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SJÖGREN'S SYNDROME: MUCH MORE THAN SICCA SYMPTOMS: A LITERATURE REVIEW

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ABSTRACT

Sjögren's syndrome (SS) is a long-term autoimmune disease that mainly results in dry eyes and mouth due to dysfunction of the lacrimal and salivary glands. It can also lead to a wide range of systemic symptoms, potentially involving multiple organ systems. The disorder is categorized as primary (pSS) when it arises on its own, or secondary when it occurs alongside other autoimmune conditions. Diagnosis is frequently delayed by several years after symptom onset, and even after a diagnosis is made, no therapies currently exist that target the root cause of the disease. In this article, we focus on the systemic manifestations of Sjögren's syndrome and their treatment. We also present current research directions related to the disease's pathogenesis and therapy, while highlighting specific areas that require further investigation. Advancing knowledge in these fields may contribute to improving the quality of life for SS patients and to the development of more personalized and effective treatment approaches.

KEYWORDS

Sjögren's Syndrome, Autoimmunity, Sicca Syndrome

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Introduction.

Sjögren's Syndrome is a chronic systemic autoimmune disease of unknown origin, marked by immune-driven damage to the salivary and lacrimal glands. This results in dryness of the mouth (xerostomia) and eyes (xerophthalmia). The condition is estimated to affect between 0.5% and 1% of the general population, with middle-aged women being the most commonly affected group (Mavragani and Moutsopoulos, 2013). Several hypotheses have been proposed regarding the pathogenesis of primary Sjögren's Syndrome, involving disruptions in both innate and adaptive immune responses. Additionally, dysfunction at the intersection of immune regulation and the neuro-endocrine system has also been implicated in the development of glandular impairment (Fox et al., 2021). While SS is traditionally viewed as a disease primarily affecting secretory organs—particularly the salivary and lacrimal glands—resulting in dryness of the mouth and eyes, it is also associated with a wide spectrum of clinical manifestations beyond glandular involvement (Mavragani and Moutsopoulos, 2013). Some patients with SS may exhibit clinical features that overlap with other rheumatic conditions, such as systemic lupus erythematosus (SLE), making it difficult to distinguish SS from similar diseases (Goldblatt and O'Neill, 2013). Current treatment options for SS are often inadequate, with limited effectiveness in preserving salivary gland function or controlling disease activity.

As a result, SS remains a complex and challenging rheumatic condition that poses significant health risks (Wang et al., 2021). Given the immense social and economic burden caused by SS, we aimed in this review to characterize the current paradigm of the pathogenesis and treatment of SS to motivate and inform the development of efficient treatment strategies.

Therefore, an early diagnosis is crucial to the effective management of SS. This review provides an overview of those challenges and unmet needs in the early diagnosis and management of SS.

Historical outline

In 1892, Mikulicz was the first to describe a patient exhibiting sicca symptoms along with bilateral enlargement of the parotid glands. The term"sicca syndrome" was later introduced by Gougerot in 1925. Eight years afterwards, in 1933, Henrik Sjögren identified a systemic condition he termed"keratoconjunctivitis sicca" (Andre and Böckle, 2022). He described 19 female patients suffering from pronounced dryness of the eyes and mouth, accompanied by lymphocytic infiltration in the lacrimal and salivary glands, as well as systemic manifestations. (Akpek et al., 2019).

Pathogenesis

The exact pathogenesis of Sjögren's disease remains unclear, but it is believed to be

a multifactorial process involving a combination of genetic predisposition and environmental factors that initiate an abnormal immune response (Parisis et al., 2020; Tian et al., 2021). Many of the genes linked to Sjögren's disease are associated with disruptions in immune regulation, especially those involved in innate immunity and inflammatory signalling pathways. It is proposed that the onset of Sjögren's Syndrome involves an initiating phase in which environmental factors—such as viral infections—interact with genetic predisposition and epigenetic modifications to disrupt the integrity of the salivary gland epithelium (Maleki-Fischbach et al., 2024). Multiple viruses have been suggested as potential environmental triggers for SS, including Epstein-Barr virus (EBV), cytomegalovirus (CMV), human herpesvirus type 8 (HHV-8), human T-lymphotropic virus type 1 (HTLV-1), hepatitis C virus, and enteroviruses.

