in quality of life. Even with treatments that can alleviate symptoms and suppress the immune system, which can help slow the disease and control its progression, the problem is the duration of the disease and the difficulty in keeping patients up to date with the progress of tests. And the tailored treatment method adds optimism for better care, lowering the chances of problems - such as lymphomas.

Keywords: 'Sjögren's syndrome', 'mucosal dryness', 'rheumatological markers', ‘arthritis’ and ‘lymphoma’

Introduction:

Sjögren's syndrome (SS) is a chronic autoimmune rheumatic disease that causes damage to the exocrine glands and also produces autoantibodies in the blood. Usually, progression of the disease takes place in most cases weeks to several months and even years. [1]

It can either be a primary disorder (being idiopathic) or a secondary form linked to systemic autoimmune diseases like rheumatoid arthritis (RA), systemic lupus erythematosus(SLE). Based on genetics, environmental (including hormonal or viral) and psychological concepts believe that SS progresses by immune system activation. [5,6]

Referring to the European medical literature of the late 19th century, cases of Sjögren's syndrome seem to be occurring in individuals, but Sjögren's was largely described by Henrik Sjögren who was a Swedish ophthalmologist. The first comprehensive account of Sjögren's syndrome in a series of patients was published by him in 1933, as part of his PhD thesis. Dr. Sjögren presented the cases of 19 women, all having experience in dry eyes and dry mouth, with two-thirds also suffering from chronic arthritis. He was the first to highlight the systemic nature of the disease and to recognize the connection among its three hallmark symptoms: dry eyes, dry mouth, and arthritis. Additionally, he was the first ophthalmologist to apply rose bengal dye to examine eye surface damage caused by dryness and introduced the term *keratoconjunctivitis sicca* to distinguish SS-related dry eyes from those due to vitamin A deficiency, known as xerophthalmia. As a result of these contributions, the syndrome continues to carry his name.[1]

Purpose:

This review is intended to involve a deep insight into Sjögren's syndrome that is more on the symptoms, frequency, genetic causes, pathophysiological and immunological mechanisms that are involved, and the diagnosis and treatment methods etc. Its main focus is on awareness spreading of the disease, the facilitation of its early diagnosis, and the improvement of therapeutic approaches for the public. It is also intended to be a guide for incorporating the available evidence-based practices into daily clinical care and addressing problems such as treatment adherence and management of systemic complications that are frequently associated with SS, and ultimately aiming to improve patient outcomes.

Material and methods:

The present study is a systematic review of literature available on diagnosis and management of Sjögren's syndrome from existing studies. They conducted a comprehensive search within PubMed, Embase and Scopus for peer-reviewed articles, clinical trials and reviews published between 1950 and 2025. Keywords were used to identify studies on the clinical manifestations of SS with Title and abstract search 'Sjögren's syndrome', 'mucosal dryness', 'rheumatological markers', 'arthritis' and 'lymphoma'. We included studies providing information on diagnostic criteria as well as treatment and patient outcome, striving for publications in non-English languages or not providing original data. Data extraction concentrated on procedural treatments, efficacy of treatments and long-term results, especially about risk of malignancies like lymphoma in particular. The results were then collated to emphasize emerging trends and refine the understanding of how SS is managed.

Epidemiology:

Primary Sjögren's syndrome (pSS) is a common disease accounting for approximately 0.5% of the general population and is idiopathic, M:F approximately - 9:1 [2].

pSS has two major peaks in disease onset: the first after menarche (ages 20 to 30), the second after menopause (ages mid-50s). Sjögren's syndrome has been reported worldwide in adults and less frequently in children, and there does not appear to be any racial or geographic bias in incidence. The signs and symptoms of SS are described as not specific so they can easily be mistaken for other diseases or side effects of medications that the patient is presently on. Misdiagnosis is therefore common and is thought to be responsible for the failure to diagnose approximately half of the population affected by the disease.[3]

Etiology:

