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SJÖGREN'S SYNDROME: PATHOGENESIS, DIAGNOSIS, MANIFESTATIONS, AND MODERN TREATMENT – A NARRATIVE REVIEW

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ABSTRACT

Sjögren's syndrome is a chronic, systemic autoimmune disease whose symptoms affect multiple organs and systems. However, a characteristic feature of this syndrome is exocrine gland dysfunction, manifesting as dry eye and dry mouth. Other typical symptoms include fatigue, musculoskeletal pain, and systemic manifestations such as cutaneous vasculitis, interstitial lung disease, and neuropathy. Sjögren's syndrome, as with other rheumatoid diseases, is more common in women than in men, most often in middle age [1]. Patients with this syndrome also have an increased cardiovascular risk and an increased risk of non-Hodgkin's lymphoma. The first case with dry eye symptoms was described in 1892 by Jan Mikulicz-Radecki, a Polish-German surgeon [2]. We differentiate between primary Sjögren's syndrome and the secondary form associated with other autoimmune diseases, such as rheumatoid arthritis. More than half of patients demonstrate elevated levels of antinuclear antibodies (Ro). The etiology of Sjogren's syndrome remains poorly understood, but several genetic, epigenetic, and environmental factors have been proposed. Diagnosis is based on symptoms of dry eye syndrome, the presence of characteristic autoantibodies, and morphological findings from a minor salivary gland biopsy. Treatment of Sjogren's syndrome is based on symptomatic therapies for dry eyes and the oral cavity. This review also focuses primarily on modern biologic medications and new, promising therapeutic options.

KEYWORDS

Sjögren’s Syndrome, Xerophthalmia, Xerostomia, Ro/SSA Antibody, La/SSB Antibody, Pulmonary Fibrosis, Treatment

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Methods

This review article was written using a literature review of the PubMed database (2021-2025). It focuses on the etiology, epidemiology, pathogenesis, clinical manifestations, diagnosis, and, above all, treatment of Sjogren's syndrome, including new therapeutic options. The effectiveness of some new biologic agents in Sjogren's syndrome is summarized.

Introduction

Sjogren's syndrome is a systemic, chronic connective tissue disease characterized by a generalized sicca syndrome. It is an immunologically mediated disease of unknown etiology that primarily affects the salivary and lacrimal glands, leading to xerostomia and xerophthalmia, respectively. Symptoms of Sjogren's syndrome can affect virtually all systems and organs, including changes in the lungs, kidneys, and gastrointestinal tract, as well as neurological damage.

History

The first patient with symptoms of dryness and bilateral parotid gland swelling was described by surgeon Jan Mikulicz-Radecki in 1892. In 1933, Swedish ophthalmologist Henrik Sjögren described the systemic disease as a combination of xerostomia and xerophthalmia with rheumatoid arthritis (RA).

Epidemiology

Sjogren's syndrome is one of the most common autoimmune diseases in the population. It is most frequently diagnosed in women, nine times more often than in men, between the fifth and sixth decades of life. Clinical cases of younger onset and even rare cases of juvenile Sjogren's syndrome also exist. Juvenile Sjogren's syndrome most often appears around the age of ten. Characteristic clinical symptoms include recurrent parotitis, joint pain, and possibly normal laboratory test results. Based on a study conducted by the EULAR-SS Task Force, the diagnosis of Sjogren's syndrome is, on average, seven years earlier in

Black/African-American patients. Asian patients also have a significantly higher incidence (27:1) in women than in men [3]. Risk factors that indicate higher disease activity and may contribute to increased mortality in Sjogren's syndrome include diagnosis at an older age, male gender, parotid enlargement, abnormal parotid scintigraphy, parenchymal organ involvement, vasculitis, positive anti-La antibodies, decreased complement levels, and cryoglobulinemia [4]. Disease activity is assessed in clinical trials using the ESSDAI (European Sjögren's Syndrome Disease Activity Index). The most common causes of death in patients with Sjogren's syndrome are infections, cardiovascular disease, and hematologic and solid malignancies. Patients with Sjogren's syndrome have a statistically significant increased risk of death compared to the general population.