Additionally, paramyxovirus—the cause of mumps—has been shown to persist in salivary tissue and may serve as a triggering factor for autoimmune pathogenesis in genetically susceptible individuals (Shen et al., 2019). Cytokines, B cell growth factors, and elevated levels of serum B cell-activating factor (BAFF) are key contributors to the pathogenesis of Sjögren's syndrome.

These factors are dysregulated in SS patients and are associated with the presence of autoantibodies against Ro and La antigens (Shen et al., 2019). Elevated concentrations of cytokines, particularly type I interferons and B cell-activating factors, along with various chemokines, facilitate the recruitment of lymphocytes and dendritic cells to the exocrine glands. This immune cell infiltration drives the chronic inflammatory process characteristic of SS (Maleki-Fischbach et al., 2024).

Diagnosis

In Sjögren's disease, excessive activation of B lymphocytes leads to the generation of numerous circulating autoantibodies. Commonly used biomarkers include antibodies against Sjögren's syndrome-related antigens A and B (anti-SSA/Ro and anti-SSB/La), antinuclear antibodies (ANA), and rheumatoid factor (RF). Anti-SSA/Ro antibodies, which are found in approximately 75% of individuals with the disease, play a significant role in diagnosis (Brito-Zerón et al., 2018). These antibodies, identified through solid-phase immunoassays using both Ro60 and Ro52 antigens, are relatively specific to Sjögren's disease (Trier et al., 2013). Diagnostic criteria for Sjögren's disease have been established by expert panels and were initially intended for use in clinical trial enrollment, but they now serve as diagnostic guidelines. According to the 2017 classification criteria jointly developed by the American College of Rheumatology (ACR) and the European Alliance of Associations for Rheumatology (EULAR), a scoring system is used to diagnose the condition. This system considers factors such as anti-SSA/Ro antibody presence, focal lymphocytic sialadenitis focus score, ocular staining, Schirmer's test results, and unstimulated salivary flow rate (Maleki-Fischbach et al., 2024).

Clinical manifestations

Sicca symptoms

Dryness of the eyes and/or mouth represents the most frequently reported symptomatology among patients with SS. Up to 98% of individuals report experiencing at least one of these manifestations, while 89% present with both symptoms (Baldini et al., 2014).

Patients often describe difficulty swallowing dry foods or an inability to speak for extended periods without the need for hydration. Additionally, recurrent or persistent swelling of the major salivary glands is commonly observed, affecting approximately one-third of patients (Negrini et al., 2021). Dry eye associated with SS is a progressive disorder that significantly impairs patients' quality of life, not only due to persistent ocular discomfort but also as a result of visual impairment. Moreover, SS may give rise to serious ocular complications, including corneal melt or perforation, uveitis, scleritis, retinal vasculitis, and optic neuritis (Akpek et al., 2019).

General manifestations

In addition to the conventional involvement of the salivary and lacrimal glands in SS, the condition has also been linked to a broad spectrum of systemic manifestations. These may stem from periepithelial lymphocytic infiltration in parenchymal organs such as the kidneys, lungs, and liver, or from immune complex deposition secondary to B cell hyperactivity, leading to conditions such as purpura, peripheral neuropathy, and glomerulonephritis (Mavragani and Moutsopoulos, 2013). Additionally, general symptoms including fatigue, sleep disturbances, and diffuse musculoskeletal pain are frequently observed (Maleki-Fischbach et al., 2024).