Behind autoimmune diseases it seems, as with many other secondary autoimmune diseases: the fundamental cause of Sjögren's is not known. Although likely with a genetic predisposition, probably involving the major histocompatibility complex (MHC) region, which might be one of the triggers when epigenetic factors interact with viral or environmental pathogens to produce an aberrant immune response. However, people who share particular haplotypes identified in the HLA-DQA DQB region seem to have a higher relative risk of getting the disease although it is worldwide distributed. [2,4]

Numerous familial cases of Sjögren's syndrome support a genetic predisposition to the disease in multiple affected members of the same family. Family history of the disease is associated with a higher risk of SS than overall population risk. Genetic considerations are also backed by evidence in studies of twins. This suggests genetic susceptibility to autoantibodies as seen in SS may be linked to polymorphic MHC (major histocompatibility complexes) genes, which are prone to variation and also implicated in autoimmune illnesses. However more research is needed to support this association. [2,3]

Scientific research also indicates that genetic susceptibility promoting a higher interferon (IFN) response to various stimuli may be a key event in the onset or persistence of the disease. [6,7]

The exact mechanisms are unknown, but in all patients with SS illness is mediated through four principle steps: (1) external triggering; (2) damage or dysfunction of the salivary gland epithelial cells (3) migration of T lymphocytes: and their inflammation through lymphocytic exocrine gland invasion (4) excessive B cell activation producing rheumatoid factor and autoantibodies against Ro(SS-A) and La(SS-B). There are called autoantibodies that do not target specific organs. In contrast, autoantibodies aimed at certain organs are very uncommon. The presence of these autoantibodies is associated with an early onset of Sjögren's syndrome, more severe disease, long-lasting process, recurrent swelling of the parotid gland, and the development of extraglandular manifestations. Thus, their identification may be a valuable measure to predict disease course in the early stages of the disease. Patients with earlier disease onset have higher serum titres of Ro/SSA and La/SSB antibodies, and also a higher prevalence of RF, that are associated with increased severity of clinical manifestations in these individuals. [3]

SS has long been considered to be triggered by environmental exposures, most notably viral infections in the course of a lifetime. The ongoing activation status of epithelial cells reactivity could be explained by an 'endogenous intrinsic activator' such as a viral pathogen within those cells that is always active and so far unstirred. This is further supported by salivary glands displaying type I interferon (IFN) signature and thus elevated expression of type I IFNs, as is seen chronically in response to an infection. Those and other viruses, such as hepatitis C virus (HCV) or HIV can cause chronic sialadenitis that is clinically similar to SS but lacks endemic features (e.g., autoantibody production against Ro/SSA and La/SSB) and sex bias. Multiple viruses, such as CMV (cytomegalovirus), Epstein-Barr virus (EBV), retroviral elements and human herpesviruses including HHV-6 (human herpesvirus 6) and the more recent Coxsackie virus, have been detected in the salivary gland tissues of SS patients in the setting of literature. [2,7]

Another important aspect in pathophysiology of SS is the endocrine system. Androgens are associated with a destruction, by the cellular immune response, of the exocrine glands and estrogens in the balance modulate this action. Estrogen functions as an immune stimulant. It has significant roles in lymphocyte development, differentiation, proliferation, antigen presentation, cytokine and antibody production, cell survival, and apoptosis. It has been demonstrated to enhance B-cell-mediated immune responses that result in a high concentration of antibody. It is interesting that Sjögren's syndrome is most prevalent during various time points of decreasing reproductive hormonal levels in women (e.g., menopause), indicating that decreased estrogen levels or shifts in the estrogen-to-androgen ratio may be involved in the etiology of disease. Another proinflammatory hormone, prolactin, augments estrogen activity but inhibits its production in high concentrations. As an immune enhancer, prolactin is associated with T lymphocyte reproduction, induction of interleukin-2 receptors, production of interferon-gamma, and antibody production. [3,9]

Symptoms:

Sjögren's syndrome basically involves the malfunction and gradual damage of the exocrine glands, mainly because of lymphocyte infiltration and an overactive immune system. It's a bit tricky to pin down, but about 80% of people in the major patient group actually fall under this syndrome. One worrying issue, for example, is dry eyes. They're not just uncomfortable but can lead to more serious complications. Women seem to be affected by primary Sjögren's syndrome (pSS) quite a bit more than men. In children, the most common symptom is recurrent parotitis, which is inflammation of the salivary glands. [15,18]

Oral symptoms

Dry mouth, or xerostomia can lead to problems like oral thrush (which happens in roughly a third of cases), tooth decay (happens in about 65%), and gum disease. Then, dry eyes xerophthalmia can make them sensitive to light, cause ongoing irritation, and even damage the corneal epithelium. Eye damage isn't unheard of either. But it's not just dryness. Folks with Sjögren's often complain about other symptoms such as hoarseness, a dry cough that doesn't clear up, dry skin, and for women, painful intercourse (dyspareunia) is common, sadly. Quality of life in pSS patients can really be impacted. When researchers measure it with the SF-36 scale it's clear that the symptoms weigh heavily on daily functioning and wellbeing. A hallmark symptom reported by around 70-80% of pSS patients is fatigue, which seems to grind people

down. Pain is also a frequent complaint and can be tied to fibromyalgia or just widespread joint pain, known as polyarthralgia. Depression and anxiety show up more in patients with pSS than in healthy folks. [15,16]

Ocular Manifestations:

The primary eye issue related to Sjögren's syndrome is dry eye disease (DED). DED is a complex issue which affects the eye's tear film and surface which in turn causes irritation, blurred vision, and unstable tear film which in turn may cause damage to the eye's surface. Also it is a common issue of high tear salt and eye surface irritation. A type of Dry Eye Disease (DED) that results from reduced tear production due to issues with the tear glands is very much related to Sjögren's syndrome. In these people immune cells go into overdrive and attack the eye's tear producing glands which leads to cell death and reduction in tear output which in turn causes dry eyes with poor water content. [17]

Skin Manifestations:

Dry skin and itching are usual skin issues in those with Sjögren's syndrome, with up to 68.4% of patients experiencing dry skin. Although first thought to stem from sweat gland issues, this has not been definitively confirmed. Present data indicates that the problem could originate from a damaged skin layer. The precise cause of itching in Sjögren's syndrome is unknown, and it doesn't always match the level of skin dryness. Surprisingly, itch intensity seems to be higher in Sjögren's syndrome than in other connective tissue disorders. Inflammatory blood vessel inflammation is the second most frequent skin sign, seen in about 30% of individuals, based on different research. It frequently appears as a visible purple rash, but sometimes it can also show up as a rash that isn't easily felt or as hives, particularly on the lower legs. Raynaud's condition appears in 16–35% of individuals and usually shows up less severely in Sjögren's syndrome than in other similar tissue disorders. Other skin issues might involve lichen planus, vitiligo, and ring-shaped granuloma. [15,18]

Joint Symptoms:

In primary Sjögren's syndrome (pSS), joint issues usually show up as even, on-and-off, non-damaging joint disease. Arthritis is a common clinical sign, seen in 15–90% of patients. It often impacts the joints near the middle of the fingers (35%), the joints connecting the hand to the

fingers (35%), and the wrists (30%). The joint swelling is usually even and harmless, showing up as recurring joint pain. Participation of the central bone structure is rarely seen.

Muscle discomfort (muscle pain) is also a common issue in individuals with pSS. Muscle inflammation, a condition causing muscle swelling is uncommon, impacting roughly 2 out of every 100 people. When it happens, it's typically linked to unknown muscle inflammation or shows up as a combination with other immune system disorders. [15,18,20]

Neurological Symptoms:

The nervous system is another frequent location affected by Sjögren's syndrome. Brain and body signs are often seen and can show up soon after the illness starts, with important brain-related issues impacting around 20% of those affected. People with the main Sjögren's condition frequently have general body symptoms, including muscle and joint pain without swelling, extreme tiredness, lack of strength, nerve damage, and signs similar to fibromyalgia. Due to overlapping clinical features, pSS can sometimes resemble multiple sclerosis. Nerve damage, especially in the sense nerves, is the most frequently mentioned nervous system issue. Head nerve problems are also known, often harming the ear nerve, causing deafness and unsteadiness. Sensory dysfunction of the trigeminal and facial nerves is also commonly documented. At present, there isn't a universally accepted plan for managing nerve damage related to pSS. Painkillers are usually for slight nerve pain, but tougher nerve and muscle issues might need treatments that calm the immune system, like prednisone, azathioprine, cyclophosphamide, or IVIG sh. Also, around three-quarters of those with Sjögren's syndrome have some level of mental function decline, and numerous suffer from mental health issues like sadness or worry disorders. Following lymphoma, psychological and mental health issues are among the most severe overall problems caused by Sjögren's syndrome. [15,18]

Lung Involvement:

About 20% of Sjögren's syndrome patients experience lung issues often showing up as a constant dry cough. Between 10% and 35% of cases involve frequent lung infections. Interstitial lung disease (ILD) and its complications can lead to death, highlighting the need to spot and treat it . [18]

Renal Involvement:

Sjögren’s syndrome doesn't often affect the kidneys, with 10% or fewer patients having issues. The main kidney problems are tubulointerstitial nephritis and membranoproliferative glomerulonephritis. Tubulointerstitial nephritis can cause renal tubular acidosis because of problems with acid-base balance. It's key to keep an eye on kidney function, as about 24% of people with primary Sjögren's syndrome (pSS) have kidney failure (meaning a glomerular filtration rate below 60 ml/min). [18,19]

Extraglandular Manifestations and Lymphoma Risk:

About 71% of pSS patients show extraglandular involvement. This can affect lymph nodes, nervous system, lungs, skin, joints, kidneys, and muscles. Lymphoma stands out as the most serious complication posing the highest death risk. Research indicates pSS patients have a fivefold higher chance to develop lymphoma compared to others. MALT lymphoma occurs most often starting in the parotid glands. This type tends to grow as a low-grade tumor. Ongoing parotid gland swelling serves as a key sign for potential lymphoma. Other common types include diffuse large B-cell lymphoma and MALT lymphoma. While Sjögren’s syndrome affects more women (9 women for every 1 man), men with pSS might face a higher risk of non-Hodgkin's lymphoma. Signs linked to increased lymphoma risk include: lasting, one-sided salivary gland swelling, swollen lymph nodes, enlarged spleen, skin vasculitis, cryoglobulinemia, and kidney inflammation. [15,18, 21]

Associated Autoimmune Conditions:

pSS is also associated with other autoimmune and viral conditions, including: hepatitis C (in approximately 12% of cases), autoimmune thyroid disease (10%), autoimmune chronic active hepatitis (2%), primary biliary cholangitis (formerly primary biliary cirrhosis). [15]
Diagnostic Factors: Chronic muscular pain, salivary gland enlargement, demyelinating disorders, nerve damage, or typical laboratory abnormalities are among other frequent signs. Common hematologic results in pSS include: thrombocytopenia, normocytic anemia, modest leukopenia, and lymphopenia[15,18]

Diagnosis:

If investigating a patient for suspected Sjögren's syndrome, both oral and ocular dryness and its impact should be evaluated. Apart from a comprehensive patient history, these investigations might include a Schirmer test, slit-lamp examination with vital dye staining,

salivary flow rate determination and/or nuclear scintigraphy with salivary function analysis. ANA titer testing, rheumatoid factor (RF), and SS-A and SS-B antibody tests should be performed. Of these, the SS-A antibody is the most sensitive and specific for Sjögren's syndrome, but it is not exclusively diagnostic as it is also present in other autoimmune conditions and lacking even in up to a third of SS patients. The best diagnostic test is still a type of biopsy of a minor salivary gland (lip) taken in type,which,if positive, will show focal lymphocytic sialadenitis (FLS). [4,10]