Ethiology and pathogenesis

The etiology of Sjogren's syndrome, as with other autoimmune diseases, remains unclear. However, it is postulated that various factors—genetic, epigenetic, and immunological changes—contribute to its development. For example, familial studies show that approximately one-third of patients have a relative with another rheumatic disease. The presence of certain specific human leukocyte antigen (HLA) alleles, such as HLA DRB1*03:01, DQA1*05:01, and DQB1*02:01, increases susceptibility [5]. In addition to genetic predisposition, epigenetic factors play a significant pathogenic role—patients treated with the anti-CD20 antibody rituximab show reduced B lymphocytes. They restored DNA methylation in labial salivary gland epithelial cells.

Sjögren's syndrome is often described as an autoimmune disease characterized by inflammation of the epithelium; here, epithelial cells are both initiators and targets of the destructive process. Proinflammatory cytokines produced by epithelial cells disrupt the integrity of tight intercellular junctions, leading to the destruction of secretory glands. In predisposed individuals, exposure to key environmental factors can disrupt the immune system. Notably, during the initial disease phase, disruption of innate immune barriers through the interferon pathway plays a major pathogenic role. At the same time, uncontrolled B lymphocyte activation and proliferation of Th1 and Th17 cells further increase disease activity [6].

A potential trigger of Sjogren's syndrome may be viral infection, primarily Epstein-Barr virus (EBV). EBV has been detected in saliva, salivary gland samples, and tear gland biopsies, among other sources, and it displays a tropism for B lymphocytes [7]. Some authors demonstrate a correlation between EBV, increased disease activity, and multisystem symptoms.

Symptoms

With mechanisms introduced, attention turns to symptoms. The most important clinical symptoms of Sjogren's syndrome are dry eyes (xerophthalmia) and dry mouth (xerostomia), which occur in 92% and 94% of patients, respectively [8]. Commonly reported symptoms include fatigue, generalized pain, and sleep disturbances.

Cancer Risk

Patients with Sjogren's syndrome have a 4-7 times higher risk of developing non-Hodgkin lymphoma compared to the general population [9], with an overall incidence of 2-9% in those with primary Sjogren's syndrome [10].

Musculoskeletal involvement

In patients with primary Sjogren's syndrome, the incidence of arthralgia was 45%, with arthritis reported primarily in the proximal interphalangeal, metacarpophalangeal, and wrist joints [11].

Dermatological involvement

The most common skin lesion in Sjogren's syndrome is cutaneous vasculitis, manifested as purpura. Other dermatological manifestations that may be observed include erythema annulare, subacute cutaneous lupus erythematosus, erythema nodosum, and livedo reticularis

Cardiovascular involvement

Further system involvement includes cardiovascular complications. Based on studies, patients with primary Sjogren's syndrome have an increased risk of cardiovascular complications. These patients are at increased risk of coronary artery disease, cerebrovascular disease, heart failure, pulmonary embolism, deep vein thrombosis, and venous thromboembolism.

Pulmonary involvement

Pulmonary manifestations are also frequent in Sjogren's syndrome. Patients with Sjogren's syndrome repeatedly experience symptoms such as cough and shortness of breath. They may initially present with a chronic cough of unknown etiology, only to be diagnosed with sicca syndrome. Pulmonary involvement may present as interstitial pneumonia, bronchiectasis, and lymphocytic infiltrates, such as nodular bronchiolitis and lymphocytic bronchitis. Airway disease caused by dry mucosa, known as bronchiolitis sicca, may also occur. Pulmonary symptoms may resemble asthma if the obstruction is reversible with inhaled glucocorticosteroids.

Gastrointestinal involvement

The gastrointestinal system can also be affected. Dysphagia, which may be caused by dry mouth, is a common gastrointestinal symptom affecting up to 80% of patients. Gastrointestinal motility disorders may also result from autonomic neuropathy. Patients with Sjogren's syndrome may also present with exocrine pancreatic dysfunction. A smaller group of patients may also present with liver disease.

Neurological involvement

In addition, neurological involvement is noteworthy. The most common symptoms resulting from peripheral nervous system involvement in patients with primary Sjogren's syndrome include sensory neuropathies and axonal sensorimotor polyneuropathies. Central nervous system involvement is less common, with the predominant symptoms being focal or multifocal lesions, multiple sclerosis-like disease, and isolated optic neuritis.