Renal involvement

Although SS is generally not associated with high mortality, patients who develop renal involvement face a heightened risk of life-threatening complications. Renal manifestations are relatively uncommon, occurring in approximately 5–10% of individuals with SS (Shen et al., 2019). Kidney manifestations in pSS result from lymphocytic infiltration of the renal tubules or the deposition of immune complexes, giving rise to diverse clinical features.

The predominant histopathological finding is tubulointerstitial nephritis. Additional tubular disorders may include renal tubular acidosis with associated hypokalaemia, Fanconi syndrome, and diabetes insipidus. Glomerular involvement is less frequent and is generally associated with immune complex-mediated mechanisms (Aiyegbusi et al., 2020). Early identification of patients at elevated risk for renal disease is essential to ensure timely and appropriate management.

Liver involvement

In a retrospective analysis, elevated liver enzyme levels were observed in approximately one-third of patients with SS (Karp et al., 2010). When such abnormalities are detected, infectious etiologies must be ruled out as a first step. The estimated prevalence of autoimmune hepatitis among SS patients ranges from 1–4%, while primary biliary cholangitis occurs in approximately 4–9% of cases (Andre and Böckle, 2022).

Lungs involvement

Pulmonary involvement occurs in up to 20% of patients with SS, most commonly presenting as a persistent dry cough (Andre and Böckle, 2022). Interstitial lung disease (ILD) and its complications are significant contributors to mortality in this patient population, highlighting the importance of early detection and intervention. Standard chest radiography is inadequate for early identification; thus, high-resolution computed tomography (HR-CT), along with pulmonary function testing, including assessment of diffusion capacity, is recommended both at the time of diagnosis and for ongoing monitoring. ILD in SS frequently manifests as lymphocytic interstitial pneumonia, characterized by cystic changes in the lung parenchyma and ground-glass opacities (Yoo et al., 2022).

Joint and muscles

Musculoskeletal involvement is also prevalent in SS, with arthritis being one of the most common features. It typically presents as an intermittent, symmetric, non-destructive polyarthritis, while axial involvement is less commonly observed (Fauchais et al., 2012). The presence of erosive arthritis warrants consideration of rheumatoid arthritis (RA), as SS patients with this presentation often exhibit clinical, serologic, and radiographic features consistent with RA.

However, they can be distinguished from individuals with classic RA by differences in organ involvement and genetic predisposition (Andre and Böckle, 2022). Myalgia is frequently reported among SS patients, whereas active myositis is rare, occurring in approximately 2% of cases. When present, it is typically diagnosed in the context of inflammatory idiopathic myopathy or as part of an overlap syndrome (Flores-Chavez et al., 2018).

Cutaneous symptoms

Cutaneous involvement is relatively frequent in Sjögren's syndrome, with a variety of dermatologic manifestations observed. Common presentations include xeroderma, eyelid dermatitis, annular erythema, and cutaneous vasculitis. In addition to vasculitic features, non-vasculitic skin manifestations such as livedo reticularis—often occurring independently of vasculitis—and localized nodular cutaneous amyloidosis may also be observed. The latter may reflect underlying lymphoproliferative processes associated with SS (Generali et al., 2017)

Lymphomas in SS

In individuals with primary Sjögren's syndrome, the incidence of lymphoma is significantly higher compared to the general population. This increased risk is attributed to the underlying B cell hyperactivity that characterizes the disease. Notably, the lymphomas that develop in pSS patients are exclusively of B cell origin (Shen et al., 2019).