There are two major classification systems for Sjögren's syndrome currently: the European and the American. In accordance with initial European criteria, a primary Sjögren's syndrome (pSS) diagnosis requires fulfilling at least four of the following six criteria: 1) Dry eyes, as indicated by at least one affirmative response to three symptom-related questions 2) Dry mouth, as indicated by at least one affirmative response to three related questions 3) Ocular presentation, as demonstrated by an abnormal Schirmer's test, rose bengal stain, or other ocular dye tests 4) Histopathology, demonstrating a focus score ≥1 on minor salivary gland biopsy 5) Involvement of the salivary glands, as determined by abnormal parotid sialography, salivary scintigraphy, or reduced unstimulated salivary flow 6) Presence of autoantibodies, such as ANA, RF, anti-Ro/SSA, and/or anti-La/SSB. [11,12,13,14]

These European criteria were initially validated with great sensitivity and specificity and were widely accepted. They were, however, criticized for the possibility of misclassifying patients who fulfilled only the subjective symptom criteria without histological or serological support. The American-European Consensus Group (AECG) therefore modified the classification system to solve these issues. Under the AECG criteria, pSS would be diagnosed if four of the six criteria were fulfilled as long as at least one of them was either histological (biopsy) or serological (autoantibodies). The diagnosis would also be made definite if three of the four objective criteria were fulfilled. Importantly, ANA and RF were removed from the obligatory autoantibodies, and more conditions for exclusion were listed. The distinguishing characteristic of the AECG criteria was the presence of focal lymphocytic sialadenitis or anti-Ro/SSA and/or anti-La/SSB antibodies as mandatory, thereby stricter than the European system. The 2016 ACR-EULAR criteria were subsequently developed by the International Sjögren's Syndrome Criteria Working Group, with joint collaboration of the ACR and EULAR. The criteria have been rigorously validated and are of similar validity to the AECG criteria. They offer high sensitivity, but with slightly reduced specificity compared with prior ACR criteria. The ACR-EULAR system has some advantages: it is easier to apply in clinical practice on a day-to-day basis, often obviating the requirement for invasive investigations like salivary gland biopsy or

eye staining, if a score ≥4 is reached. This has been followed by universal international consensus and adoption of the ACR-EULAR criteria for pSS classification. [11,12,13,14]

Treatment:

Despite the progressive research which is being done into the causes of Sjögren's syndrome (SS) at present time there are no directed therapies. Management is very individualized based on disease activity and the extent of extragulatory involvement. We aim to relieve symptoms, to prevent complications which include ophthalmic and dental issues and to manage serious or what may be life threatening systemic issues which we do immunosuppressive therapy with. Initial treatments should go after oral, ocular, and systemic symptoms. What we put forward for therapy is based on disease severity, the extent of symptoms and the level of organ involvement. That is the same for primary (pSS) and secondary (sSS) Sjögren's syndrome. Currently we see that it is a mix of pharmacological and non-pharmacological interventions. In terms of the latter which include patient education on self care, the importance of giving up smoking, dietary and medication counseling, routine preventive care, immunizations and pregnancy related guidance. In secondary SS disease treatment is per the base cause. As a whole an inter professional team is recommended for best patient care. For primary disease modifying therapies are the mainstay and in moderate to severe cases which have organ involvement and present with systemic symptoms we may see the use of antimalarial drugs, immunosuppressants, or biologics. [23,24, 25, 26]

In most cases the primary therapeutic aim is to improve quality of life which we see play out especially in the treatment of dry mouth (xerostomia) and fatigue. As it pertains to dry mouth we see that we focus on prevention of infections, periodontal disease, and tooth decay. We do this by promoting very good oral hygiene, use of sugar free sweets and gum that will in turn stimulate saliva production, use of artificial salivas, and specially formulated tooth pastes. Also fluoride supplements are put into practice. In case of oral mycosis we see that anti fungal treatments provide for great relief in symptoms. Reports show also that oral pilocarpine has proved to be at the same time very safe and effective for patients with SS related xerostomia and that it in fact produces both subject and objective improvement. [22, 23,25,26]