Renal involvement

Finally, renal involvement warrants attention. One in 10 patients with Sjogren's syndrome also suffers from glomerulonephritis or tubulointerstitial nephritis, which may or may not be accompanied by renal tubular acidosis [12].

Other autoimmune disorders

Secondary Sjogren's syndrome is associated with other systemic autoimmune diseases, such as rheumatoid arthritis or systemic lupus erythematosus. However, patients with Sjogren's syndrome may also have other autoimmune diseases affecting the gastrointestinal tract, thyroid, or liver, such as celiac disease, autoimmune hepatitis, primary biliary cholangitis, hypothyroidism, Graves' disease, or even overt antiphospholipid syndrome with antiphospholipid antibodies.

Pregnancy

Patients with Sjogren's syndrome have an increased risk of obstetric complications compared to the general population, such as miscarriage, preterm birth, and low birth weight. Neonatal lupus erythematosus is significantly more common in women with positive SSA or SSB antibodies.

Diagnosis

Subjective symptoms

To be diagnosed with Sjogren's syndrome, patients must have had dry eye symptoms for at least 3 months. The patient's history should include:

Experiencing dry eyes daily for more than three months

Feeling gritty in the eyes

Using artificial tears more than three times a day

Experiencing a dry mouth daily for more than three months

Frequently needing something to drink to swallow dry food

To diagnose Sjogren's syndrome, we use the 2016 ACR/EULAR classification criteria. The patient must present at least one symptom associated with dry eyes or dry mouth (based on the 2002 AECG type I and II criteria). The ESSDAI questionnaire can also be used. The patient must score at least four points on this questionnaire. The questionnaire consists of five domains; at least one domain must be positive.

The ESSDAI questionnaire includes: the presence of lymphocytic sialadenitis, obtained by biopsy of the labial salivary gland – three points; a positive SSA antibody result – three points; an eye stain score of at least 5 according to the Whitcher protocol or a van Bijsterveld score of at least 4 in at least one eye – one point;

a Schirmer test <5 mm/5 min in at least one eye – one point; unstimulated salivary flow rate (< 0.1 ml/minute, as described by Navazesh and Kumar) – score one point [13].

Exclusion criteria include, among others, previous head and neck radiation therapy, AIDS, sarcoidosis, amyloidosis, HCV, graft-versus-host disease, and IgG4-related disease.

Severity of disease

To assess the severity of Sjogren's syndrome, we can currently use the ESSDAI or ESSPRI index. The ESSDAI comprises 12 domains, each assigned a score from 0 to 4 based on disease severity. The ESSDAI assesses general health status (fever, night sweats, weight loss), lymph nodes, glandular involvement, joints, skin, lungs, kidneys, nerves, hematological changes, and other laboratory tests, such as complement, cryoglobulins, and hypergammaglobulinemia. The ESSPRI, on the other hand, involves a subjective assessment of patient-reported symptoms, such as dryness, fatigue, and pain [14].

Treatment

In this review, we focus primarily on the treatment of Sjogren's syndrome, including new and emerging therapeutic options. Treatment of Sjogren's syndrome involves treating sicca symptoms as well as systemic immunosuppressive therapy for extraglandular symptoms.

Patients can use artificial tears, drops, gels, and eye ointments to treat xerophthalmia at least twice daily. Scleral lenses may be another therapeutic option for symptomatic treatment. For severe dry eye symptoms, short-term topical NSAIDs or topical corticosteroids, and long-term cyclosporine eye drops may be used. If cyclosporine is intolerant or ineffective, autologous serum eye drops may be used. In cases of refractory dry eye syndrome and a risk of blindness, oral muscarinic agonists or the anti-CD20 antibody rituximab may be indicated. Patients with dry mouth are at increased risk of caries, so regular dental checkups are recommended. Topical fluorides should be used, and smoking should be avoided. Treatment for xerostomia depends on its severity; sugar-free chewing gum or lozenges are used for mild symptoms. For more severe dry mouth, artificial saliva in the form of sprays, gels, or mouthwashes is used, or pilocarpine, cevimeline, a muscarinic receptor agonist, is administered orally.