Neuropsychiatric manifestations

Neurological manifestations represent a significant proportion of the extraglandular features associated with pSS. According to published studies, the prevalence of neurological involvement varies widely, ranging from approximately 8.5% to 70% among patients (Perzyńska-Mazan et al., 2018). In 25% to 60% of cases, neurological symptoms precede the diagnosis of pSS by an average of two years; in others, they arise 6 to 8 years post-diagnosis (Fauchais et al., 2012). Peripheral neuropathy—most notably sensory polyneuropathy—constitutes the most prevalent neurological complication. Central nervous system (CNS) involvement occurs less frequently, affecting an estimated 10% to 20% of patients, and often presents with lesions reminiscent of those seen in multiple sclerosis. These lesions are predominantly located in the brain's white matter (60%) and the spinal cord (40%). Additional neurological findings include cranial nerve abnormalities and autonomic nervous system dysfunction (Perzyńska-Mazan et al., 2018).Psychiatric disorders are commonly observed throughout the progression of pSS, with prevalence estimates ranging between 20% and 70%. The most frequently reported psychiatric conditions include major depressive disorder, anxiety disorders, cognitive dysfunction, and dementia, whereas transient psychotic episodes and delirium are comparatively uncommon (Ampélas et al., 2001). Early identification of neuropsychiatric manifestations in rheumatologic diseases such as pSS is essential for the timely initiation of appropriate therapeutic strategies aimed at enhancing patient quality of life (Costa et al., 2025).

Cardiovascular events

pSS is associated with an increased risk for cerebrovascular events and myocardial infarction (Valim et al., 2016). Cardiovascular risk factors such as arterial hypertension, hypertriglyceridemia, dyslipidemia, and obesity are more common in pSS, whereas SS patients smoke less frequently

compared to the general population (André and Böckle, 2022). Future studies are needed to determine if the risk of atherosclerosis is linked to the activity of SS.

Treatment

Treatment should be tailored to the type and severity of organ involvement, ideally based on multidisciplinary evaluation. Treatment of pSS patients with severe extraglandular disease should differ from that of patients with predominantly sicca features and/or general musculoskeletal manifestations. pSS treatment is mainly symptomatic, primarily directed against sicca complaints. Table 1 summarizes the methods of local treatment of dry eyes.

The traditional anti-rheumatic agents show limited efficacy in the systemic process (Thanou-Stavraki and James, 2008) Although traditional antirheumatic drugs are used empirically for polyarthritis and other Sjögren's symptoms, their efficacy in pSS overall and as disease-modifying agents is limited.

Table 1. Methods of topic treatment of dry eyes in SS (Longhino et al., 2023)

Treatments	Comments
Artificial tears	Common and effective for relieving dry eye symptoms.
Cyclosporine eye drops	Treatment of moderate-to-severe dry eye disease based on an improvement in tear production.
Lifitegrast eye drops	It is a lymphocyte function-associated antigen 1 antagonist approved by the FDA for the treatment of dry eye disease, to reduce ocular surface inflammation.
Blood-derived sera, such as autologous serum, allogeneic serum and umbilical cord serum	Used in severe cases of dry eye disease - provide hydration, nutrition and growth factors that promote cellular tropism within the epithelium, thus improving regeneration.

Systemic symptoms treatment

Glucocorticoids

To date, there have been no large-scale clinical trials evaluating the potential benefits of glucocorticoids for the glandular symptoms of SS. Without a clear assessment of their benefit-to-risk ratio in pSS, glucocorticoids should be used cautiously—at the lowest effective dose, for the shortest possible duration, and ideally avoided altogether (Fox et al., 2021). Prolonged glucocorticoid use in pSS is discouraged due to possible adverse effects such as osteoporosis, high blood sugar, weight gain, mood changes, cumulative tissue damage, and a heightened risk of infections, similar to other autoimmune conditions. Additionally, pSS patients face an increased likelihood of oral *Candida* infections and accelerated tooth decay, which further restricts the safe use of high-dose, long-term glucocorticoid therapy (Fox et al, 2021; André and Böckle, 2022).

To reduce reliance on glucocorticoids, steroid-sparing immunosuppressants are preferred, although no single agent in this category has demonstrated clear superiority over the others (André and Böckle, 2022).

Biological treatment

B cell targeting

Given the involvement of B cells in the development of SS, therapies like rituximab and belimumab (a BAFF-inhibiting antibody) have emerged as promising treatment options, having shown effectiveness in managing SS (André and Böckle, 2022). However, at present, their use is limited to patients with severe, treatment-resistant systemic manifestations. Rituximab is typically prescribed in cases involving vasculitis (Roccatello et al., 2018).