For ocular involvement in dry eye disease we have a variety of tear substitutes for treatment. In that which is an immunologic based issue at the core of dry eye we see that anti inflammatory therapy which includes the use of cyclosporine A eye drops plays a key role. Also we see that which improves comfort and quality of life include tear duct plugs and scleral contact lenses

which in turn help maintain moisture at the eye surface. Also it is very much a team effort between patient and health care provider. [26]

The care of xerostomia also includes that of dentists and otolaryngologists. In patients which have reduced saliva production dental care is very challenging which in turn compromises tolerance to removable prosthesis. But in Sjogren's Syndrome patients dental implants have reported good results. [26]

The in which we see escalation of treatment is based on disease activity and which organ system is involved. Immunosuppressive approaches do so accordingly. In which we see large scale involvement of organs we use high dose methylprednisolone and cyclophosphamide which have shown to be effective. In cases of very severe vasculitis which also includes that with cryoglobulinemia we recommend rituximab or plasmapheresis. Non Hodgkin's lymphoma we approach according to the established oncology hematology guidelines which are based on the sub type and disease stage. Targeted treatments for specific manifestations include:

- Parotid gland swelling: Short term oral corticosteroids.
- Arthritis: Hydroxychloroquine, NSAIDs, short term oral or intra articular corticosteroids, and second line disease modifying antirheumatic drugs (DMARD) like methotrexate.
- Peripheral neuropathy: Antidepressants, gabapentin, oral or IV corticosteroids, and may also include IV immunoglobulin.
- Interstitial pneumonia: Oral and intravenous corticosteroids, with cyclophosphamide for active alveolar inflammation.
- Tubulointerstitial nephritis: Potassium and bicarbonate intake.
- Cutaneous issues present in many forms and thus require a very individualized approach. Itch is usually managed as a symptom which we pay particular attention to dry skin (xeroderma) which is a result at times of sebaceous gland involvement and also may be related to nerve issues. [22,23,25,26]

Patient education is at the core of what we do in SS management. In terms of clinical presentation what we see may vary but what we put out there for patients to know about lifestyle changes, environment triggers, and to stick to daily routines is the same. When patients are empowered which comes from knowledge of their condition and in turn they play an active role in their care we see better results and improved quality of life. [22,23]

Conclusion:

Early identification of Sjögren's syndrome as part of the differential diagnosis is therefore vital for prompt and precise detection. Thorough diagnostic approach—including clinical evaluation, serological testing, imaging, and, if necessary, histopathological and immunological tests—helps to properly classify patients and direct appropriate treatment. While more intense immunosuppressive treatments are saved for serious or life-threatening systemic involvement, customized medical care helps most people manage symptoms and decelerate disease development.

Mostly affecting the eyes and mouth, Sjögren's syndrome is a chronic autoimmune illness marked by lymphocytic invasion and malfunction of exocrine glands. Its clinical range covers systemic characteristics including muscular, pulmonary, renal, neurologic, and dermatologic manifestations, however. Early detection in patients with mild or odd symptoms especially is linked with better results, therefore underscoring the need for clinical awareness and suitable screening practices.

Continuous developments in diagnostic methods and treatment techniques help Sjögren's syndrome sufferers to improve their quality of life and prognosis. Central to maximizing long-term results remain multidisciplinary care and customized treatment programs.

Disclosure

Author's Contribution:

Conceptualization: Agnieszka Suszek, Monika Suszek

Methodology: Angelika Złotnik, Małgorzata Filak

Software: Adrianna Lysko, Agata Zabierowska

Check: Agnieszka Suszek

Formal analysis: Agnieszka Walus, Małgorzata Filak

Investigation: Monika Suszek

Resources: Adrianna Lysko, Julia Surowaniec

Data curation: Angelika Złotnik

Writing – rough preparation: Agnieszka Suszek

Writing – review and editing: Agnieszka Walus, Maciej Bulwa

Visualization: Natalia Wieczorek-Durdzińska

Supervision: Agata Zabierowska, Angelika Złotnik

Project administration: Angelika Złotnik, Julia Surowaniec

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