Immunosuppressive medications (azathioprine, mycophenolate mofetil, methotrexate, leflunomide, cyclophosphamide) are recommended to shorten the duration of glucocorticoid therapy. Biological drugs that affect B lymphocytes, such as rituximab (anti-CD20 antibody), indicated primarily for vasculitis, and belimumab (anti-BAFF antibody), are effective in severe Sjogren's syndrome. Other biologic drugs being investigated for the treatment of Sjogren's syndrome include abatacept, immunoglobulins, and iguratimod. In a study of patients with Sjogren's syndrome treated with abatacept for 48 weeks, reductions in the ESSDAI and EESPRI disease activity scores were observed. Half of the patients achieved low disease activity. A reduction in the severity of sicca symptoms and improvements in laboratory test results were also demonstrated. In a 68-week study of patients with Sjogren's syndrome treated with both belimumab and rituximab, a subtotal reduction in salivary gland CD20+ B cell subpopulations and CD19+ B lymphocytes was observed, as well as a reduction in the EULAR disease activity score. Furthermore, when belimumab was used in combination with rituximab, a low EULAR disease activity score was observed. Iguratimod is a small-molecule drug used in Asia for various connective tissue diseases. Its effects include regulating B-cell subpopulations, reducing the production of immunoglobulins and proinflammatory cytokines, including interleukins and TNF. Based on studies, iguratimod may improve the secretory function of the lacrimal and salivary glands, and also has a beneficial therapeutic effect on pulmonary fibrosis and the cardiovascular system. However, additional studies are needed to assess the drug's effectiveness and safety. Hydroxychloroquine is recommended for dermatological changes in the course of Sjogren's syndrome or musculoskeletal pain. Endurance exercises that improve exercise tolerance are recommended. Cognitive-behavioral therapy can also be used in patients with fatigue. Fatigue is a difficult symptom to treat and may also herald the development of non-Hodgkin's lymphoma.

Clinical trials are ongoing for various types of biologics. Janus kinase inhibitors, BDCA-2 antibodies, and IL-12/23 antibodies are also being studied in Sjogren's syndrome. Most patients with primary Sjogren's syndrome have elevated IFN levels, so clinical trials are currently underway to explore the use of drugs that target IFN. A monoclonal antibody (BIIB059) directed against blood dendritic cell antigen 2 (BDCA2) (which has shown encouraging results for efficacy in cutaneous lupus erythematosus) is also considered suitable for use in Sjogren's syndrome [15]. Clinical trials are also underway to evaluate the efficacy of tofacitinib, a Janus kinase inhibitor that can inhibit the production of type I and II IFNs [16]. Ustekinumab, an anti-IL-12p40

antibody, is also being studied, and by blocking IL-12 and IL-23, it may also block interferon production. The S1P receptor is also expressed in the salivary and lacrimal glands, which could enable the use of drugs that inhibit the sphingosine-1-phosphate pathway, which are used in multiple sclerosis, in Sjogren's syndrome (fingolimod and ozanimod) [17, 18, 19]. Finally, mTOR inhibitors, AKT inhibitors, drugs that interfere with T cell activation, drugs that regulate the cell cycle, and other molecules (BTK, Syk, Tyk) are being studied for use in Sjogren's syndrome [20]. A new therapeutic option could be targeting B cells via CD40.

Management of the patient

An ophthalmologist and a pulmonologist should monitor a patient with Sjogren's syndrome. Visits with these specialists should occur at least annually. Echocardiography and abdominal, lymph node, and parotid gland ultrasound examinations should be performed annually. The patient should undergo periodic laboratory tests (complete blood count, blood smear, renal function tests, liver enzymes, C-reactive protein, ESR, complement, serum protein electrophoresis, venous blood gases, urinalysis, urine protein/creatinine ratio).

Conclusions

Sjogren's syndrome is a chronic connective tissue disease associated with impaired exocrine gland function. Its most prominent symptoms include dry eyes and dry mouth, but symptoms can affect many systems and organs. Treatment for Sjogren's syndrome is divided into symptomatic treatments for the dryness, such as artificial tears or saliva, and immunosuppressive therapy to address systemic symptoms. Various studies have confirmed the effectiveness of biologic drugs that target the pathogenesis of the disease (including B lymphocytes), including rituximab. There are many other biologic drugs in clinical trials, such as Janus kinase inhibitors, that could revolutionize the treatment of Sjogren's syndrome. It's important to remember that an individualized approach to the patient, including their medical history, subjective and clinical symptoms, needs, and expectations related to the treatment process, is always paramount.

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