T cell targeting

The interaction between activated CD4+ T cells and B cells plays a key role in promoting B cell hyperactivity in SS, making this interaction a compelling therapeutic target (Verstappen et al., 2019). In an open-label study, Adler and colleagues demonstrated that abatacept was both effective and well-tolerated in patients with early-stage SS. Abatacept treatment reduced salivary gland inflammation and improved saliva production.

Additionally, it resulted in increased levels of circulating B cells and a decrease in regulatory T cells (Tregs) in the salivary glands. The improvement in saliva production was similar to that observed with rituximab therapy. (Adler et al., 2013)

Cytokines targeting

Cytokines form a complex signalling network, and their dysregulation can contribute to both systemic and exocrine gland dysfunctions. In SS, most cytokine-targeted therapies have focused on members of the TNF, IFN, IL-1, IL-2, IL-6/12, IL-10, and IL-17 families (Retamozo et al., 2018). Attempts to inhibit TNF-α using agents like etanercept and infliximab did not yield significant differences compared to placebo, and infliximab was associated with several adverse effects in SS patients. Conversely, low doses of IL-2 and IFN-α have shown therapeutic benefits with minimal side effects.

Tocilizumab, which targets the IL-6 receptor, is still undergoing clinical evaluation. Given that levels of IL-22, IL-17, and IFN-γ are also elevated in SS, targeting these cytokines may hold potential for future treatment strategies (Srivastava and Makarenkova, 2020).

Future therapeutic options

Future treatments should aim to alleviate symptoms such as dry eyes and dry mouth, as well as address extraglandular manifestations, fatigue, and cognitive impairments.

Considering the shortcomings of current therapeutic options, it is proposed that novel approaches—particularly those that involve collaboration with neuroscientists and neuropsychiatrists, possibly in combination with new immune-targeting strategies—may offer more effective solutions for managing pSS (Fox et al., 2021). The efficacy of various medications is currently being investigated in clinical studies - Seror et al, 2021.

It should be stressed that future therapeutic approaches are not limited to B cells but also target other areas of the immune response (Janus kinase inhibitors, BDCA-2 antibodies, Il-12/23 antibodies). Targeting pro-inflammatory cytokines or blocking their receptors may offer

a promising therapeutic option for certain SS patients. This method could complement existing treatments. However, the roles of many cytokines remain unclear because of the complex and varied nature of SS. Therefore, in-depth investigation of the early stages of the disease, along with a better understanding of how it progresses in both patients and mouse models, is essential for creating more personalized and effective treatment strategies (Srivastava and Makarenkova, 2020). As with other diseases, the ultimate goal in SS is to provide each patient with a personalized treatment approach tailored to their specific needs.

Conclusion and Future Perspectives

In SS, genetic predisposition works together with environmental factors, such as viral infections, which can trigger or worsen the autoimmune response. While both genetic and environmental influences are thought to contribute to the development of SS, the underlying disease-causing mechanisms remain largely unclear. Enhancing treatment options for SS requires addressing several key questions. Identifying the risk factors associated with varying systemic complications in SS patients is particularly important. There is also a need to establish a standardized approach for assessing disease activity and patient-reported outcomes.

Furthermore, investigating the connection between salivary gland symptoms and extra-glandular manifestations, as well as uncovering the molecular mechanisms underlying fatigue and organ involvement, is crucial. By directly confronting these issues, we can deepen our understanding of SS and pave the way for more effective therapies. We stress the importance of prioritizing targeted therapies, treatments with minimal side effects, and combination approaches in future research efforts. SS is still primarily associated with glandular manifestations. However, recognizing this condition as a systemic disease with diverse extraglandular symptoms is essential for understanding its complex pathophysiology.

A thorough comprehension of these mechanisms is crucial for the development of effective and modern therapeutic strategies.

Authors' contributions statement

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